



European Monitoring Centre  
for Drugs and Drug Addiction

**DRAFT**

**Technical report on 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide  
(CUMYL-4CN-BINACA)**

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (CUMYL-4CN-BINACA)* to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (CUMYL-4CN-BINACA)*

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## Introduction

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as CUMYL-4CN-BINACA, are a group of substances that mimic the effects of tetrahydrocannabinol (THC), which is a substance found in cannabis <sup>(1)</sup>. THC is responsible for many of the psychoactive effects of cannabis which give that feeling of being 'stoned' (or 'high') (Gaoni et al, 1964; Huestis et al., 2001; Pertwee, 2014). THC causes these effects by activating a receptor in the brain called the cannabinoid receptor type 1 (CB<sub>1</sub> receptor) (Huestis et al., 2001; Pertwee, 2005a). This receptor is part of a signalling system in the body called the endocannabinoid system, which helps regulate, among other things, behaviour, mood, pain, appetite, sleep, and the immune system (Pertwee, 2015) <sup>(2)</sup>. Because synthetic cannabinoids activate the CB<sub>1</sub> receptor in a similar way to THC, some of their effects appear to be similar to cannabis. Most prominently, they are able to create a feeling of being 'stoned'.

Synthetic cannabinoids were originally developed by scientists to study the endocannabinoid system, as well as provide insights into disease, and to help make new medicines (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015; Reggio, 2009). From around 2006, they began to appear in Europe in products called 'Spice' that were sold as 'legal' replacements to cannabis (Auwärter et al., 2009; EMCDDA, 2009; Jack, 2009). In these products, synthetic cannabinoids had been mixed with plant (herbal) material which could then be smoked as cigarettes ('joints') (Auwärter et al., 2009; EMCDDA, 2009; EMCDDA, 2017a; Jack, 2009). Such products have been referred to by a variety of names, including 'herbal smoking mixtures', 'herbal incense', 'Spice', 'K2', and 'synthetic cannabis'. Since 2008, almost 180 synthetic cannabinoids have been identified on the drug market in hundreds of different products. They are the largest group of substances that are monitored by the EMCDDA through the European Union Early Warning System on New Psychoactive Substances (EU Early Warning System) (EMCDDA, 2017b).

In accordance with the Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances <sup>(3)</sup>, on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for the synthetic cannabinoid 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA) on the basis of data reported by the Member States through the EU Early Warning System. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the Institutions of the European Union in July 2017 (EMCDDA, 2017c). On 14 September 2017, the Council of the European Union requested that a risk assessment on CUMYL-4CN-BINACA should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for the risk assessment, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as

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<sup>(1)</sup> (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol.

<sup>(2)</sup> The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors, the endocannabinoids (such as anandamide) which act as endogenous agonists for these receptors, and the processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism. Important exogenous agonists for the cannabinoid receptors are (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol (THC) which is the major active substance in cannabis, and the synthetic cannabinoids found in legal high-type smoking mixtures. Data from laboratory studies suggests that the endocannabinoid system plays an important protective role. For example, in response to some diseases the body increases the amount of endocannabinoids it produces which can reduce unwanted symptoms or slow disease progression (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015).

<sup>(3)</sup> OJ L 127, 20.5.2005, p. 32.

well as drafting a technical report. This technical report has been prepared for the risk assessment of CUMYL-4CN-BINACA that will be held at the EMCDDA premises in Lisbon on Tuesday 7 and Wednesday 8 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.17.SAT.0084.1.0 and CT.17.SAT.0110.1.0).

### **Data sources**

The information in this technical report is derived from:

- data reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with the Council Decision (EMCDDA, 2017c); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling CUMYL-4CN-BINACA.

### **Search strategy**

Literature searches used both chemical structure and text queries in online databases; searches were conducted in early October 2017. The retrieved publications were then reviewed for additional relevant references (snowballing technique).

Chemical structure-based searches were done in SciFinder<sup>®</sup> (American Chemical Society, Chemical Abstract Service) and Reaxys<sup>®</sup> (Elsevier) databases using both the exact structure of CUMYL-4CN-BINACA and a similarity search. Structural and text-based searches in the SureChEMBL patent database retrieved no relevant hits.

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science<sup>™</sup> (Thomson Reuters), and in popular English-language drug forums. The search terms used were: 'SGT-78'; '4-CN-CUMYL-BINACA'; 'CUMYL-CB-PINACA'; 'CUMYL-CYBINACA'; '4-cyano CUMYL-BUTINACA'.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed above. The searches returned no hits.

Cursory, though repeated, inspections of Internet forums covered Bluelight, Drugs-forum, ecstasydata.org, Erowid, Eve&Rave, Reddit and The Vespiary.

Additionally, the scientific networks of the authors were contacted to obtain information.

### **Note**

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product claimed to be used may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of CUMYL-4CN-BINACA and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

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### **Acknowledgements**

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## Section A. Physical, chemical, pharmaceutical and pharmacological information

### A1. Physical, chemical, and pharmaceutical information

#### A1.1. Physical and chemical description

##### *Chemical description and names*

1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide, also known as CUMYL-4CN-BINACA (Figure 1), is a synthetic cannabinoid receptor agonist (synthetic cannabinoid) originally developed by Bowden and Williamson (Bowden and Williamson, 2014) under the code name SGT-78. The common name for the substance is derived after its structural features <sup>(7)</sup>: a cumyl group (CUMYL), a cyano group linked to the 4-position (4-CN) of an *N*-butyl tail (B), an indazole core (INA), and a carboxamide linker (CA).

Five synthetic cannabinoids have been recently controlled under Schedule II of the United Nations Convention on Psychotropic Substances, 1971: JWH-018 <sup>(8)</sup>, AM-2201 <sup>(9)</sup>, MDMB-CHMICA <sup>(10)</sup>, 5F-APINACA (5F-AKB-48) <sup>(11)</sup> and XLR-11 <sup>(12)</sup>. Apart from CUMYL-4CN-BINACA (EMCDDA, 2017c), other synthetic cannabinoids which have also been the subject of EMCDDA–Europol Joint Reports in 2017 are: AB-CHMINACA <sup>(13)</sup> (EMCDDA, 2017d), ADB-CHMINACA <sup>(14)</sup> (EMCDDA, 2017e), and 5F-MDMB-PINACA (5F-ADB) <sup>(15)</sup> (EMCDDA, 2017f).

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<sup>(7)</sup> The common name for the substance is derived after its structural features. Different naming systems exist and are used for applying short/code names to synthetic cannabinoids; see also: <http://isomerdesign.com/PiHKAL/tableSC.php?domain=tk>

<sup>(8)</sup> JWH-018: (Naphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone.

<sup>(9)</sup> AM-2201: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](naphthalen-1-yl)methanone.

<sup>(10)</sup> MDMB-CHMICA: Methyl (2*S*)-2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino-3,3-dimethylbutanoate. MDMB-CHMICA was the subject of an EMCDDA–Europol Joint Report that was submitted to the EU Institutions in April 2016 and was subsequently risk assessed by the Scientific Committee of the EMCDDA in July 2016 (EMCDDA, 2017g)

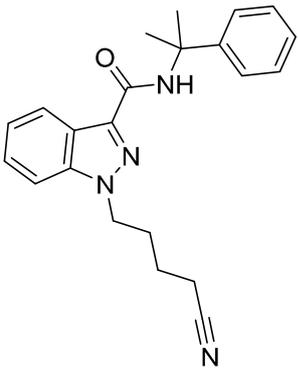
<sup>(11)</sup> 5F-APINACA: *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

<sup>(12)</sup> XLR-11: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

<sup>(13)</sup> AB-CHMINACA: *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

<sup>(14)</sup> ADB-CHMINACA: *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

<sup>(15)</sup> 5F-MDMB-PINACA (5F-ADB): Methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate.


C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O
360.46 g/mol
<b>Figure 1.</b> The molecular structure, molecular formula and molecular weight of CUMYL-4CN-BINACA

### **Names and other identifiers**

*Systematic International Union of Pure and Applied Chemistry (IUPAC) name:*

1-(4-Cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide

*Chemical Abstract name:*

1H-Indazole-3-carboxamide, 1-(4-cyanobutyl)-N-(1-methyl-1-phenylethyl)-

*Other names:*

1-(4-Cyanobutyl)-N-(1-methyl-1-phenyl-ethyl)indazole-3-carboxamide;

1-(4-Cyanobutyl)-N-(1-methyl-1-phenylethyl)-1H-indazole-3-carboxamide;

1-(4-Cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide

*Chemical Abstract Service Registry Numbers (CAS RN) <sup>(16)</sup>:*

1631074-54-8

*PubChem SID:*

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<sup>(16)</sup> The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

117650402 (<sup>17</sup>)

*IUPAC International Chemical Identifier Key (InCHI Key)* (<sup>18</sup>):

JGTSOWOPISVAHG-UHFFFAOYSA-N

*SMILES* (<sup>19</sup>):

c13ccccc3n(CCCCC#N)nc1C(=O)NC(C)(C)c2ccccc2

*Common names:*

SGT-78; 4-CN-CUMYL-BINACA; CUMYL-CB-PINACA; CUMYL-CYBINACA; 4-cyano CUMYL-BUTINACA.

*Street names:*

4-CN-CUMYL-BINACA; SGT-78; CUMYL-CB-PINACA; CUMYL-CYBINACA; 4-cyano-CUMYL-BUTINACA; 'Spice'; 'K2', 'legal weed', 'synthetic cannabis', 'herbal incense'.

Manufacturers of herbal smoking mixtures frequently change the synthetic cannabinoids in the products, which means that product names are not a reliable source of information regarding the actual substances that are present (e.g. Frinculescu et al., 2017, Moosmann et al., 2015).

### ***Identification and analytical profile***

#### *Physical description*

In its pure form CUMYL-4CN-BINACA has been described as a crystalline solid (Cayman Chemical Company, 2016b) and light yellow solid with a melting point of 89.9 °C (Ölmez et al., 2017). CUMYL-4CN-BINACA has been typically seized in powder form and in herbal/plant material which has been mixed with the substance. A more detailed description of seizures and collected samples can be found in Section C.

#### *Chemical stability and typical reactions*

For long-term storage it is recommended that CUMYL-4CN-BINACA, supplied as a solid, is stored at -20 °C (Cayman Chemical Company, 2016b).

#### *Analytical profile*

Analytical data for CUMYL-4CN-BINACA, obtained from reference material, test purchases or isolation from herbal mixtures, have been published recently (Table 1).

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(<sup>17</sup>) <https://pubchem.ncbi.nlm.nih.gov/compound/117650402>

(<sup>18</sup>) InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

(<sup>19</sup>) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

**Table 1.** Studies associated with the identification and chemical analysis of CUMYL-4CN-BINACA (amongst other substances) published in the scientific literature.

Techniques <sup>a</sup>	Comment	Reference
<sup>1</sup> H-NMR	Synthesis and characterization for pharmacological investigations.	Bowden and Williamson (2014)
UV	Characterization of reference material.	Cayman Chemical Company (2016b)
GC-MS, ATR-FTIR, NMR	Isolation from 'herbal mixture' and characterization.	Hungarian Institute for Forensic Science (2016)
GC-MS, LC-TOF-MS, GC-MS, GC-IR, IC	Characterization of powdered sample obtained from test purchase.	Slovenian National Forensic Laboratory (2016)
LC-QTOF-MS	Serum analysis involving fatal intoxication.	El Zahran et al. (2017)
GC-MS, FT-IR, NMR	Isolation from 'herbal mixture' and characterization.	Ölmez et al. (2017)
LC-QTRAP-MS/MS	<i>In vitro</i> metabolism study using pooled human liver microsomes.	Öztürk et al. (2017)
GC-MS, FT-IR, NMR, LC-Q-Orbitrap-MS/MS	Isolation from 'herbal mixture' and characterization followed by detection in postmortem femoral blood samples.	Yeter (2017)
<sup>a</sup> NMR: nuclear magnetic resonance spectroscopy; UV: ultraviolet spectroscopy; GC: gas chromatography; MS: mass spectrometry; ATR: attenuated total reflectance; FT: Fourier transform; IR: infrared spectroscopy; LC: liquid chromatography (various forms); TOF: time-of-flight; GC-IR: GC coupled with condensed phase IR detection; IC: ion chromatography; Q: quadrupole; MS/MS: tandem mass spectrometry.		

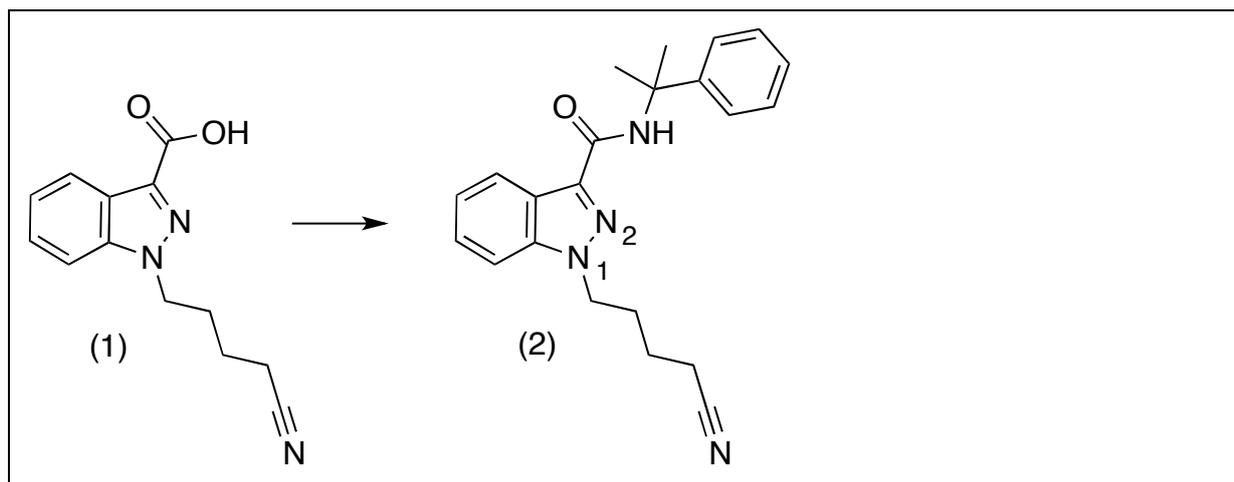
The analysis of biological samples requires sensitive methods of analysis, e.g. liquid chromatography coupled to tandem mass spectrometry approaches, especially when blood-derived samples are involved. The detection of metabolites of synthetic cannabinoids is a frequently chosen method for urine analysis although there are examples where the parent cannabinoid has been successfully targeted for quantitative analysis in this particular matrix (e.g. Minakata et al., 2017).

### **Methods and chemical precursors used for the manufacture**

#### *Synthesis*

Information about the methods used for the synthesis of CUMYL-4CN-BINACA has not been reported to the EMCDDA. The patent application published by Bowden and Williamson (2014) briefly mentions several generalised methods of synthesis, though details were not included. The key precursor is 1-(4-cyanobutyl)-1*H*-indazole-3-carboxylic acid (1), which can either be converted to an acid chloride before being reacted with 2-phenylpropan-2-amine (cumylamine), or it can undergo a coupling reaction with cumylamine directly to give CUMYL-4CN-BINACA (2) (Figure 2). The N1-alkylated carboxylic acid intermediate (1) may be obtained from a variety of precursors including methyl 1*H*-indazole-3-carboxylate or 1*H*-indazole-3-carboxylic acid. Similar straightforward procedures have also

been employed for the preparation of many closely related synthetic cannabinoids (e.g. Buchler et al., 2009, Longworth et al., 2017a).



**Figure 2.** One possible final step in the synthesis of CUMYL-4CN-BINACA (2) from 1-(4-cyanobutyl)-1*H*-indazole-3-carboxylic acid (1) (Bowden and Williamson, 2014). Option 1: a) conversion to an acid chloride intermediate using, for example, thionyl chloride (SOCl<sub>2</sub>), oxalyl chloride (COCl<sub>2</sub>) or phosphorous oxychloride (POCl<sub>3</sub>) followed by reaction with 2-phenylpropan-2-amine (cumylamine); option 2: a) amide bond coupling with cumylamine using a carboxyl group activating reagent provides (2) (e.g. *N,N'*-dicyclohexylcarbodiimide (DCC) or *O*-(benzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HBTU); *N,N*-diisopropylethylamine (DIPEA), triethylamine or *N,N*-diisopropylamine may be used as a base. 3-(Ethyliminomethyleneamino)-*N,N*-dimethylpropan-1-amine (EDC)/benzotriazol-1-ol (HOBt)/DIPEA may also be used as recently demonstrated by Longworth et al., (2017a) for the preparation of other CUMYL-based analogues. The two nitrogen atoms found in the indazole ring of CUMYL-4CN-BINACA have been numbered indicate the site of alkylation.

### **Typical impurities encountered in seized and collected samples**

There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA. However, it has been reported that the preparation of various indazole-based synthetic cannabinoids can result in the formation of another regioisomer that is alkylated at the N2-position, which was shown to depend on the base used for the alkylation reaction (Banister et al., 2015, Buchler et al., 2009, Longworth et al., 2016). Reports on the detection of these synthesis by-products could not be identified but the N2-alkylated isomer, sold as '4-cyano CUMYL-BUTINACA isomer 2', is also commercially available as an analytical reference standard (Cayman Chemical Company, 2016a).

### **A1.2. Physical/pharmaceutical form**

Data from seizures and collected samples reported to the EMCDDA show that CUMYL-4CN-BINACA has typically been detected as powders and as plant material that has been mixed with the substance. Other forms have also been encountered, which include liquids (EMCDDA, 2017c). The patent by Bowden and Williamson (2014) included the use of synthetic cannabinoids in a range of pharmaceutical compositions which depended on the methods used for administration. These were similar to uses described in a patent on structurally related indazole-based synthetic cannabinoids (including N1-(4-cyanobutyl)-substituted indazole carboxamides, amongst others) published by Pfizer Inc. (Buchler et al., 2009).

For the production of smoking mixtures, the substance is dissolved in an organic solvent (e.g. acetone) and applied to the plant material—such as damiana (*Turnera diffusa*) or marshmallow

(*Althaea officinalis*)—either via spraying or soaking and subsequent evaporation of the solvent (EMCDDA, 2017a).

### **A1.3. Route of administration and dosage**

The most common route of administration for synthetic cannabinoids is smoking ready-to-use or self-prepared ‘herbal mixtures’ as a joint or utilizing a vaporizer, ‘bong’ or pipe. Because these ready-to-use products rarely state the ingredients, most users may be unaware that they are using CUMYL-4CN-BINACA.

In addition, and, unknown to users, the concentrations of synthetic cannabinoids found in smoking mixtures can vary dramatically, which may range from low mg/g to hundreds of mg/g, depending on the potency of the substance and manufacturing practices involved (e.g. Ernst et al., 2017, Frinculescu et al., 2017, Langer et al., 2016a, 2016b, Langer et al., 2014, Moosmann et al., 2015) (Section D3.4).

#### *Dosage*

Limited information is available regarding the dose and the dose regimens of CUMYL-4CN-BINACA but it has been reported that this compound might be active at a dose of 0.1 mg (inhalation via glass pipe) making it approximately 2-3x more potent than the N1-pentyl analogue CUMYL-PINACA (SGT-24) <sup>(20)</sup> but around 3x less potent than the N1-(5-fluoropentyl) substituted analogue CUMYL-5F-PINACA (SGT-25) <sup>(21)</sup> <sup>(22)</sup>. As highlighted in the introduction, users do not typically know purity, amount and/or composition of the ingested substance. A recently published study reporting on the identification of CUMYL-4CN-BINACA in a herbal mixture revealed the isolation of 65 mg of the substance from a 5 g sample, which would translate to a concentration (assuming homogenous distribution within the sample matrix) of 13 mg/g (Ölmez et al., 2017), not including potential losses that might have occurred during the isolation procedure. Such a concentration is especially concerning in respect for its potential to cause poisoning. In comparison, one of the originally developed formulations with interim product approval in New Zealand containing CUMYL-PINACA was produced and marketed at 5 mg/g (Psychoactive Substances Regulatory Authority, 2015).

## **A2. Pharmacology, including pharmacodynamics and pharmacokinetics**

Pharmacologically, CUMYL-4CN-BINACA is a cannabinoid receptor agonist.

### ***Pharmacodynamics***

The limited available data suggest that CUMYL-4CN-BINACA binds to and activates the cannabinoid CB<sub>1</sub> receptor. For example, using human embryonic kidney cells (HEK) expressing the CB<sub>1</sub> receptor (radioligand [<sup>3</sup>H]CP-55,940), CUMYL-4CN-BINACA showed a 1.5-fold lower affinity than Δ<sup>9</sup>-THC in the low nanomolar range, whereas CUMYL-4CN-BINACA’s affinity toward the CB<sub>1</sub> receptor was 5.75-times higher than WIN-55,212-2 (US DEA, 2017). Functional activity was measured using an adenylate cyclase assay via inhibition of forskolin-stimulated (30 μM) cAMP formation and efficacy

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<sup>(20)</sup> CUMYL-PINACA: 1-pentyl-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.

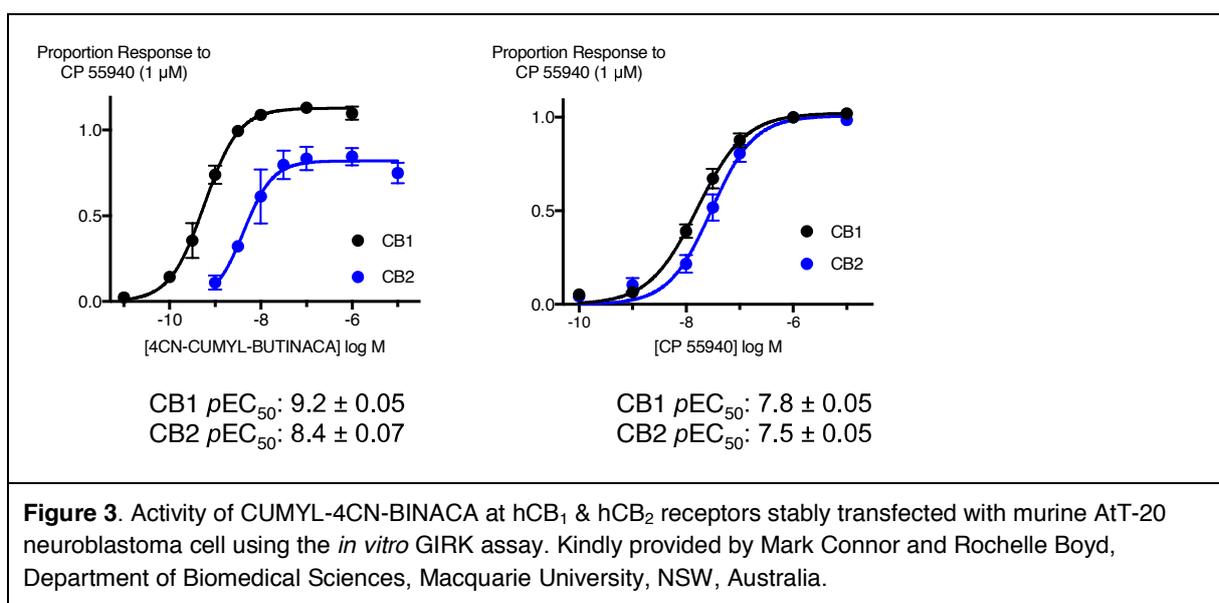
<sup>(21)</sup> CUMYL-5F-PINACA: 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.

<sup>(22)</sup> Personal communication with the now defunct Stargate International Company (New Zealand).

was compared relative to inhibition induced by 1  $\mu$ M CP-55,940. Based on the determination of the subnanomolar  $EC_{50}$  values<sup>(23)</sup>, CUMYL-4CN-BINACA was 5-times more potent than the full agonist CP-55,940 with equal efficacy and 254-times more potent than  $\Delta^9$ -THC ( $E_{max}$  = 78.5% relative to CP-55,940) under the *in vitro* conditions studied (US DEA, 2017).

Based on an *in vitro* assay evaluating the changes of membrane potentials following G-protein activation (G protein-gated inwardly rectifying potassium channels (GIRKs)) (e.g. Banister et al., 2015), it was found that CUMYL-4CN-BINACA was a potent full agonist at both CB receptor subtypes with a 6.3-fold higher potency at CB<sub>1</sub> compared with CB<sub>2</sub> ( $EC_{50}$  CB<sub>1</sub> = 0.631 nM;  $EC_{50}$  CB<sub>2</sub> = 3.98 nM) (Figure 3). CUMYL-4CN-BINACA was also slightly more effective (~6-fold) in stimulating the response relative to CP-55,940 that was used as a comparator at a 1  $\mu$ M concentration.

In separate studies, some closely related analogues were found to be potent (sub- to low nanomolar  $EC_{50}$  values) and efficacious cannabinoid receptor agonists. For example, CUMYL-5F-PINACA (SGT-25) was determined to be 5.3- and 9.5-times more potent than CUMYL-PINACA (SGT-24)<sup>(24)</sup> in activating hCB<sub>1</sub> and hCB<sub>2</sub> when using an *in vitro* membrane potential assay (G protein-gated inwardly rectifying potassium channels (GIRKs)) (Longworth et al., 2017a).



CUMYL-5F-PINACA was found to be 398- and 24-times more potent than  $\Delta^9$ -THC and CP-55,490 (hCB<sub>1</sub>), respectively, and two times more potent than CP-55,490 at hCB<sub>2</sub> ( $\Delta^9$ -THC inactive unless 30  $\mu$ M was used).

In comparison, CUMYL-PINACA was found to be 74- and 4.5-times more potent than  $\Delta^9$ -THC and CP-55,490 (hCB<sub>1</sub>), respectively, and 4.7-times less potent than CP-55,490 at hCB<sub>2</sub> in the GIRK assay (Longworth et al., 2017a). On the other hand, in another investigation employing an *in vitro* [<sup>35</sup>S]GTP $\gamma$ S binding assay, the rank order for these two synthetic cannabinoids was found to be reversed. CUMYL-PINACA ( $EC_{50}$  = 5.12 nM) was found to be ~3-times more potent than its 5F-

<sup>(23)</sup>  $EC_{50}$  represents the half maximal effective concentration.

<sup>(24)</sup> CUMYL-PINACA: 1-Pentyl-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide.

counterpart ( $EC_{50} = 15.1$  nM) at  $CB_1$  and approximately equipotent ( $EC_{50} = 47.5$  and  $34.8$  nM) at  $CB_2$ . The  $EC_{50}$  values determined for CP-55,940 were  $0.735$  nM ( $CB_1$ ) and  $0.469$  nM ( $CB_2$ ), thus, making the positive control compound more potent than the two synthetic cannabinoids under these assay conditions (Asada et al., 2017).

No information is available on the effect of CUMYL-4CN-BINACA on other, non-cannabinoid receptor targets that could also been involved in the observed pharmacological and toxicological effects of the substance.

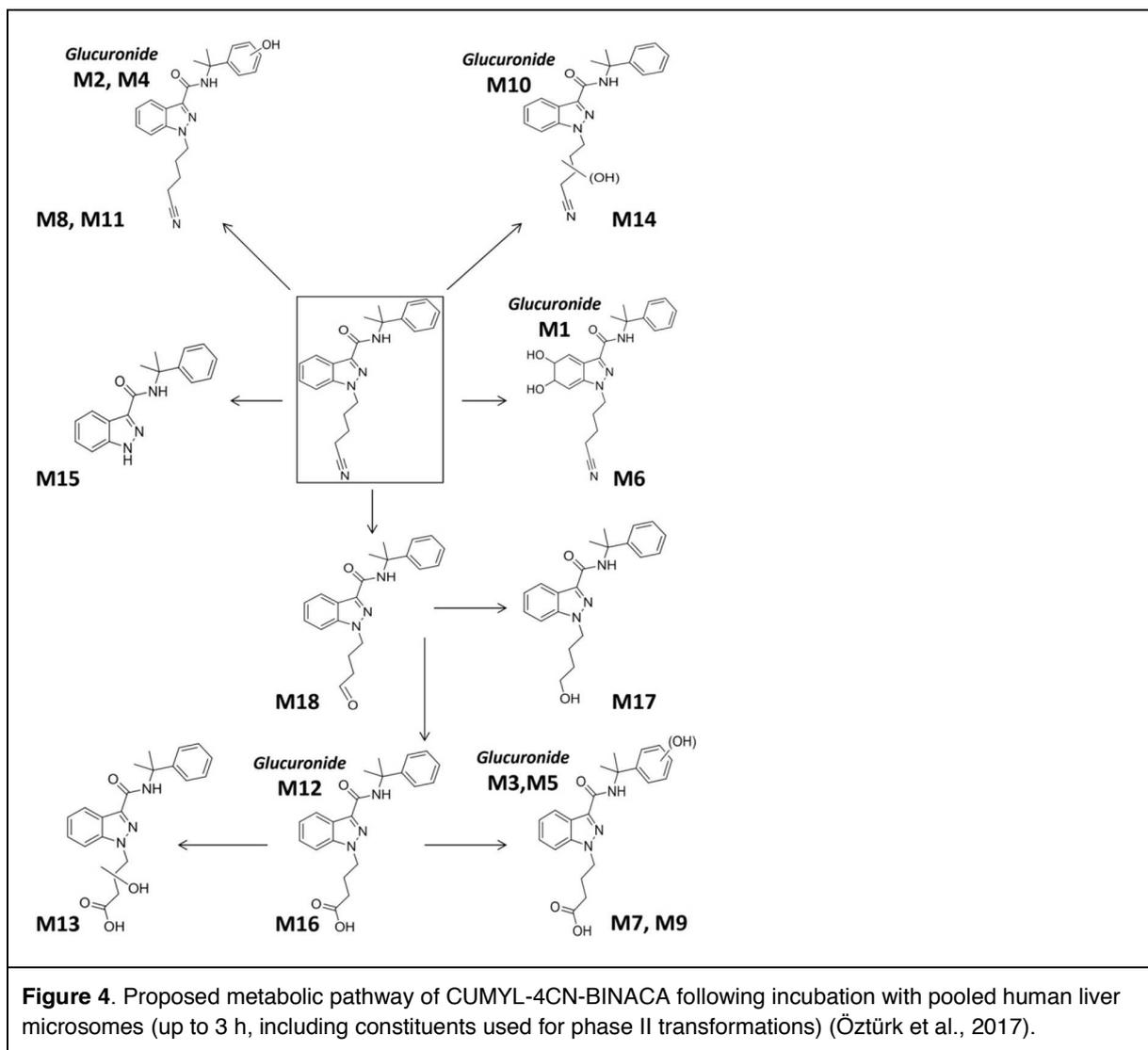
### **Animal studies**

Information derived from animal studies could not be identified, although it seems conceivable that CUMYL-4CN-BINACA would display activity in assays that probe for  $\Delta^9$ -THC-like properties such as drug discrimination or mouse tetrad tests similar to what has been demonstrated with other synthetic cannabinoids (Järbe and Raghav, 2017, Wiley et al., 2017).

### **Pharmacokinetics**

An incubation study with 150-donor pooled human liver microsomes (up to 3 h, including constituents used for phase II transformations) detected 18 metabolites that were formed by monohydroxylation, *N*-dealkylation, oxidative decyanation and formation of the aldehyde, alcohol, and carboxylic acid formation, glucuronidation and combinations thereof (Öztürk et al., 2017). An estimation of differences in signal responses suggested that the N1-(4-butanolic acid) transformation product (M16) was the most abundant species, followed by the N1-(4-hydroxybutyl) metabolite M17 (Figure 4). Other abundant metabolites were M18 (N1-(4-oxobutyl)), M15 (*N*<sup>1</sup>-dealkyl), M12 (M16-Gluc) and M8 (hydroxyphenyl species; position not specified).

In addition, the analytical methodology was applied to the analysis of 80 authentic urine specimens where 15 metabolites could be identified, and three of the metabolites identified in the *in vitro* assay (M15, M17 and M18), together with the parent molecule, were not detectable in urine. The abundance of M6, M7, M8, M9, M11, M14, and M16 increased following enzymatic hydrolysis with  $\beta$ -glucuronidase. In urine, M16, M12, M5, M10 and M4 were considered to be among the top 5 most abundant species (Öztürk et al., 2017). Based on the findings reported in this study, targeting the transformation products hydroxylated at the 'cumyl moiety' (hydroxycumyl) and/or the N1-(4-cyanobutyl) tail might be suitable for specifically confirming ingestion of CUMYL-4CN-BINACA whereas others, such as the N1-(4-butanolic acid) species, although relatively abundant, might not be specific enough, given that it seems possible that this might also be formed during the transformation of CUMYL-5F-PINACA (SGT-25), similar to other N-(5-fluoropentyl) substituted synthetic cannabinoids (Diao and Huestis, 2017). In a recent investigation, a total number of 28 phase I metabolites were detected in human urine samples, which revealed a pathway that included *N*-desalkylation, hydroxylation, formation of dihydrodiols, formation of the 4-hydroxybutyl metabolite and further oxidation to the butanoic acid species, as well as combinations of these reactions. The 4-butanolic acid transformation product and a metabolite monohydroxylated at the CUMYL moiety (thus suggesting specific confirmation of drug intake) were the most abundant species detected in this matrix. CUMYL-4CN-BINACA intake could be confirmed in 50 out of 204 urine samples that were confirmed positive for synthetic cannabinoid use during the period of January–March 2017 (Franz et al., 2017).



The authors of the metabolism study also mentioned that the relative abundance of the main metabolites (M16, M8, and M11 and their glucuronides) corresponded to high blood concentrations of CUMYL-4CN-BINACA found in 73 of 80 cases although details were not reported (Öztürk et al., 2017).

User reports on the Internet about CUMYL-4CN-BINACA's effect profile seem limited. One account following inhalation of 100 micrograms using a glass pipe suggests that effects were noticeable within 20 seconds with built up and peak effects within a couple of minutes. The first 10 minutes were considered 'a little overwhelming although manageable'. Significant anxiety was noticed but followed by 'a very clean, smooth, relaxed high'. Colours were perceived as 'brightened and music was excellent'. The effects were considered 'fading relatively quickly' <sup>(25)</sup>.

#### *Inter-individual genetic variability in metabolising enzymes*

<sup>(25)</sup> Personal communication with the now defunct Stargate International Company, New Zealand.

No information specific to CUMYL-4CN-BINACA was identified.

### ***Interactions with other substances and other interactions***

No studies were identified that have examined the interaction of CUMYL-4CN-BINACA with other substances, including medicinal products.

### ***Effects on ability to drive and operate machines***

No studies of the effects of CUMYL-4CN-BINACA on the ability to drive and operate machines have been performed. However, it has been reported that intoxications elicited by a variety of synthetic cannabinoids significantly impair the mental and physical ability that is required to drive and operate machines (Capron, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015). This effect is likely to extend to CUMYL-4CN-BINACA.

### **A3. Psychological and behavioural effects**

While there is limited data, the psychological and behavioural effects of CUMYL-4CN-BINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids (e.g. Griffiths and Griffin, 2016; Peterson and Couper, 2015; See also Section D). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurova et al., 2016). In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported. (See also Section D1 and Section D3.4.)

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

CUMYL-4CN-BINACA is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests CUMYL-4CN-BINACA is used for other legitimate purposes.

There are no reported uses of CUMYL-4CN-BINACA as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Number returned no results.

There is no marketing authorisation (existing, on-going or suspended) for CUMYL-4CN-BINACA neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA, 2017c).

There is no information to suggest that CUMYL-4CN-BINACA is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not CUMYL-4CN-BINACA is currently used in the manufacture of a medicinal product.

## **Section B. Dependence and abuse potential**

### **B1. Animal data**

No studies were identified that have investigated the dependence and/or abuse potential of CUMYL-4CN-BINACA in animal models.

## **B2. Human data**

No studies were identified that have investigated the dependence and/or abuse potential of CUMYL-4CN-BINACA in humans. However, it has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal symptoms when use is abruptly discontinued following a regular use (Cooper, 2016, Macfarlane and Christie, 2015, Van Hout and Hearne, 2017).

## **Section C. Prevalence of use**

### ***Information from seizures, collected and biological samples***

CUMYL-4CN-BINACA was formally notified on 4 March 2016 by the EMCDDA on behalf of Hungary, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 1 gram of green herbal material that was seized in January 2016 by the Hungarian Police in Orosháza. The substance was analytically confirmed by ATR-FT-IR, GC-MS, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR by the Hungarian Institute for Forensic Science.

It is important to note that although the first report was made by Hungary in 2016, the first known seizure of CUMYL-4CN-BINACA took place in Estonia in October 2015. The substance was identified in 7.65 g of powder by Customs in Tallinn. The shipment originated in the Czech Republic.

Since then, a total of 11 Member States (Estonia, Finland, France, Germany, Hungary, Lithuania, Romania, Slovenia, Spain, Sweden and the United Kingdom) and Turkey have reported detections <sup>(26)</sup> of CUMYL-4CN-BINACA (EMCDDA, 2017c).

No quantitative information on CUMYL-4CN-BINACA in these samples was reported to the EMCDDA.

As the substance is not routinely screened for, detections of CUMYL-4CN-BINACA may be under-reported. Three Member States (Austria, Slovenia and Sweden) reported that CUMYL-4CN-BINACA is part of routine screening in some (but not all) of their laboratories.

### ***Information from seizures***

A total of 10 Member States and Turkey reported seizures <sup>(27)</sup> of CUMYL-4CN-BINACA to the EMCDDA and/or Europol.

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<sup>(26)</sup> Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. 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.)

<sup>(27)</sup> Many 'seizures' relate to individual case-level data, however, some data reported to the EMCDDA are aggregated at the country level. Data is drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (progress and final reports) and from individual Reporting Forms submitted on an ad hoc basis.

Information reported to the EMCDDA and Europol indicates that 2461 seizures of CUMYL-4CN-BINACA have been reported by 10 countries: Estonia (1 seizure), Finland (1), France (1), Germany (4), Hungary (197), Lithuania (1), Romania (1), Spain (1), Sweden (66), the United Kingdom (2) and Turkey (2186). The majority of the seizures comprise police cases at street-level, with some notable larger seizures made by customs and confiscations in prisons.

#### *Powders*

Five Member States (France, Germany, Lithuania, Spain and Sweden), reported 40 seizures of CUMYL-4CN-BINACA in powder form, amounting to a total of just under 52 kg.

The largest single seizure of CUMYL-4CN-BINACA in powder form was made by Spanish Customs and amounted to 50 kg. The consignment originated in China.

In January 2017, at Roissy Airport in France, customs intercepted over 1.5 kg of powder which also contained the synthetic cathinone 4-CEC (4-chloroethcathinone). The shipment originated in China and had the Netherlands as the final destination.

#### *Herbal material*

Five Member States (Germany, Hungary, Romania, Sweden, and the United Kingdom) reported seizures of CUMYL-4CN-BINACA in herbal materials, amounting to a total of 3.6 kg.

In addition, Turkey reported 2186 seizures of herbal material amounting to over 257 kg<sup>(28)</sup>. In the herbal materials seized, CUMYL- 4CN-BINACA was commonly found mixed with other synthetic cannabinoids.

#### *Other physical forms*

In a small number of cases, CUMYL-4CN-BINACA was also detected in blotter form (1 case, Finland) and other unspecified physical form (1 case, United Kingdom; 1 case, Estonia).

#### **Information from collected samples**

One collected sample was reported by Slovenia, which consisted of 5 g of off-white powder purchased from an online vendor that was believed to be based in China.

#### **Information from biological samples**

Serious adverse events (deaths and acute intoxications) with confirmed exposure to CUMYL-4CN-BINACA from biological samples are discussed in Section D.

In addition to these, a total of 135 detections where CUMYL-4CN-BINACA was analytically confirmed in biological samples was reported by 2 Member States: Hungary (133) and Sweden (2).

These related to:

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<sup>(28)</sup> This is a minimum estimate provided by the Turkish national focal point.

- 16 cases of persons suspected of driving under the influence of drugs (including five traffic accidents), all reported by Hungary;
- 119 cases reported as aggregated data associated with forensic case work (no details specified).

### ***Availability, supply, price***

The available data suggests that CUMYL-4CN-BINACA is often sold in smoking mixtures, which in some cases are branded 'legal-high' products that are sold in physical shops and online. It is also possible that some smoking mixtures are sold directly in the illicit market. Similar to other products containing synthetic cannabinoids, products containing CUMYL-4-CN-BINACA are marketed as 'legal' replacements to cannabis. The composition of the mixtures is not typically stated in the packages.

### *Information on production*

No information was received in relation to the production of CUMYL-4CN-BINACA. Based on the limited information reported to the EMCDDA and Europol related to seizures by customs, some of the CUMYL-4CN-BINACA that has been intercepted in Europe has originated in China.

### *Information on trafficking*

Information related to trafficking routes is limited to the seizures reported above.

Information reported to the EMCDDA and Europol indicates that China may be one source of the substance. The available information reported to the EMCDDA on the country of origin is summarised below.

- The two largest single seizures of CUMYL-4CN-BINACA; 50 kg in powder form seized in Spain, and over 1.5 kg of powder seized in France, both originated in China.
- The test purchase made as part of the RESPONSE project, and reported by Slovenia, was apparently shipped from China.
- A seizure made by Estonian customs (7.65 grams, unspecified form) was from incoming mail arriving from the Czech Republic.

### *Availability from Internet vendors*

The available data suggests that CUMYL-4CN-BINACA is sold openly online under its own name in powders and in herbal mixtures (where the ingredients/composition is sometimes not stated). A structured search of online vendors on the surface web by the EMCDDA <sup>(29)</sup> found that the substance

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<sup>(29)</sup> The search for online vendors of CUMYL-4CN-BINACA on the surface web was performed on 01/06/2017 using previously established methodology (EMCDDA, 2017c). The search identified 5 vendors that appeared to be based in, and/or claim to have presence in China (n=2; 1 of which in Hong Kong), Hungary (n=1) and Sweden (n=1); the remaining website did not list a location. Three websites listed quantities and prices for CUMYL-4CN-BINACA. The remaining sites only provided prices on request.

is available online in small and wholesale amounts as a 'research chemical' and as 'aroma blends', a common reference to 'legal-high' type products containing synthetic cannabinoids.

On the websites identified, CUMYL-4CN-BINACA powders were available in amounts ranging from 10 grams to 1 kg. Prices varied according to the amounts on sale and ranged from EUR 2.67 per gram to EUR 13 per gram. Herbal smoking mixtures claiming to contain CUMYL-4CN-BINACA were available on one website, in amounts ranging from 5 to 15 grams, with a mean price of EUR 1.00 per gram.

The availability of CUMYL-4CN-BINACA on the darknet is not currently known.

### ***Prevalence of use***

No studies were identified that have investigated the prevalence of use of CUMYL-4CN-BINACA in the general population.

Similar to other synthetic cannabinoids, CUMYL-4CN-BINACA is often sold and used as a 'legal' substitute for cannabis, typically in plant material which has been mixed with the substance (EMCDDA, 2009; EMCDDA, 2017a). The composition of these products varies over time, with substances being changed in response to, or, in anticipation of, the introduction of control measures. This may have implications on the availability of CUMYL-4CN-BINACA and its prevalence of use. Overall, the available information does not suggest widespread use of the substance.

Because of the variability in the composition of smoking mixtures, and the fact that the ingredients are not typically disclosed, most users will be unaware that they are using CUMYL-4CN-BINACA. As a result, the prevalence of use of CUMYL-4CN-BINACA should be considered in the wider context of the prevalence of use of herbal smoking mixtures, commonly referred to as 'spice'.

The use of 'spice'-like products has been studied in some European countries in general population surveys or in specific populations such as students, 'clubbers' and/or internet users. The results of these surveys are not comparable as they use different methodology and samples but overall they indicate generally low prevalence levels in these groups (EMCDDA, 2017a).

There is evidence that in some groups, such as high risk drug users and other marginalised groups, the prevalence of use of synthetic cannabinoids, particularly as smoking mixtures, may be higher. This includes individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) because some drug tests/screens will be unable to detect synthetic cannabinoids. In addition some vulnerable populations, such as the homeless and prisoners, specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle (EMCDDA, 2017a; Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

## **Section D. Health risks**

### **D1. Acute health effects**

#### **D1.1. Animal data**

Data on the acute toxicity, abuse liability or dependence producing potential of CUMYL-4CN-BINACA could not be identified.

#### **D1.2. Human data**

No clinical studies were identified that have examined the acute health effects of CUMYL-4CN-BINACA and/or its metabolites in humans. Data from serious adverse events associated with CUMYL-4CN-BINACA are discussed below. In general, the acute health risks associated with CUMYL-4CN-BINACA appear to be similar to those found with other synthetic cannabinoids.

As synthetic cannabinoids activate the CB<sub>1</sub> receptor in a similar way to THC, their effects appear to have some similarities with cannabis (Auwärter et al., 2009). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Winstock et al., 2013; Zaurava et al., 2016).

Severe and fatal poisoning also appears to be more common with synthetic cannabinoids as compared to cannabis. This can include severe cardiovascular toxicity (including sudden death), rapid loss of consciousness/coma, respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour (Adams et al., 2017; Brennehan et al., 2016; Capron, 2016; Ford et al., 2017; Hermanns-Clausen et al., 2013; EMCDDA, 2017c, EMCDDA, 2017d, EMCDDA, 2017e; EMCDDA, 2017g; Kasper et al., 2015; Pap, 2016; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Tait et al., 2016; Trecki et al., 2015; Tyndall et al., 2015; Winstock et al., 2013; Zaurava et al., 2016). (See Section D3.4.)

In addition, some of the features of poisoning—particularly loss of consciousness, respiratory depression, and behavioural effects—may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury (EMCDDA, 2017g; Tait et al., 2016; Yeter, 2017). The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

Overall, poisoning with synthetic cannabinoids may be made worse when other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics), are used at the same time.

There is no approved antidote to poisoning caused by synthetic cannabinoids.

### ***Acute intoxications reported by the Member States***

A total of 5 acute intoxications with confirmed exposure to CUMYL-4CN-BINACA were reported by Hungary (4 cases) and Sweden (1). The cases occurred during 2016. No further details are available on the cases from Hungary.

In the case from Sweden, it was reported that the individual was found outside and lost consciousness. The patient was treated in intensive care. The only other substances detected were amlodipine and naproxen. No further details are available.

### ***Acute intoxications identified from other sources***

No reports were identified from other sources that involved acute intoxications with confirmed exposure to CUMYL-4CN-BINACA.

### ***Deaths reported by the Member States***

A total of 11 deaths were reported by 2 Member States: Sweden (8) and Hungary (3). In all cases, exposure to CUMYL-4CN-BINACA was analytically confirmed from post-mortem samples.

The Hungarian deaths occurred in 2016 and (where known) the Swedish deaths occurred between September 2016 and November 2016.

Demographic data were available for the deaths from Sweden and involved 7 males (88%) and 1 female (12%). The mean age of the males was 43 years (median 40) and ranged from 29 to 61 years; the female was 29 years old.

#### *Circumstances and cause of death*

The deaths from Hungary were described as being drug related but no additional information was available. In all but one of the deaths that occurred in Sweden, there was a lack of information regarding any symptoms experienced by the deceased prior to death. In one case the deceased was described as becoming unconscious immediately after smoking a synthetic cannabinoid product and whilst he was taken to hospital he died two days later in intensive care. In the majority of instances, the individuals were found dead, predominantly in a home environment (either their own, a friend's or family member's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

The cause of death was available in 7 out of 11 cases. In 5 deaths, CUMYL-4CN-BINACA was either the cause of death or is likely to have contributed to death (even in presence of other substances); other substances were detected in 7 cases. In 2 deaths, an alternative cause of death was cited (drowning in one and drug toxicity in the other). CUMYL-4CN-BINACA was the only drug present in 2 deaths, with one being associated with death occurring 2 days after hospital admission providing an opportunity for continued drug elimination whilst alive.

CUMYL-4CN-BINACA was quantified in 8 cases. Post-mortem femoral blood concentrations between 0.1 and 8.3 ng/g blood were recorded (median 0.75 ng/g blood). Due to the toxicity of potent synthetic cannabinoids, a post-mortem blood concentration cannot necessarily be used to determine a 'fatal' concentration. In the majority of circumstances involving synthetic cannabinoids, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use and the varying circumstances in which they are used.

A range of other substances were detected in the deaths, including: benzodiazepines, gabapentinoids (gabapentin and pregabalin), antidepressants, antipsychotics, synthetic cathinones, opioids (buprenorphine and methadone) and antihistamines. No other synthetic cannabinoids were detected in the deaths.

Overall, whilst other substances may have contributed some toxicity, the potent nature of CUMYL-4CN-BINACA means the primary toxic contribution could be attributed to the drug and death may not have occurred if CUMYL-4CN-BINACA had not been used. Sufficient case data were available in 8 of the 11 deaths. An assessment of the toxicological significance score (TSS) incorporating the above considerations in these deaths, showed that CUMYL-4CN-BINACA had a TSS value of 3 (high) in 6 out of 8 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining 2 deaths, an alternative cause of death was cited (TSS value of 1, low).

#### ***Deaths identified from other sources***

Deaths involving the use of CUMYL-4CN-BINACA in Turkey have been described in the paper by Yeter (2017). In this study, 2350 post-mortem blood samples collected between 1 July 2016 and 31 December 2016 were analysed. Exposure to CUMYL-4CN-BINACA was confirmed in 85 samples. Decedents were male and aged between 18 and 49; concentration in blood range 0.2–66.4 ng/mL, mean of 5.6 ng/mL). In 11 cases CUMYL-4CN-BINACA was the only substance detected (with the exception of alcohol in 7 cases) (blood concentration in range: 0.4–34.3 ng/mL) (Table 2). In 6 out of

11 cases in which CUMYL-4CN-BINACA was the only drug present, CUMYL-4CN-BINACA intoxication was reported as the cause of death. In the remaining 5 cases, the cause of death was reported to be severe skeletal injuries (due to falling from a height; 3 cases) and drowning (found dead in a river; 2 cases).

**Table 2.** Summary of 11 deaths in Turkey during 2016 where CUMYL-4CN-BINACA was detected alone (Yeter, 2017).

Case	Age (years)	CUMYL-4CN-BINACA (ng/mL)	Alcohol (mg/dL)	Circumstances of death	Cited cause of death
1	22	34.3	0	History of drug abuse, falling from a height	Severe skeletal injuries
2	45	4.2	14	Found dead at home	CUMYL-4CN-BINACA intoxication
3	42	1.8	84	Falling from a height	Severe skeletal injuries
4	38	0.4	23	Found dead at hotel	CUMYL-4CN-BINACA intoxication
5	32	2	149	Found dead in car	CUMYL-4CN-BINACA intoxication
6	31	1.0	0	Falling from a height	Severe skeletal injuries
7	29	11.9	0	Found dead in street	CUMYL-4CN-BINACA intoxication
8	18	0.9	0	Found dead in river	Drowning
9	49	1.3	204	Found dead at home	CUMYL-4CN-BINACA intoxication
10	25	0.9	18	Found dead at home	CUMYL-4CN-BINACA intoxication
11	37	18.7	25	Found dead in river	Drowning

In the remaining 74 cases, CUMYL-4CN-BINACA was detected along with other substances at blood concentrations ranging from 0.2 to 66.4 ng/mL (mean of 4.1 ng/mL). In these cases, the causes of death were: multidrug intoxications (70.3%), severe skeletal injuries (14.9%), and others (14.8%; gunshot/stab/chop wounds/hanging). All of the samples were taken from males (age of 18–52 years, mean = 29.5 years). CUMYL-4CN-BINACA was not detected in urine samples. In addition to CUMYL-4CN-BINACA, 5F-MDMB-PINACA (40.5%), ADB-FUBINACA (27.0%) and ADB-CHMINACA (2.7%) were also detected in the same samples. Other drugs identified with CUMYL-4CN-BINACA included MDMA (13.5%), cannabis (8.1%), heroin (5.4%), cocaine (5.4%) and amphetamine/methamphetamine (5.4%). CUMYL-4CN-BINACA was detected alone in only 12.9% of the samples, and it was the most common drug (23.9%) detected amongst the post-mortem samples.

## D2. Chronic health effects

While there is limited data for CUMYL-4CN-BINACA, the chronic health risks might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

### **D2.1. Animal data**

No studies were identified that have investigated the chronic health effects of CUMYL-4CN-BINACA in animals.

### **D2.2. Human data**

No studies were identified that have investigated the chronic health effects of CUMYL-4CN-BINACA in humans.

## **D3. Factors affecting public health risks**

### **D3.1. Availability and quantity of the new psychoactive substance on the market**

CUMYL-4CN-BINACA is sold on the surface web as a powder and in 'legal-high' type products such as herbal smoking mixtures. The substance is available in small and wholesale amounts. In herbal smoking mixtures it is not frequently stated if the product contains CUMYL-4CN-BINACA or any other synthetic cannabinoid. As a result, many users will not be aware that they are using the substance.

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

The availability of information, degree of knowledge and perceptions amongst users concerning CUMYL-4CN-BINACA and its effects are limited. There is considerable variability both within and between different batches of synthetic cannabinoid products, in terms of both the substances and the amount present. For that reason, most individuals will be unaware that they are using CUMYL-4CN-BINACA.

Unknown to users, synthetic cannabinoids have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning (Allibe et al., 2016; Brenneman et al., 2016; Pap, 2016).

Opioids (such as U-47,700 and furanylfentanyl) have also been identified in smoking mixtures/plant material. Users will be unaware of this, and the use of such opioid-containing products could pose a risk of life-threatening respiratory depression. This risk will be especially high in individuals with no tolerance to opioids (Coopman et al., 2017; EMCDDA, 2017h).

### **D3.3. Characteristics and behaviour of users**

No studies were identified that have examined the characteristics and behaviour of users of CUMYL-4CN-BINACA.

Synthetic cannabinoids are sold and used as a 'legal' replacement for cannabis (EMCDDA, 2009; EMCDDA, 2017a). In addition some users specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. In most cases they are smoked using a cigarette of plant material that has been mixed with one or more of the cannabinoids. Because these products rarely state the ingredients, most users will be unaware that they are using synthetic cannabinoids.

People who use synthetic cannabinoids may include recreational users (including cannabis users), high-risk drug users, and groups who experiment with the substances (such as psychonauts). They

may also include individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) because some drug tests/screens will be unable to detect some of the cannabinoids (especially those that are relatively new to the drug market). In the past few years, synthetic cannabinoids have become increasingly used by vulnerable groups (such as the homeless and prisoners).

#### **D3.4. Nature and extent of health consequences**

The limited information available on the pharmacology, dependence and abuse potential, and acute health effects of CUMYL-4CN-BINACA have been discussed above (Section A2, Section B, Section D1 and Section D2).

Compared to cannabis, more pronounced effects as well as severe and fatal poisoning appear to be more common with synthetic cannabinoids (EMCDDA, 2017c; EMCDDA, 2017d, EMCDDA, 2017e, EMCDDA, 2017f, EMCDDA, 2017g; Tait et al., 2016; Winstock et al., 2013; Zaurova et al., 2016). The reasons for this are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the cannabinoids, including CUMYL-4CN-BINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonists, compared to THC. This means that even at very small doses they can activate the CB1 receptor much more strongly than THC (Banister et al., 2016; Ford et al., 2017; Reggio, 2009; Tai and Fantegrossi, 2017).

Secondly, the process for mixing the synthetic cannabinoids with the plant material (which are the most common way of using these substances) can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of cannabinoids(s) to add, while the mixing process makes it difficult to dilute the substances sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general (Ernst et al., 2017; Frinculescu et al., 2016; Langer et al., 2014; Langer et al., 2016), as well as products where the cannabinoids are clumped together forming highly concentrated pockets within the plant material (Frinculescu et al., 2016; Moosmann et al., 2015; Schäper et al., 2016). These issues are made worse as the products are typically smoked allowing the substances to be rapidly absorbed into the systemic circulation (bloodstream) and to reach the brain.

The combination of these two factors makes it difficult for users to control the dose that they are exposed to, and can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

These two factors are also responsible for outbreaks of poisonings caused by smoking mixtures, which have ranged in size from four or five victims to over 800. Mass poisonings can overwhelm emergency responders and other local healthcare systems. Many of the outbreaks that have been reported so far are from the United States, but they have also occurred in Russia and Europe (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Trecki et al., 2015; Tyndall et al., 2015).

Driving while under the influence of synthetic cannabinoids places users and others at risk of injury (Capron, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015). In a recent case series of 36 drivers suspected of driving under the influence of drugs in Washington, United States, where 5F-MDMB-PINACA was the predominate psychoactive substance identified, 50% of the drivers were found unconscious and 28% has been involved in collisions with

single/multiple cars (Capron, 2016). Similarly, the operation of machinery while under the influence of synthetic cannabinoids may place the user and others at risk of injury.

### **D3.5. Long-term consequences of use**

While there is limited data for CUMYL-4CN-BINACA, the long-term consequences of use might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

### **D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks**

There is limited data on the conditions which CUMYL-4CN-BINACA is obtained and used.

Sources appear to include internet retailers, physical shops, friends and other acquaintances, and street-level drug dealers (Section D3.1). In addition, most users will be unaware that they have sourced and used CUMYL-4CN-BINACA (Section C and Section D1.2.1). The available data suggests that CUMYL-4CN-BINACA is used in the same environments as cannabis, including the home, and, to a lesser extent, in recreational settings.

## **Section E. Social Risks**

The available data suggests that the acute behavioural effects of CUMYL-4CN-BINACA bear some similarities to cannabis but are more pronounced and severe.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

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

There is no specific information on the individual social risks that may be associated with the use of CUMYL-4CN-BINACA.

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

While there is no specific information on the possible effects of CUMYL-4CN-BINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

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

There is no specific information on the possible effects of CUMYL-4CN-BINACA on society as a whole.

### **E4. Economic costs**

There are no data on the effects of CUMYL-4CN-BINACA on economic costs.

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

There are no data on the possible effects of CUMYL-4CN-BINACA related to the cultural context.

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

While no specific examples are available on the possible appeal of CUMYL-4CN-BINACA to specific user groups, it is reasonable to assume CUMYL-4CN-BINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, and those in drug treatment).

In addition, and, of particular note, is that synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems as well as creating new ones for these groups. For example, in prisons, alongside the adverse health effects, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying, and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment (Blackman et al., 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

#### **Section F. Involvement of organised crime**

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of CUMYL-4CN-BINACA.

Slovenia reported a collected sample to Europol and the EMCDDA where the country of origin was apparently China.

The largest single seizure of CUMYL-4CN-BINACA reported to the EMCDDA was made by Spanish Customs. The seizure amounted to 50 kg and was en-route from China. In addition, French customs reported a seizure of 1.5 kg of powder, also containing 4-CEC (4-chloroethcathinone), which was en-route from China and the final destination was the Netherlands. Estonian customs reported a seizure of CUMYL-4CN-BINACA which originated in the Czech Republic.

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

No information was reported nor identified concerning the impact of CUMYL-4CN-BINACA on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

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

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of CUMYL-4CN-BINACA.

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

No information was reported nor identified concerning incidents of violence related to the availability of CUMYL-4CN-BINACA.

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

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of CUMYL-4CN-BINACA.

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

No information was reported nor identified concerning the economic costs and consequences related to the availability of CUMYL-4CN-BINACA.

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

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of CUMYL-4CN-BINACA.

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

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of CUMYL-4CN-BINACA.

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## **Annex 2. List of participants at the risk assessment meetings of 1-(4-Cyanobutyl)-N-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA)**

7-8 November 2017

### **A. Extended Scientific Committee**

**Dr Anne Line BRETTEVILLE-JENSEN**

Norwegian Institute for Alcohol and Drug Research, Oslo  
Chair of the Scientific Committee

**Professor Dr Gerhard BUEHRINGER**

Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

**Professor Dr Paul DARGAN**

Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

**Dr Marina DAVOLI**

Department of Epidemiology, Lazio Regional Health Service, Rome

**Professor Dr Gabriele FISCHER**

Medical University Vienna, Center of Public Health, Vienna

**Professor Dr Henk GARRETSEN**

Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

**Professor Dr Krzysztof KRAJEWSKI**

Department of Criminology, Jagiellonian University, Krakow

**Dr Fernando RODRÍGUEZ de FONSECA**

Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

**Professor Dr Rainer SPANAGEL**

Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

**Dr Wim BEST**

Utrecht University, Faculty of Science, Freudenthal Institute, Utrecht

**Dr Simon BRANDT**

School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

**Professor Dr Gaetano Di CHIARA**

Biomedical Sciences Department, University of Cagliari, Cagliari

**Professor Dr Éva KELLER**

Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

**Dr Claude GUILLOU**

Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

**Edith HOFER**

Organised Crime and Drugs Policy Unit, DG HOME, European Commission

**Dr Leon Van Aerts**

Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

**Werner VERBRUGGEN**

Europol's Drug Unit, Europol

**Paul GRIFFITHS**

Scientific Director, EMCDDA

**Dr Roumen SEDEFOV**

Head of Unit, Supply reduction and new drugs unit, EMCDDA

**B. Invited Experts**

**Professor Dr Volker AUWÄRTER**

Freiburg University, Institute of Forensic Medicine, Freiburg

**Dr Robert KRONSTRAND**

Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

**Professor Dr Bela SZABO**

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

**Dr István UJVÁRY**

Budapest University of Technology and Economics, Budapest

**C. EMCDDA Staff**

**Anabela ALMEIDA**

Action on new drugs sector, Supply reduction and new drugs unit

**Rachel CHRISTIE**

Action on new drugs sector, Supply reduction and new drugs unit

**Michael EVANS-BROWN**

Action on new drugs sector, Supply reduction and new drugs unit

**Ana GALLEGOS**

Action on new drugs sector, Supply reduction and new drugs unit

**Rita JORGE**

Action on new drugs sector, Supply reduction and new drugs unit

**Joanna DE MORAIS**

Action on new drugs sector, Supply reduction and new drugs unit

**Sofía SOLA**

Action on new drugs sector, Supply reduction and new drugs unit