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CUMYL-4CN-BINACA

Report on the risk assessment of 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

Contents

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- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
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- Dr Mark Connor and Rochelle Boyd, Department of Biomedical Sciences, Macquarie University, New South Wales, Australia.

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Foreword

This publication presents the data and findings of the risk assessment on CUMYL-4CN-BINACA (1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide), carried out by the extended Scientific Committee of the EMCDDA on 7 and 8 November 2017.

The Risk Assessment Report, which was submitted to the European Commission and the Council of the European Union on 14 November 2017, examines the health and social risks of the drug, information on international trafficking and the involvement of organised crime, as well as a consideration of the potential implications of subjecting the drug to control measures. CUMYL-4CN-BINACA is the eighteenth new psychoactive substance to be risk assessed under the terms of Council Decision 2005/387/JHA.

On the basis of the Risk Assessment Report — and on the initiative of the European Commission — on 14 May 2018, the Council decided that CUMYL-4CN-BINACA should be subject to control measures across the Member States. This decision was adopted in the final stage of the three-step process — early warning, risk assessment and control of new psychoactive substances — established by the Council Decision 2005/387/JHA. This legal framework allows the EU institutions and Member States to act on all new and potentially threatening narcotic and psychotropic drugs which appear on the European drug scene, with the EMCDDA and Europol, in collaboration with their respective networks playing a central role in the early detection of such substances as well as the harms caused by their use — information that underpins risk assessment, and, ultimately, decision-making.

In this respect we would like to acknowledge the excellent work done by the networks of the EMCDDA and Europol, as well as those of the EMA — the Reitox national focal points, Europol national units and the national competent authorities responsible for medicinal products — who played an essential role in collecting and providing national data.

Finally, we would like to thank all the participants in the risk assessment process for the high quality of work carried out. The resulting report is a valuable contribution at European level, which gives clear support to political decision-making.

Dr Anne Line Bretteville-Jensen
Chair, Scientific Committee of the EMCDDA

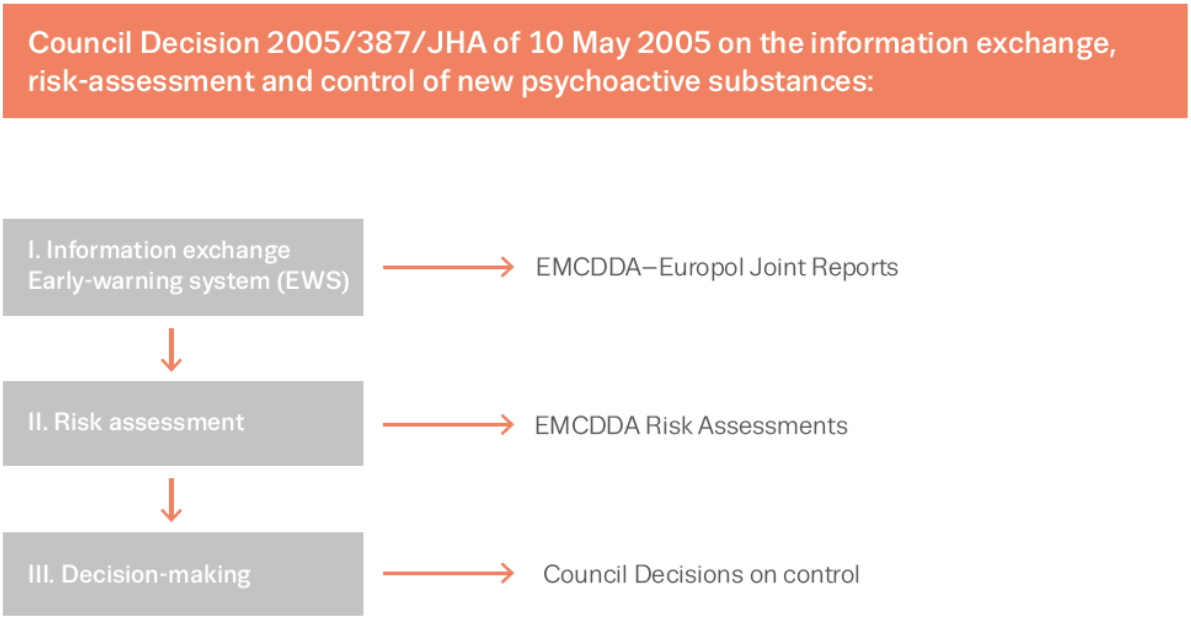
Alexis Goosdeel
Director, EMCDDA

EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances.

It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website: www.emcdda.europa.eu/activities/action-on-new-drugs



Europol–EMCDDA Joint Report on CUMYL-4CN-BINACA (1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide) — a summary

Europol–EMCDDA Joint Report on a new psychoactive substance: 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

In March 2017, the EMCDDA and Europol examined the available information on a new psychoactive substance 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide, commonly known by the abbreviation CUMYL-4CN-BINACA, through a joint assessment based upon the following criteria: (1) the amount of the material seized; (2) evidence of organised crime involvement; (3) evidence of international trafficking; (4) analogy with better-studied compounds; (5) evidence of the potential for further (rapid) spread; and (6) evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information available on CUMYL-4CN-BINACA satisfied criteria 1, 4, 5 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on CUMYL-4CN-BINACA as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 6 June 2017.

The resulting Joint Report on CUMYL-4CN-BINACA was submitted to the Council, the Commission and the EMA on 3 July 2017. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in CUMYL-4CN-BINACA, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:
www.emcdda.europa.eu/publications/joint-reports/cumyl-4cn-binaca

Risk Assessment Report on a new psychoactive substance: 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA)

Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (commonly known as CUMYL-4CN-BINACA). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ([1]). It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on CUMYL-4CN-BINACA, is provided below.

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

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([1]) EMCDDA (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

([2]) OJ L 127, 20.5.2005, p. 32.

([3]) The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New Psychoactive Substances ('EU Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox national focal points and Europol National Units in the Member States, the European Commission, and the European Medicines Agency.

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

if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

CUMYL-4CN-BINACA was formally notified on 4 March 2016 by the EMCDDA on behalf of the Hungarian national focal point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 1 gram of green herbal material seized in January 2016 by police. Following an assessment of the available information on CUMYL-4CN-BINACA, and, in accordance with Article 5 of the Council Decision, on 3 July 2017 the EMCDDA and Europol submitted a *Joint Report* on CUMYL-4CN-BINACA ([6]) to the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and, in accordance with Article 6 of the Council Decision, on 14 September 2017 the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of CUMYL-4CN-BINACA was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of CUMYL-4CN-BINACA, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 7 and 8 November 2017 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

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

- Technical report on 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA) ([6]);
- Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter 'user websites');

([5]) In compliance with the provisions of the United Nations Single Convention on Narcotic Drugs, 1961, and the United Nations Convention on Psychotropic Substances, 1971.

([6]) EMCDDA (2017), EMCDDA–Europol Joint Report on a new psychoactive substance 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA), EMCDDA, Lisbon. Available at: http://emcdda.europa.eu/publications/joint-reports/cumyl-4cn-binaca

- Additional information provided during the course of the risk assessment meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ([1]); and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]).

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with CUMYL-4CN-BINACA. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

Physical, chemical and pharmacological description

1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA) is a synthetic cannabinoid receptor agonist (synthetic cannabinoid) originally patented under the code name SGT-78. The common name for the substance is derived after its structural features ([7]): 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).

Synthetic cannabinoids such as CUMYL-4CN-BINACA are functionally similar to Δ^9-tetrahydrocannabinol (THC), the major psychoactive principle of cannabis. Like THC, they bind to and activate the CB_1 and CB_2 cannabinoid receptors which form part of the endocannabinoid system — a system that helps regulate a large number of physiological functions in the body such as behaviour, mood, pain, appetite, sleep, the immune system, and the cardiovascular system. Many synthetic cannabinoids were first developed to study the endocannabinoid system as well as to explore their potential as therapeutic agents to treat a number of diseases and their symptoms (such as neurodegenerative diseases, drug dependence, pain disorders, and cancer).

Since around 2006, 'legal high' products containing synthetic cannabinoids have been sold in Europe as 'herbal smoking mixtures' and marketed as 'legal' replacements for cannabis. These products are made by dissolving the synthetic cannabinoids in solvents such as acetone or methanol and then mixing them

([7]) Different naming systems exist and are used for applying short/code names to synthetic cannabinoids. http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids

with, or, spraying them on, plant material such as the herbs Damiana (*Turnera diffusa*) and Lamiaceae (such as *Melissa*, *Mentha* and *Thymus*). Such products are generally referred to by a variety of names in Europe, including 'Spice' ([8]), 'herbal smoking mixtures', 'herbal incense', and 'synthetic cannabis'. Manufacturers of 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. Almost 180 synthetic cannabinoids, in hundreds of different products, have been identified on the European drug market since 2008. They are the largest group of substances that are monitored by the EMCDDA through the EU Early Warning System.

A number of cannabinoids are controlled under the United Nations Convention on Psychotropic Substances, 1971 (Schedule II). These are: the major active principle of cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC) ([9]), as well as the synthetic cannabinoids JWH-018 ([10]), AM-2201 ([11]), MDMB-CHMICA ([12]), 5F-APINACA (5F-AKB-48) ([13]), and XLR-11 ([14]).

In its pure form CUMYL-4CN-BINACA has been described as a crystalline solid or a light yellow solid.

Information provided from seizures and collected samples reported to the EMCDDA have noted that CUMYL-4CN-BINACA is typically found in herbal/plant material (including as commercially-branded 'legal high' products) and as a powder. To a lesser extent, other forms, such as blotters, have also been reported.

The analytical identification of CUMYL-4CN-BINACA in physical and biological samples is possible using standard analytical techniques. These include chromatographic and mass spectrometric methods.

Analytical reference material is important for correct identification and for facilitating the quantification of CUMYL-4CN-BINACA in physical and biological samples. Such material is commercially available.

Route of administration and dosage

The most common way of using synthetic cannabinoids such as CUMYL-4CN-BINACA is by smoking either ready-to-use or homemade 'smoking mixtures' as a cigarette ('joint') or by using a vaporizer, 'bong', or pipe. Some synthetic cannabinoids, including CUMYL-4CN-BINACA, have also been offered in the form of e-liquids for vaping in e-cigarettes. Additionally, users might also prepare CUMYL-4CN-BINACA

([8]) Which is a reference to the most common brand name used for these types of products when they first appeared on the European market.
([9]) Including some of its named isomers and their stereochemical variants.
([10]) JWH-018: naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone.
([11]) AM-2201: 1-(5-fluoropentyl)-1*H*-indol-3-yl]-(naphthalen-1-yl)-methanone.
([12]) MDMB-CHMICA: methyl (2*S*)-2-{[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino-3,3-dimethylbutanoate. MDMB-CHMICA was risk assessed by the Scientific Committee of the EMCDDA in July 2016.
([13]) 5F-APINACA: *N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.
([14]) XLR-11: [1-(5-fluoropentyl)-1*H*-indole-3-yl] (2,2,3,3-tetramethylcyclopropyl)methanone.

containing e-liquids at home. To a lesser extent, other routes of administration for synthetic cannabinoids have been reported; these include oral and rectal.

Limited information is available regarding the dose and the dose regimens of CUMYL-4CN-BINACA. User reports specifically about CUMYL-4CN-BINACA were not particularly revealing. It is not possible to discern the 'typical' dosages administered as most individuals use herbal smoking mixtures. Nonetheless, based on data from the analysis of a product, a gram of herbal material could contain more than 10 mg of CUMYL-4CN-BINACA (and potentially other synthetic cannabinoids). These compounds may be active at less than 1 mg.

Pharmacology

Data on the pharmacodynamic effects of CUMYL-4CN-BINACA show that it is a potent and full agonist at the CB_1 receptor (i.e. activates the receptor) of the endocannabinoid system. CUMYL-4CN-BINACA is also a potent and full agonist at the CB_2 receptor.

Data on the pharmacokinetics of CUMYL-4CN-BINACA are limited to the identification of metabolites. So far, 15 metabolites have been identified in humans. The pharmacological effects of these metabolites have not been investigated.

No studies were identified that have investigated the pharmacodynamics of CUMYL-4CN-BINACA on other pharmacological targets.

Interactions with other substances, medicines, and other forms of interactions

No studies were identified that have investigated the potential interactions of CUMYL-4CN-BINACA.

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. This includes: relaxation, euphoria, lethargy, confusion, anxiety, and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, 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. In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported.

Legitimate uses

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 available CAS Registry Numbers returned no hits.

There is no marketing authorisation (existing, on-going, or suspended) for CUMYL-4CN-BINACA in the European Union or in the Member States that responded to the request for information that was undertaken as part of the Joint Report process ([6]).

There is no information to suggest that CUMYL-4CN-BINACA is currently used in the manufacture of a medicinal product in the European Union ([6]). 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.

Chemical precursors that are used for the manufacture

The chemical precursors and the synthetic routes used to manufacture CUMYL-4CN-BINACA are known from the literature, but the existing patent does not provide details of the synthesis. From what is known, the key precursor is 1-(4-cyanobutyl)-1*H*-indazole-3-carboxylic acid 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. The method is straightforward and has been used to prepare many closely related synthetic cannabinoids.

Commercially available domestic or industrial products which could be used for synthesis of CUMYL-4CN-BINACA may contain potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for smoking mixtures may also contain toxicologically relevant substances (such as pesticides that could potentially be present in the plant material).

Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of CUMYL-4CN-BINACA, as well as its abuse liability and dependence potential. Similarities to, and, differences from, other chemically or pharmacologically related substances should also be considered.

It is important to note that when interpreting information from acute intoxications and deaths as well as information from user websites, individuals may have used other pharmacologically active substances in addition to CUMYL-4CN-BINACA. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the effects reported.

Some individuals may use CUMYL-4CN-BINACA in combination with other drugs (either intentionally or unintentionally). CUMYL-4CN-BINACA is typically encountered in combination with other substances in commercially branded ‘legal high’ products, and, in particular, with other synthetic cannabinoids. Analyses of various seized products have shown that the composition can vary significantly over geographical areas and time. Therefore, the users are unlikely to be aware of the substance(s) being ingested and doses used (by whatever route). This presents an inherent risk to the individual.

As synthetic cannabinoids such as CUMYL-4CN-BINACA mimic the effects of THC, their effects appear to have some similarities with cannabis. This includes: relaxation, euphoria, lethargy, confusion, anxiety,

and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor performance. In some cases, these effects appear to be much more pronounced and severe when compared to cannabis.

Severe and fatal poisonings have occurred with synthetic cannabinoids. This can include severe cardiovascular toxicity (including sudden death), severe central nervous system depression (such as rapid loss of consciousness/coma), respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychotic episodes, and aggressive and violent behaviour.

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. The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

The reasons for these more pronounced and severe effects, as well as severe and fatal poisoning, 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 synthetic cannabinoids, including CUMYL-4CN-BINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonist as compared to THC. This means that even at very small doses they can activate the CB_1 receptor much more strongly than THC.

Secondly, the process for making smoking mixtures (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, as well as products where the cannabinoids are clumped together forming highly concentrated pockets within the plant material. 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 involving smoking mixtures suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

Currently, there is no approved antidote to poisoning caused by synthetic cannabinoids.

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.

Acute toxicity

The acute toxicity of CUMYL-4CN-BINACA and/or its metabolites have not been studied in non-clinical and clinical studies. In addition to the acute intoxications and deaths reported to the EMCDDA (discussed

below), cases of acute intoxications and deaths have also been reported in the literature. The limited data suggests that intoxication/poisoning with CUMYL-4CN-BINACA may be similar to other synthetic cannabinoids.

Acute intoxications

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.

Deaths

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

The deaths in Hungary occurred in 2016 and (where known) the deaths in Sweden 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.

Cause of death and toxicological significance

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). However, post-mortem blood concentrations 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, gabapentin, 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).

Circumstances 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 while 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.

Ability to operate machinery and drive

No studies of the effects of CUMYL-4CN-BINACA on the ability to drive and operate machines have been performed. However, it is has been reported that intoxications caused by a range of synthetic cannabinoids significantly impair the mental and physical ability that is required to drive and operate machines.

Chronic toxicity

No studies were identified that investigated the chronic health effects of CUMYL-4CN-BINACA and/or its metabolites.

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of CUMYL-4CN-BINACA. Given what is currently known about the pharmacology of CUMYL-4CN-BINACA, including some similarities to THC, it is reasonable to consider that the substance may have both a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with CUMYL-4CN-BINACA may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with CUMYL-4CN-BINACA are unavailable.

Extent, frequency, and patterns of use

The available data suggest that CUMYL-4CN-BINACA is typically sold as commercial branded 'legal high' smoking mixtures in head shops as well as on the Internet as 'legal' replacements for cannabis. It may also be sold directly on the illicit drug market. Overall, the available information does not suggest widespread use of the substance.

No surveys were identified that have investigated the prevalence of CUMYL-4CN-BINACA use in the general population or in specific user groups.

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 should be considered in the wider context of the prevalence of use of herbal smoking mixtures (sometimes referred to as ‘spice’).

The use of herbal smoking mixtures has been studied in some European countries in general population surveys and 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.

It is reasonable to assume that 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, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds.

In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

Availability and quality on the market

CUMYL-4CN-BINACA was formally notified on 4 March 2016 by the EMCDDA on behalf of Hungary. 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. Since then, CUMYL-4CN-BINACA has been detected in 11 Member States (Estonia, Finland, France, Germany, Hungary, Lithuania, Romania, Slovenia, Spain, Sweden, and the United Kingdom) and Turkey. As the substance is not routinely screened for, detections of CUMYL-4CN-BINACA may be under reported.

CUMYL-4CN-BINACA is sold online either as commercial ‘legal high’ ‘herbal mixtures’ or as a powder. The presence of CUMYL-4CN-BINACA (or any other synthetic cannabinoid) is not typically disclosed on the packaging/advertising of smoking mixtures.

Due to the high potency of some synthetic cannabinoids, the amount of powder needed for each packet can be in the order of tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of ‘legal highs’ (Section 6).

Detailed information with regards to route-specific by-products produced during the synthesis of CUMYL-4CN-BINACA is currently not available. There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA.

As discussed above, in general, smoking mixtures appear to pose a high risk of poisoning/acute toxicity because of the high potency of synthetic cannabinoids, the manufacturing process used, and the route of administration.

Characteristics and behaviour of users

Information on the characteristics and behaviour of users of CUMYL-4CN-BINACA is limited.

‘Legal high’ products containing CUMYL-4CN-BINACA are marketed as ‘legal’ replacements to cannabis. It is therefore likely that a range of different cannabis users would be interested in these products. The available data suggests that CUMYL-4CN-BINACA is used by cannabis users, including those who are

regularly subjected to drug testing procedures. To a lesser degree it is also used by psychonaut-type users.

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.

In most cases, it appears that CUMYL-4CN-BINACA is not specifically sought after by users who will typically purchase it unknowingly as part of a smoking mixture product.

Nature and extent of health consequences

Information on the nature and extent of health consequences are mostly limited to those discussed in relation to individual health risks.

The high potency of the synthetic cannabinoids, coupled to the unintentionally high doses that users are exposed to, is also responsible for outbreaks of mass poisonings involving smoking mixtures. Such outbreaks have ranged in size from four or five to over 800 victims, including deaths. While many of the outbreaks that have been reported so far are from the United States, they have also occurred in Russia and Europe. Mass poisonings can rapidly overwhelm emergency responders and other local healthcare systems.

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. Opioids have also been identified in smoking mixtures; while the overall number of detections appears to be relatively small, it could pose a risk of severe opioid poisoning, including life-threatening respiratory depression, especially in individuals with no tolerance to opioids. Users of smoking mixtures will be unaware of this risk.

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.

Conditions under which the substance is obtained and used

There is limited data on the conditions under 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. As highlighted, most users will be unaware that they have sourced and used CUMYL-4CN-BINACA as they will be using smoking mixtures. The available data suggests that CUMYL-4CN-BINACA is used in similar environments to cannabis, including the home, other recreational settings, and prisons.

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.

Individual social risks

While there is no specific information on whether the use of CUMYL-4CN-BINACA causes individual social risks, any such risks may have some similarities with those associated with cannabis and other synthetic cannabinoids. These may impact on education or career, family, or other personal and social relationships and may result in marginalisation.

Possible effects on direct social environment (e.g. neglect of family, violence)

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.

Possible effects on society as a whole (public order and safety, acquisitive crime)

While there is no specific information on the possible effects of CUMYL-4CN-BINACA on society as a whole, as noted, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. In particular, concern was expressed in this regard to use in certain environments such as prisons and psychiatric institutions. In addition, the detection of CUMYL-4CN-BINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

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.

Due to the lack of data, it is not possible at this time to estimate the social risk associated with the trafficking and distribution of CUMYL-4CN-BINACA.

Economic costs

Due to the lack of data, it is not possible at this time to estimate whether CUMYL-4CN-BINACA is associated with greater healthcare costs than other drugs.

Possible appeal to specific population groups

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 after by those looking for ‘legal’ substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds.

In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

Information on manufacturing, trafficking, distribution, and the level of 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.

No information has been received by Europol indicating synthesis of CUMYL-4CN-BINACA within the European Union. Information reported to the EMCDDA and Europol indicates that chemical companies based in China may be one source of CUMYL-4CN-BINACA, as well as of other synthetic cannabinoids. Seizures, particularly of bulk powders of synthetic cannabinoids, are frequently reported to have occurred at international European airports and to have been shipped by such companies.

For CUMYL-4CN-BINACA, single seizures of powders in excess of 1 kg were reported by France and Spain. 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. The seizure reported by France was made by customs at an international airport and the package was *en route* from China to the Netherlands.

Powders of synthetic cannabinoids, including CUMYL-4CN-BINACA, are imported into the European Union where they are typically processed and packaged into commercial smoking mixtures or sold as powder. There are indications of a significant trade in synthetic cannabinoid products within Europe, with customs and police in many countries making regular seizures of such products, including herbal smoking products containing CUMYL-4CN-BINACA.

CUMYL-4CN-BINACA has been available on the European drug market since at least October 2015. 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 of CUMYL-4CN-BINACA. Information reported to the EMCDDA and Europol indicates that CUMYL-4CN-BINACA has been seized as herbal material (approximately 261 kg; 257 kg of which reported by Turkey) or powder form (approximately 52 kg; 50 kg of which reported by Spain).

The available data suggests that herbal smoking mixtures containing CUMYL-4CN-BINACA are being sold directly in the illicit market. The United Kingdom and Lithuania have reported seizures of CUMYL-4CN-BINACA which occurred in prisons or other custodial settings.

Information on any assessment in the United Nations system

The World Health Organization (WHO) is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971. At the time that the Joint Report was prepared ([6]), the WHO informed the EMCDDA that CUMYL-4CN-BINACA was not currently under assessment nor had it been under assessment by the United Nations system.

Description of the control measures that are applicable in the Member States

Nine Member States (Croatia, Cyprus, Denmark, Finland, Latvia, Lithuania, Luxembourg, Sweden, and the United Kingdom) reported that CUMYL-4CN-BINACA is controlled under drug control legislation.

- In Croatia, CUMYL-4CN-BINACA is controlled within the 'List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs', Official Gazette no. 10/16.
- In Cyprus, CUMYL-4CN-BINACA is controlled as a Class B drug within the Narcotic Drugs and Psychotropic Substances Law 1977.
- In Denmark, CUMYL-4CN-BINACA is controlled as of 15 June 2017 by an amendment of the Executive Order on Controlled Substances.
- In Finland, CUMYL-4CN-BINACA is controlled as a 'psychoactive substance banned from the consumer market'.
- In Latvia, CUMYL-4CN-BINACA is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'.
- In Lithuania, CUMYL-4CN-BINACA is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-868 (29/06/2016) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Luxembourg, CUMYL-4CN-BINACA is controlled by way of generic definition by the Grand-ducal decree of 20/04/2009.
- In Sweden, CUMYL-4CN-BINACA is regulated under the Act on the Prohibition of Certain Goods Dangerous to Health, as of 25 January 2017.
- In the United Kingdom, CUMYL-4CN-BINACA is controlled by way of generic definition under the 1971 Misuse of Drugs Act.

Five Member States (Austria, Belgium, Germany, Hungary, and Poland) and Turkey reported that CUMYL-4CN-BINACA is controlled under specific new psychoactive substances control legislation.

- In Austria, CUMYL-4CN-BINACA is covered by the Austrian Act on New Psychoactive substances.
- In Belgium, CUMYL-4CN-BINACA is controlled by way of generic definition.
- In Germany and Hungary, CUMYL-4CN-BINACA is controlled under specific NPS control legislation. No additional details were provided.

- In Poland, CUMYL-4CN-BINACA is controlled according to the general definition of the 'substitute drug' (Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, Journal of Laws "Dz.U." No. 213, item 1396). Pursuant to Article 44b of the Act on counteracting drug addiction, it is prohibited to manufacture and introduce substitute drugs to trade.

- In Turkey, CUMYL-4CN-BINACA is controlled by way of generic definition under specific new psychoactive substances control legislation.

Thirteen Member States (Bulgaria, Czech Republic, Estonia, France, Greece, Ireland, Italy, Malta, the Netherlands, Portugal, Romania, Slovenia, and Spain), and Norway reported that CUMYL-4CN-BINACA is not subject to control measures at the national level.

Slovakia did not provide information on the control status of CUMYL-4CN-BINACA.

Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance CUMYL-4CN-BINACA to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Convention on Psychotropic Substances, 1971.

- There are no studies on the possible consequences of such control measures on CUMYL-4CN-BINACA. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of CUMYL-4CN-BINACA and hence the further expansion of the current open trade in this substance.

- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.

- This control option could facilitate the detection, seizure and monitoring of CUMYL-4CN-BINACA related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.

- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.

- This control option could create an illicit market in CUMYL-4CN-BINACA with the increased risk of associated criminal activity, including the involvement of organised crime.

- This control option could impact on both the quality/purity and price of any CUMYL-4CN-BINACA still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.

- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.

- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of CUMYL-4CN-BINACA on the market post-control, should this control option be pursued.

- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

Conclusion

1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA) is synthetic cannabinoid receptor agonist. Information on the pharmacology of CUMYL-4CN-BINACA suggests that it is a potent and full agonist at the CB_1 receptor and CB_2 receptor. It shows similar effects to THC but with additional life-threatening toxicity. The high potency of CUMYL-4CN-BINACA and the large and variable content of the substance in smoking mixtures constitute a high risk of poisoning.

CUMYL-4CN-BINACA is often sold as a 'legal' replacement for cannabis. It is typically administered by smoking a herbal mixture that is either from a ready-to-use commercial 'legal high' product, or, less commonly, that is self-prepared. Similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint') but it may also be smoked in a pipe or 'bong'. CUMYL-4CN-BINACA can also be inhaled using an e-cigarette or other vaporisation device.

CUMYL-4CN-BINACA has been available on the drug market in the European Union since at least October 2015 and has been detected in 11 Member States and Turkey. It is sold online as commercially branded 'legal high' products and powders. It may also be sold directly on the illicit drug market.

The available data suggests that CUMYL-4CN-BINACA is used by cannabis users, by those who are regularly subjected to drug testing procedures (including those in prison), and by 'psychonauts'. It may also be used by high risk drug users and other marginalised groups (such as prisoners) as synthetic cannabinoids have gained a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle. However, no further information on the size and demand and the characteristics of these groups of people is available.

Five acute intoxications with confirmed exposure to CUMYL-4CN-BINACA have been reported by 2 Member States.

Eleven deaths with confirmed exposure to CUMYL-4CN-BINACA have been reported by 2 Member States. In at least 5 of these cases, CUMYL-4CN-BINACA was either the cause of death or is likely to have contributed to the death.

Due to the nature of CUMYL-4CN-BINACA, both non-fatal intoxications and deaths are likely to be under-detected and under-reported.

There is currently no approved antidote to poisoning caused by synthetic cannabinoids such as CUMYL-4CN-BINACA.

Reports suggest a possibility for violence and aggression following use of synthetic cannabinoids. In particular, concern was expressed in this regard to use in certain environments, such as prisons and psychiatric institutions. In addition, the detection of CUMYL-4CN-BINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

There is no specific information on the involvement of organised crime in the manufacture, distribution (trafficking), and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the CUMYL-4CN-BINACA detected within the European Union. The largest single seizure of CUMYL-4CN-BINACA was in Spain in 2016, when 50 kg of

powder that originated in China was seized by customs. During 2017, CUMYL-4CN-BINACA continued to be seized by law enforcement within the European Union.

CUMYL-4CN-BINACA has no recognized human or veterinary medical use in the European Union, nor, it appears, elsewhere. There are no indications that CUMYL-4CN-BINACA may be used for any other purpose aside from as an analytical reference standard and in scientific research.

CUMYL-4CN-BINACA is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. CUMYL-4CN-BINACA is not currently under assessment by the United Nations system.

Nine Member States control CUMYL-4CN-BINACA under drug control legislation. Five Member States and Turkey control CUMYL-4CN-BINACA under other legislation.

As for any new psychoactive substance, many of the questions related to CUMYL-4CN-BINACA that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between CUMYL-4CN-BINACA and other substances; the dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control CUMYL-4CN-BINACA has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks arising from the use of CUMYL-4CN-BINACA. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, pharmacologically analogous substances that may replace CUMYL-4CN-BINACA are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Should control measures be adopted, they should be accompanied by the gathering and dissemination of accurate information on CUMYL-4CN-BINACA to users, practitioners, policy makers, and decision makers.

ANNEX 1

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

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 ([1]). 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_1 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) ([2]). Because synthetic cannabinoids activate the CB_1 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).

([1]) (–)-*trans*-Δ^9-tetrahydrocannabinol.

([2]) The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB_1 and CB_2 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*-Δ^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).

In accordance with the Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances ([3]), 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 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® (American Chemical Society, Chemical Abstract Service) and Reaxys® (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.

([3]) OJ L 127, 20.5.2005, p. 32.

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science™ (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.

Report prepared by

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Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

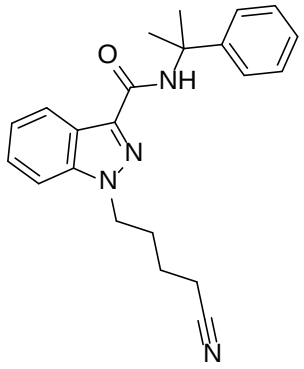
Chemical description and names

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 ([6]): 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 ([7]), AM-2201 ([8]), MDMB-CHMICA ([9]), 5F-APINACA (5F-AKB-48) ([10]) and XLR-11 ([11]). 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 ([12]) (EMCDDA, 2017d), ADB-CHMINACA ([13]) (EMCDDA, 2017e), and 5F-MDMB-PINACA (5F-ADB) ([14]) (EMCDDA, 2017f).

([6]) 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
([7]) JWH-018: (Naphthalen-1-yl)(1-pentyl-1H-indol-3-yl)methanone.
([8]) AM-2201: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](naphthalen-1-yl)methanone.
([9]) 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)
([10]) 5F-APINACA: *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.
([11]) XLR-11: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.
([12]) AB-CHMINACA: *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.
([13]) ADB-CHMINACA: *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.
([14]) 5F-MDMB-PINACA (5F-ADB): Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate.

FIGURE 1
The molecular structure, molecular formula and molecular weight of CUMYL-4CN-BINACA.


$C_{22}H_{24}N_4O$
360.46 g/mol

Names and other identifiers

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

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

Chemical Abstract name:

1*H*-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)-1*H*-indazole-3-carboxamide;

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

Chemical Abstract Service Registry Numbers (CAS RN) ([15]):

1631074-54-8

PubChem SID:

117650402 ([16])

IUPAC International Chemical Identifier Key (InCHI Key) ([17]):

JGTSOWOPISVAHG-UHFFFAOYSA-N

SMILES ([18]):

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.

([15]) 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.
([16]) https://pubchem.ncbi.nlm.nih.gov/compound/117650402
([17]) InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.
([18]) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

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).

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

Techniques [a]	Comment	Reference
^{1}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	*In vitro* 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)

[a] 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).

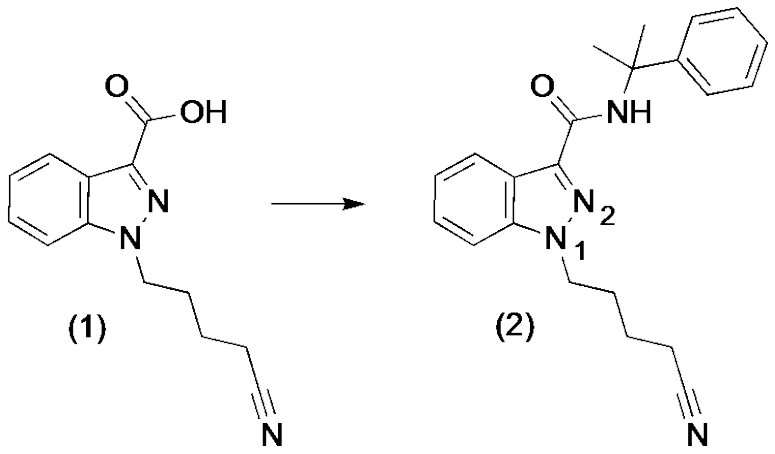
Methods and chemical precursors used for the manufacture

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 ($SOCl_2$), oxalyl chloride $(COCl)_2$ or phosphorous oxychloride ($POCl_3$) 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) ([19]) but around 3x less potent than the N1-(5-fluoropentyl) substituted analogue CUMYL-5F-PINACA (SGT-25) ([20]) ([21]). As highlighted in the introduction, users do not typically know purity, amount and/or composition

([19]) CUMYL-PINACA: 1-pentyl-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.
([20]) CUMYL-5F-PINACA: 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.

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_1 receptor. For example, using human embryonic kidney cells (HEK) expressing the CB_1 receptor (radioligand [^{3}H]CP-55,940), CUMYL-4CN-BINACA showed a 1.5-fold lower affinity than Δ^9-THC in the low nanomolar range, whereas CUMYL-4CN-BINACA's affinity toward the CB_1 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 was compared relative to inhibition induced by 1 µM CP-55,940. Based on the determination of the subnanomolar EC_{50} values ([22]), CUMYL-4CN-BINACA was 5-times more potent than the full agonist CP-55,940 with equal efficacy and 254-times more potent than Δ^9-THC (E_{max} = 78.5% relative to CP-55,940) under the *in vitro* conditions studied (US DEA, 2017).

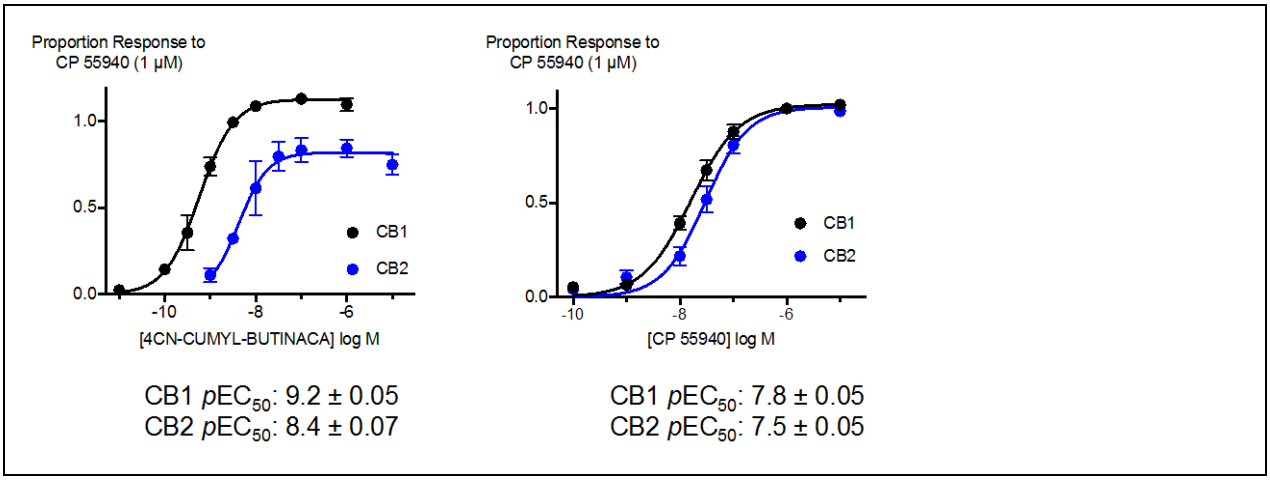
Based on an *in vitro* assay evaluating the changes of membrane potentials following G-protein activation (G protein-gated inwardly rectifying potassium channels (GIRKs)) (e.g. Banister et al., 2015), it was found that CUMYL-4CN-BINACA was a potent full agonist at both CB receptor subtypes with a 6.3-fold higher potency at CB_1 compared with CB_2 (EC_{50} CB_1 = 0.631 nM; EC_{50} CB_2 = 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 µM 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) ([23]) in activating hCB_1 and hCB_2 when using an *in vitro* membrane potential assay (G protein-gated inwardly rectifying potassium channels (GIRKs)) (Longworth et al., 2017a).

([21]) Personal communication with the now defunct Stargate International Company (New Zealand).
([22]) EC_{50} represents the half maximal effective concentration.
([23]) CUMYL-PINACA: 1-Pentyl-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.

FIGURE 3

Activity of CUMYL-4CN-BINACA at hCB_1 & hCB_2 receptors stably transfected with murine AtT-20 neuroblastoma cell using the *in vitro* GIRK assay. Kindly provided by Mark Connor and Rochelle Boyd, Department of Biomedical Sciences, Macquarie University, NSW, Australia.



CUMYL-5F-PINACA was found to be 398- and 24-times more potent than Δ^9-THC and CP-55,490 (hCB_1), respectively, and two times more potent than CP-55,490 at hCB_2 (Δ^9-THC inactive unless 30 µM was used).

In comparison, CUMYL-PINACA was found to be 74- and 4.5-times more potent than Δ^9-THC and CP-55,490 (hCB_1), respectively, and 4.7-times less potent than CP-55,490 at hCB_2 in the GIRK assay (Longworth et al., 2017a). On the other hand, in another investigation employing an *in vitro* [^{35}S]GTPγS 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-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 Δ^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-butanoic 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^1-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 β-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-butanoic 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 we as combinations of these reactions. The 4-butanoic 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).

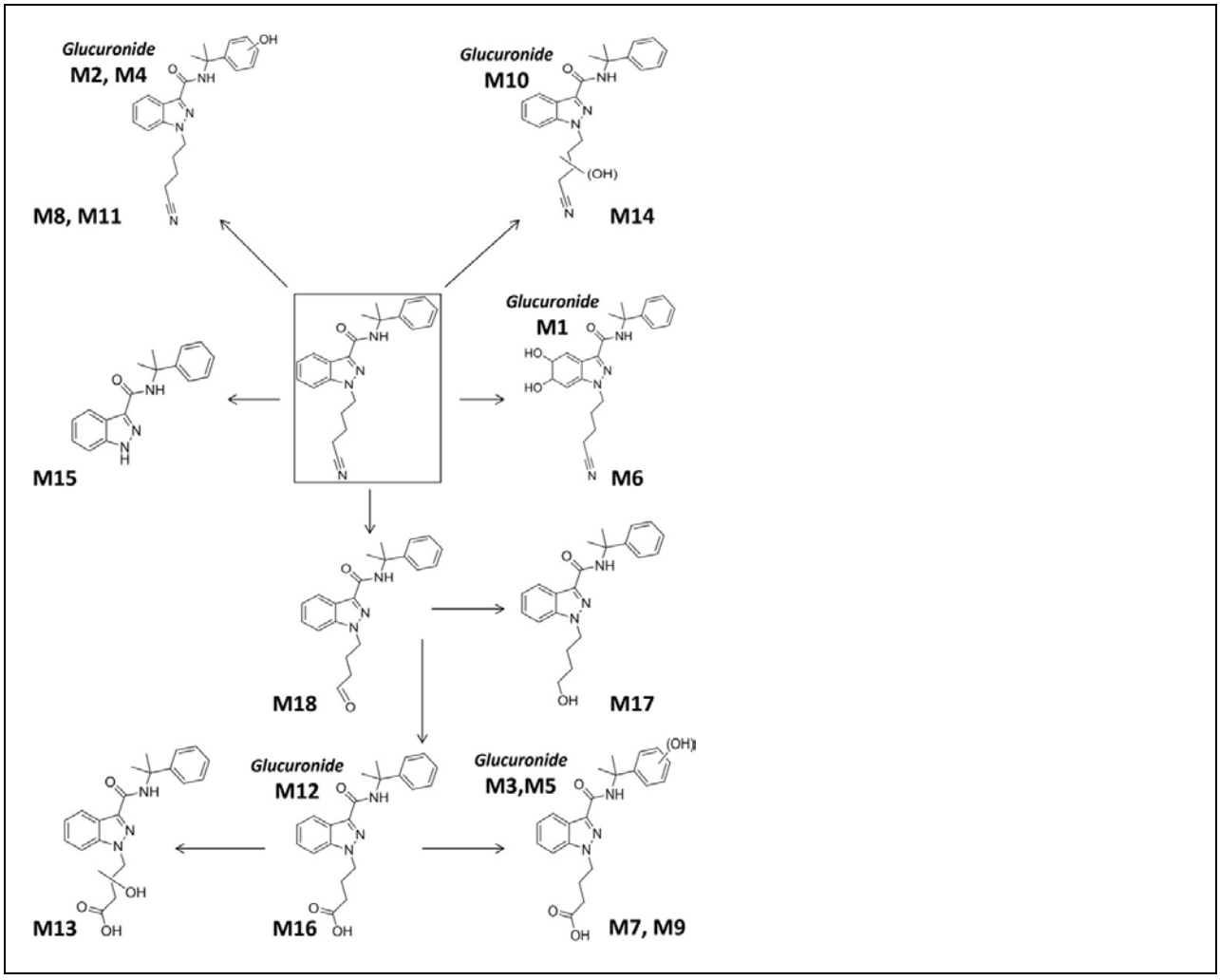
The authors of the metabolism study also mentioned that the relative abundance of the main metabolites (M16, M8, and M11 and their glucuronides) corresponded to high blood concentrations of CUMYL-4CN-BINACA found in 73 of 80 cases although details were not reported (Öztürk et al., 2017).

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' ([24]).

([24]) Personal communication with the now defunct Stargate International Company, New Zealand.

FIGURE 4

Proposed metabolic pathway of CUMYL-4CN-BINACA following incubation with pooled human liver microsomes (up to 3 h, including constituents used for phase II transformations) (Öztürk et al., 2017).



Inter-individual genetic variability in metabolising enzymes

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 is 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, ^{1}H-NMR and ^{13}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 ([25]) 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 ([26]) of CUMYL-4CN-BINACA to the EMCDDA and/or Europol.

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.

([25]) 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.)

([26]) 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.

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 ([27]). 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:

- 16 cases of persons suspected of driving under the influence of drugs (including five traffic accidents), all reported by Hungary;

([27]) This is a minimum estimate provided by the Turkish national focal point.

- 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 ([28]) found that the substance 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.

([28]) 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.

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_1 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; Zaurova 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; Brenneman 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; Zaurova 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-4-CNBINACA, 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 quality 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 in respect to its health and social 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

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

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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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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Related publications and websites

EMCDDA

| Risk assessment of new psychoactive substances — operating guidelines, 2010 www.emcdda.europa.eu/html.cfm/index100978EN.html

EMCDDA and Europol

| EMCDDA-Europol Joint Report on a new psychoactive substance 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (CUMYL-4CN-BINACA*)*, 2017 www.emcdda.europa.eu/publications/joint-reports/cumyl-4cn-binaca

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