ACMD

Advisory Council on the Misuse of Drugs

Synthetic cannabinoid receptor agonists (SCRA)

An updated harms assessment and a review of classification and scheduling under the Misuse of Drugs Act 1971 and its Regulations

Contents

1. Introduction

1.1. Synthetic cannabinoid receptor agonists (SCRA) are chemicals that stimulate the endogenous cannabinoid receptors within the body responsible for mediating the pharmacological effects of tetrahydrocannabinol (THC), the major active ingredient of cannabis. They are sometimes referred to as synthetic cannabinoids, but this term is misleading, as some examples are not structurally related to naturally occurring cannabinoid compounds. The first examples of SCRA were created in the 1980s to research cannabinoid receptor pharmacology and to explore the therapeutic potential of drugs interacting with the cannabinoid receptor system.

1.2. Due to the increased online availability of published research studies and patents describing their synthesis [Norman et al., 2020], recreational use of these compounds was commercialised in Europe in the mid-2000s and in the United States of America (USA) in late-2000s [White, 2017; EMCDDA, 2018a]. SCRA were previously sold openly in the UK by high street retail outlets, often referred to as 'head shops'. These products, typically consisting of inert herbal materials infused or sprayed with SCRA, are often generally referred to as 'spice', with specific products sold in attractive packaging using brand names such as *K2, Mamba, Annihilation, Pandora's Box, Clockwork Orange and Kronic*, as well as *Spice* [NEPTUNE, 2015; Waugh et al 2016; Norman et al., 2020]. As of March 2020, there have been nearly 700 different SCRA brand and street names identified worldwide [Spice Addiction Support, 2020]. These compounds have been amongst the most common types of novel psychoactive substances (NPS) encountered in the UK and elsewhere over the last decade.

1.3. Many specific examples of SCRA were controlled in the UK by legislation introduced in 2009, 2012 and 2016 (see below). However, the numbers of different substances and their chemical complexity allow medicinal chemists to synthesise examples that evade legislation based on chemical structure. As of August 2020, almost 200 different SCRA compounds had been identified analytically in Europe and reported to the EMCDDA. There are many further opportunities for structural modifications and the potential for many further analogues to appear in the future [Potts et al., 2020].

1.4. The enactment of the Psychoactive Substances Act (PSA) in May 2016 has prohibited the production and supply of psychoactive materials, including SCRA, removing their open sale and significantly reducing general population use [Home Office, 2018]. Whilst there is evidence to suggest that recreational use has declined since 2016, prevalence of use in specific user sub-groups has remained high and there have been media reports of 'spice epidemics' in major UK cities and prisons [Gray et al., 2020]. These substances have developed a reputation as powerful and cheap intoxicants among vulnerable groups, such as the homeless and prisoners, who use them in part for their 'mind-numbing' effects [EMCDDA, 2018b; Gray et al., 2020].

1.5. In November 2018, the possibility of reclassification of SCRA was debated in Parliament and the then Minister for Policing and the Fire Service committed

to seeking advice on this issue from the Advisory Council on the Misuse of Drugs (ACMD). This advice was commissioned in February 2019 and requested the ACMD to provide:

1. An updated harms assessment to the ACMD's previous reports on synthetic cannabinoids and provide necessary advice on this issue.
2. A recommendation on whether the current classification under the Misuse of Drugs Act 1971 (MDA) and the schedule under the Misuse of Drugs Regulations 2001 (MDR) of synthetic cannabinoids is appropriate.
3. If not appropriate, a recommendation on whether all or some synthetic cannabinoids should be moved to a different classification or schedule.

1.6. The ACMD has therefore compiled this report, which examines evidence that has emerged since it last provided advice on the harms of SCRA. For the purposes of the report, the ACMD conducted a literature review of papers submitted since 2012, as this was the last time a harms assessment was conducted on this drug group.

2. Previous ACMD advice and legal status of SCRA in the UK

2.1. In July 2009, the ACMD submitted a report on major cannabinoid agonists [ACMD, 2009]. Although only a small number of compounds were forensically identified in the then legally available 'spice', the ACMD recommended that a generic definition should be used to control SCRA under the MDA in order to prevent illicit manufactures utilising the range of chemically different but functionally similar major cannabinoid agonists. The ACMD proposed five generic definitions for SCRA, based on the published research of JW Huffman's research team, and listed five additional substances by name (HU-210, Nabilone, WIN-55212-2, HU-243, and CP 50,556-1). Following this advice, these 'first generation' cannabinoids were controlled as Class B under the MDA and placed under Schedule 1 of the MDR at the end of 2009.

2.2. In 2012, prompted by evidence that gaps in the definition were being exploited, the ACMD provided further advice to expand the generic definition for SCRA and confirmed that class B under the MDA and schedule 1 of the MDR remained appropriate [ACMD, 2012]. These 'second generation' compounds were controlled in early 2013.

2.3. Evidence of harmful SCRA that fell outside of the generic definition in the MDA subsequently began to emerge. The ACMD responded by publishing a further report in November 2014 to recommend a broad 'third generation' SCRA generic definition. The 2014 review reported effects of new materials that had similar or more potent effects than those materials already controlled, although no new evidence on harms was considered [ACMD, 2014].

2.4. Compounds captured by the ‘third generation’ generic definition were controlled as Class B Schedule 1 substances in December 2016. However, due to the broad nature of the generic definition, some compounds without psychoactive effects were unintentionally captured under this definition, inadvertently subjecting them to strict controls. In December 2017, the ACMD provided follow up advice, to address concerns that the broad definition was creating barriers to therapeutic research [ACMD, 2017]. It was recommended that the scope of the ‘third generation’ definition should be reduced to remove many of the compounds from the definition that were unintentionally caught from the original definition. The suggested amendments were applied in November 2019 [Home Office, 2019] and consequently, research was permitted on the excluded compounds without the requirement for a Home Office licence. It should be noted, however, that some compounds without cannabinoid receptor agonist activity, are still captured by the updated generic definition.

2.5. Over the past decade, the ACMD has intermittently considered the available evidence on this drug group. Despite a gradual expansion of the generic definition with each ‘generation’, the ACMD has previously advised that Class B under the MDA and Schedule 1 of the MDR remained an appropriate measure of control. The main harms evidenced in these reports that qualified SCRA for Class B level of control include:

- reports of emergency room presentations in Germany for psychosis-like panic attacks, heart and circulatory problems;
- anecdotal user reports of severe adverse effects, including increased heart rate, panic attacks and convulsions;
- cannabinoid-related toxicity causing tachycardia, agitation, drowsiness, vomiting, hallucinations and nausea; and
- acute withdrawal associated with cessation of long-term use of these products suggesting that their use may be associated with dependence.

2.6. The harms associated with this diverse drug group detailed in previous ACMD reports were largely ‘potential harms’ because:

- much less analytical information was available;
- the physical harms of SCRA use were not well documented; and,
- limited evidence of social harms was available at the time of publication.

3. Chemistry, nomenclature and pharmacology

3.1. SCRA are complex molecules and there are large numbers of specific examples. The chemical structures of SCRA fall into four distinct groups:

1. **Compounds with structures related to THC** are named individually in the MDA or covered as a cannabinol derivative. e.g. Nabilone, HU-210, HU-243, CP 50,556-1 (Levonantradol).

2. **Cyclohexylphenols,** which are covered by a generic definition in the MDA.
3. **Compounds structurally related to JWH-018** which are covered by generic definitions in the MDA.
4. **Compounds with similar structures to those in group 3** but which cannot easily be included in a generic definition and are therefore named individually in the MDA, for example WIN-55,212-2.

3.2. In 2011, the EMCDDA developed alpha-numeric systematic abbreviated names to describe compounds structurally related to JWH-018, utilising a four-group pharmacophore model [Shevyrin et al 2016] that comprises 'core', 'tail', 'linker' and 'linked' (aka 'head' or 'secondary structure') groups [EMCDDA, 2017; Potts et al., 2020]. Where possible, EMCDDA nomenclature has been used in this report (see Annex D).

3.3. Different systems of nomenclature have been used to refer to the same substance and this can produce confusion. Some SCRA can be described using non-systematic abbreviated alphanumeric names such as AKB-48, 2NE1 and XLR-11. Others use a code to represent the company or person responsible for their original discovery, followed by a number that identifies the specific compound, for example the 'WIN-', 'HU-', 'CP-','JWH-' and 'AM-' series of compounds. This system identifies the originator laboratory, but the number provides no information about the chemical structure or pharmacological properties.

3.4. Chemical structures can be described very precisely using the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, but the names generated are complex and unwieldy for general use. An example is *(2S)-2-([1-(cyclohexylmethyl)-1H-indol-3-yl]formamido)- 3,3-dimethylbutanoate*, a compound that is also referred to using the EMCDDA's simpler alpha-numeric systematic abbreviated name MDMB-CHMICA [Potts et al 2020].

3.5. Most SCRA affect both type 1 and type 2 cannabinoid receptors (CB_1 and CB_2) but to different degrees. SCRA typically act as full agonists at CB_1 and CB_2 receptors and can therefore produce more pronounced effects than their naturally occurring counterpart THC, which is only a partial agonist at CB_1 and CB_2 receptors [Atwood et al., 2011; Ligresti et al 2016; Akram et al., 2019]. Activity at the CB_1 receptor produces the intoxicating effects sought by users and the SCRA entering the NPS market are those with structures that target this receptor. There is evidence that more recently encountered 'third-generation' SCRA that have come to dominate the UK market, such as 5F-MDMB-PINACA and AMB-FUBINACA are more potent agonists at CB_1 receptors than those previously encountered, for example, JWH-018 [Banister et al., 2016; Antonides, 2019].

3.6. Limited information is available on the human pharmacology of SCRA. A controlled administration study demonstrated that inhalation of 2mg or 3mg of the first-generation compound JWH-018 was tolerated by recreational cannabis users, while producing some impairment in cognitive functioning. The maximum reported 'high' occurred one hour after inhalation [Theunissen et al., 2018]. A second study revealed variable subjective responses to higher

doses of JWH-018, with some people reporting no subjective intoxication and others maximal subjective intoxication. Those with more pronounced intoxication had higher serum drug concentrations; indicating variability in the drug delivery by inhalation. The study demonstrated that doses as low as 2mg can induce unpredictable psychological effects that vary from weak to moderate. Successive inhalations from a given mixture may therefore provoke sudden and unexpected levels of impairment and increase the risk of overdosing [Theunissen et al., 2019].

4. Clinical and legitimate uses

4.1. A consultation with the Medicines and Healthcare products Regulatory Agency (MHRA) confirmed that there are some cannabis-based medicinal products licenced and available for therapeutic use in the UK (e.g. Epidyolex [EMC, 2020a] and Sativex [EMC, 2020b]). The only synthetic material which affects the CB_1 receptor that is currently licenced as a medicinal product is Nabilone. This is prescribed under close medical supervision (preferably in a hospital setting) to treat nausea and vomiting caused by cytotoxic chemotherapy, if the patient is unresponsive to conventional antiemetics [British National Formulary, 2020]. Due to its risk of diversion as a THC analogue, Nabilone is controlled as an individually named product under the MDA (Class B) and is a Schedule 2 material under the MDR.

The MHRA does not hold any records of unlicensed SCRA products being imported for named patient prescriptions (as of June 2020). Also at this time there were no clinical trials identified on the European Union (EU) clinical trials register involving SCRA compounds that were either named individually or captured by the SCRA generic definitions in the MDA.

5. Illicit use and supply

5.1. Smoking, inhalation, insufflation, and ingestion are the main ways in which SCRA are used [White, 2017]. Pure compounds are in powder form at room temperature, but these powders are dissolved in solvent and then sprayed on inert plant material or a sheet of paper which is then smoked. Preparing SCRA in this form can lead to spots of high concentrations on the paper, causing inconsistent dosing during administration and leading to significant risk to the user. Other methods of administration include vaporising (‘vaping’) SCRA liquid solutions using an e-cigarette and ingestion of pills or powders [Peacock et al., 2019; Norman et al., 2020]. Prisoners have been known to use e-cigarettes modified to expose the heating element to smoke SCRA impregnated papers as well as using the steam from kettles to evaporate the compound for inhalation.

5.2. Multiple types of SCRA, in a variety of forms (herbal, papers, powder, liquids) have appeared in UK markets, but there is no evidence to suggest that SCRA are being manufactured in the UK. Forensic analysis has determined that most SCRA material seized originates from China. Supply is primarily imported through Fast Parcel and post modes, with links to some organised

crime groups arranging importation into the UK via Europe alongside other controlled substances.

5.3. The UK SCRA market has evolved to favour different iterations of novel SCRA compounds over time. Disappearances of specific SCRA from seizures have been linked to legislative changes in China [Norman et al., 2020], evidencing further that SCRA encountered in the UK are imported rather than manufactured in the UK. In a study of prison seizures in Scotland, Norman et al [2020] found a shift in the prevalence of commonly encountered compounds from 5F-MDMB-PINACA (5F-ADB) and AMB-FUBINACA to 5F-MDMB-PICA and 4F-MDMB-BINACA in late 2018, in line with the State Council of China bringing these two SCRA (along with six others) under legislative control on 29 August 2018 (see Annex A).

5.4. SCRA are likely to be distributed regionally through a process called 'community deal' whereby one user visits a main dealer to buy drugs and then distributes purchased products to others. As of March 2020, SCRA were priced at £10 a gram, with £5 deals also widely accessible. In a custodial setting, the cost is expected to be 10 times higher than the street value, but this will vary from prison to prison. Like other controlled substances, SCRA are smuggled into prisons using drones, corrupt prison staff or prisoners hiding items within body orifices when entering the prison.

[*paragraph 5.5. has been redacted from the published version of this report*]

6. Prevalence and patterns of use in the UK

6.1. Originally introduced to the UK as a 'legal high' with marketing predominantly aimed at young people in city centres [Peacock et al., 2019], SCRA use has now shifted substantially to rough sleepers and prison populations across the UK [Gray et al 2020; Norman et al., 2020]. Levels of use recorded in general population surveys remain relatively low when compared with traditional illegal substances [Ralphs, 2017a].

6.2. The annual Crime Survey for England and Wales (CSEW) does not explicitly report SCRA use but does collect information on the nature of NPS use. Self-reported NPS use (over the previous 12 months) was measured at 0.9% in 16– to 59-year olds and 2.8% in 16– to 24-year olds in 2014/15. By 2018/19, use had fallen to 0.5% and 1.4% respectively. 'Herbal smoking mixtures' (likely to contain SCRA) were the most prevalent NPS form used in 2016/17, representing 40% of total NPS use. By 2018/19, use of smoking mixtures had fallen behind powder, crystals, tablets and 'other' types of NPS use, making up only 24% of total NPS use [CSEW, 2019]. The Smoking, Drinking and Drug Use among Young People in England (SDD) survey does not report against SCRA use.

6.3. The Scottish Crime and Justice Survey (SCJS) [2019] has only reported drug use in their most recent report (2017/18), which demonstrated that 0.2% of

respondents reported SCRA use over the previous 12 months [Scottish Crime and Justice Survey, 2019].

6.4. Information on the prevalence of SCRA use was not available in the equivalent survey covering Northern Ireland, the All Ireland Drug Prevalence Survey [Department of Health Northern Ireland, 2017] as this only provides data up until 2015. A pilot drugs module was included in the 2017/18 Northern Ireland Health Survey and included a question on last year prevalence of usage of New Psychoactive Substances and Synthetic Cannabis, finding less than 0.1% in each category [Department of Health Northern Ireland, written submission of September 2020].

6.5. Unlike some other NPS, self-reported use of SCRA is very low amongst the festival-going population of the UK. In 2018, a sample of 2,250 attendees across 11 English festivals were surveyed. Of these, over three quarters (78%) reported lifetime use of cannabis and over half (58.2%) reported use within the last year. By comparison, self-reported lifetime prevalence of the use of spice was 3.6% and use within the last year was 0.7%. [Measham, 2020].

6.6. Drug treatment services in England have seen a decline in new presentations of problematic SCRA use (referred to in the data as 'predominantly cannabinoid' NPS use). In the reporting year 2015/16 National Drug Treatment Monitoring System (NDTMS) reported a peak of 1,024 new treatment presentations citing problematic SCRA use (0.74% of total treatment population) which fell to 716 (0.54% of total treatment population) in the reporting year 2018/19, in line with the enactment of the PSA [PHE 2019]. Problematic SCRA use of people currently in treatment saw an increase between 2015/16 and 2018/19 in those receiving opioid-related treatment (390 patients using SCRA in 2015/16 to 745 in 2018/19), but this trend was not reflected in people receiving non-opiate (596 in 2015/16 to 296 in 2018/19) or alcohol-related treatments (291 in 2015/16 to 163 in 2018/19) [PHE, 2016; PHE, 2019].

6.7. The use of SCRA within the homeless population has been documented in several studies [Smith and Staton, 2019; Joseph et al 2017, 2019; Ralphs et al., 2017b; Manseau et al 2017]. In interviews conducted by Gray et al (2020), homeless outreach workers and drop-in staff noted recurrently that the use of SCRA was pervasive among their clients, affecting 95 to 99% of their homeless clients. Motivations for SCRA use were similar to those for traditional drugs, namely to escape from the reality of life on the streets and to provide relief from the physical conditions of a street-based lifestyle. Their low cost, ease of access and high potency contribute to popularity in the homeless population [Gray et al., 2020]. The narratives in this study showed that the motivations to use SCRA are distinct from those associated with the recreational use of natural cannabis and serve specific functions in the context of homelessness. One of these is the exploitative and aggressive practices from dealers since the selling of SCRA has moved from the head shops to the street [Ralphs, 2018].

6.8. In 2014, drug use in prisons saw a significant shift from traditional illegal substances and diverted medications to SCRA [Ralphs et al., 2017a]. A 2016 survey of 625 male prisoners across nine prisons in England and Wales found that 33% of participants had used spice in the last month, eclipsing illicitly produced alcohol ('hooch', 15%), cannabis (14%) and heroin (14%) as the most common substances used [User Voice, 2016]. Motivations for use whilst in custody are a combination of potent effects and the ability to avoid detection in urine toxicology [White, 2017; Weinstein et al., 2017; Ralphs et al., 2017a; Gray et al., 2020]. Given the high potency of SCRA, their effective dose is small and the concentrations of drug and metabolites in urine may be very low, making clinical detection more difficult [Cohen et al., 2012]. In addition, commercially available on-site testing kits may not detect prevalent substances and rapidly become outdated when localised markets shift to novel compounds. Although SCRA can be identified by liquid or gas chromatography with mass spectrometry, these tests are complex and expensive, analytical standards may not be available and most secure units do not have access to these methods [Klega and Keehbauch, 2018].

6.9. In the general population SCRA users are predominantly younger adult males who also use other drugs. The Welsh Emerging Drug and Identification of Novel Substances (WEDINOS) reported that between 2017 -2019, the age range of individuals submitting SCRA samples was 16 to 58 years, with 88% being male [WEDINOS, 2020]. The National Poisons Information Service (NPIS) has previously published information on those with suspected SCRA exposure discussed in telephone enquiries to the NPIS between 2011 and 2014. Of these, 80% were male; ages ranged from 12 to 78 years with a median of 21 years and 37% younger than 18 years of age [Waugh et al 2016].

6.10. SCRA-associated deaths registered in England between 2015 and 2019 has demonstrated a significant increase in the proportion of decedents in older age groups, and a decrease of decedents in the younger age groups (data provided by the National Programme on Substance Abuse Deaths [NPSAD]). There has also been a shift in the deprivation decile scores of decedents, with higher scores (meaning decedent from the least deprived areas) not featuring amongst SCRA-associated deaths registered in 2019. This is, however, derived from reports received by NPSAD as of February 2020, so may represent an incomplete number of death registrations for 2019.

7. Prevalent SCRA identified in the UK

7.1. Information on the prevalence of specific SCRA compounds in the UK is available from studies analysing:

- submitted drug product (WEDINOS);
- drug seizures (the Home Office Forensic Early Warning System [FEWS], Manchester Drug Analysis and Knowledge Exchange [MANDRAKE], Eurofins);
- test purchases (TICTAC);
- samples from patients attending hospital with severe toxicity (the Identification of Novel Psychoactive Substances [IONA] study); and,

- post-mortem analysis (LGC Group and NPSAD).

Details are provided in Annex B.

7.2. Over the last five years, the most commonly reported SCRA in these data sets were initially 5F-APINACA (5F-AKB-48) and MDMB-CHMICA (2015 to 2016), with 5F-MDMB-PINACA (5F-ADB), AMB-FUBINACA (FUB-AMB), and 5F-PB-22 becoming more prevalent between 2016 and 2018. Since early 2019 the most prevalent compounds have been 4F-MDMB-BINACA, 5F-MDMB-PICA and MDMB-4en-PINACA. A quantification study conducted by the University of Dundee analysed seized material from Scottish prisons and demonstrated a clear change in SCRA prevalence from 5F-MDMB-PINACA and AMB-FUBINACA (dominant substances identified until late 2018) to 5F-MDMB-PICA and 4F-MDMB-BINACA (dominant substances identified in late 2018 and early 2019) [Norman et al., 2020].

7.3. All of these compounds are captured by the third-generation SCRA generic definition in the MDA and are controlled as Class B substances.

8. Fourth-generation SCRA

8.1. For the purpose of this report, the term ‘fourth-generation’ refers to SCRA which are outside the scope of the current MDA generic definition control.

8.2. Illicit manufacturers continue to explore novel structures that retain CB_1 agonist activity but will evade increasing national and international control on known SCRA materials. Since 2016, the EMCDDA have reported approximately ten new SCRA identifications within Europe each year. Many of these are simple variants of already known materials and are covered within the scope of the UK generic controls. However, other more novel SCRA, which are outside the UK generic, are also being identified. These appear to have been developed from structures rediscovered in published patents resulting from pharmaceutical research intended to develop CB_1 or CB_2 active medicinal products.

[*paragraphs 8.3. – 8.7. have been redacted from the published version of this report*]

8.8. As yet, none of the ‘fourth-generation’ materials have been recorded as making a significant entry into the UK SCRA market, which continues to be dominated by indole and indazole-based materials (see Annex D). There remains an ongoing risk that such compounds may emerge, and continuing vigilance is important, although as CB_1 agonists they would be subject to the provisions of the PSA.

9. Physical health harms

9.1. Interpretation of physical health harms

9.1.1. Interpretation of the physical health harms of SCRA is complicated by the common co-use of other substances and the number of different SCRA that have been misused. Individual SCRA may vary in their pharmacology and adverse effects but there is very limited comparative information available.

9.2. Mortality

9.2.1. Increasing numbers of SCRA-related deaths have been seen in many countries over the last decade [Peacock et al., 2019]. In the UK, the first recorded death was in 2012 and SCRA-related deaths have since increased substantially, with a total of 179 recorded between 2012 and 2019 in England and Wales where a SCRA was mentioned on the death certificate, including 60 in 2018, and 56 in 2019 [ONS, 2020]. Given that SCRA have not always been tested for during investigations of deaths, actual SCRA-related death figures will no doubt be higher.

9.2.2. NPSAD identified 179 deaths where at least one SCRA was found at post mortem in England between January 2012 and September 2020 (see Annex B). Death was considered directly related to the SCRA in 143 (84.4%) of these cases and was deemed to be accidental in all bar one case. NPSAD reported significantly higher proportions of decedents who were living in hostels, were of no fixed abode or incarcerated at time of death in comparison to all deaths reported to NPSAD from England within the same time period (2012 to 2020, as above). However, the largest proportion of deaths (61%) still involves decedents who were living in private residential accommodation. The majority of decedents who had a permanent address at time of death were living in the most deprived areas of England (deprivation deciles 1 to 3; 72% of decedents) [English Indices of Deprivation (2019)]. Decedents were also older in 2018-19 than between 2012 and 2015.

9.2.3. National Records of Scotland (NRS) have reported five SCRA-associated fatalities in deaths registered in Scotland between 2008 and 2018. In one case, AB-FUBINACA was found present at post mortem but was not implicated in the cause of death. In three cases, SCRA compounds (5F-PB-22, AKB48, AB-FUBINACA and 5F-MDMB-PINACA) were recorded as the implied cause of death alongside at least one other implied substance. In the final case, MDMB-CHMICA was recorded as the implied and only cause of death, with no other substances apart from alcohol present at post mortem.

9.2.4. Potential mechanisms for loss of life include cardiac dysrhythmias, seizures, reduced level of consciousness with impaired ventilation and loss of airway reflexes, central nervous system depression and liver or kidney failure. Death may also result from indirect causes that result from intoxication such as trauma or accidents. Additionally, co-misuse with other substances is common and these may cause or contribute to the toxicity observed [Labay et al., 2016; Tait et al., 2016]. Given the limited pharmacodynamic and pharmacokinetic data available, typical SCRA concentrations associated with toxicity or death have not been identified [Giorgetti et al., 2020a].

9.3. Emergency department (ED) presentations and hospital admissions

9.3.1. A study in Louisiana, USA, retrospectively reviewed the medical records of 218 people presenting to three inner city emergency departments (EDs) due to the effects of SCRA between March and April 2014. Whilst the majority (75.7%) of patients were discharged directly from the ED, 12.4% and 11.5% were admitted for medical or psychiatric treatment respectively. The most common symptoms documented were hypertension, tachycardia, agitation, drowsiness, nausea and confusion. A cluster analysis of the reported symptoms demonstrated four symptom 'clusters' in patients presenting following the use of SCRA [Rowley et al., 2017]:

- confusion, hostility, agitation;
- nausea, vomiting, abdominal pain;
- drowsiness; and,
- the absence of these symptoms.

9.3.2. The Euro-DEN Plus network collects information on drug-related ED presentations across participating centres in Europe, based on clinical interpretation of patient reported exposures. This study demonstrated increases in self-reported SCRA presentations to the EDs of the two participating London hospitals (St Thomas' Hospital and King's College Hospital) between 2014 and 2017. Rates of presentation at the only other participating UK hospital (York) were very low [EMCDDA, 2020].

9.3.3. In a study of 179 patients with acute drug toxicity attending the ED at St Thomas' Hospital between January 2015 and June 2015, SCRA were analytically identified in 18 (10%) cases. In most of these, toxicity resolved within eight hours and 14 patients (78%) were discharged directly from the ED without admission to hospital [Abouchedid et al 2017].

9.3.4. An unpublished study of self-reported drug-related presentations at Bristol Royal Infirmary ED between May 2017 and November 2019 showed that 'spice' was the second most frequent drug-related presentation after heroin, without consistent changes in monthly presentation numbers over the period of study.

9.3.5. Hospital activity statistics are available for poisoning involving major drug groups in England [NHS, 2019] but the information collected does not focus specifically on SCRA. Northern Ireland, Scotland and Wales also report hospital admissions according to International Classification of Diseases codes, which places cannabis and SCRA presentations under the same 'cannabinoids' category. These data are also limited by lack of analytical confirmation, as this is not done as part of routine clinical care. Additionally, coding may be inaccurate or not capture all the substances involved in the presentation [Wood et al., 2019]. Hospital admission data also does not capture the larger number of people who present to EDs and are then discharged.

9.3.6. Hospital activity statistics for England demonstrate that poisoning caused by cannabis and derivatives increased from 130 in 2012/13 to 556 in 2015/16, subsequently falling to 363 in 2018/19. Scotland has seen a small increase in

cannabinoid-related hospital admissions from 23 in 2015/16 to 31 in 2017/18, which is thought to be due to the increasing strength of synthetic varieties [PHS, 2020]. These figures, however, include presentations involving cannabis. Equally SCRA-related admissions may also be coded in other poisoning categories such as 'accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances' [NHS Digital, 2019].

9.3.7. Analysis on patient records accessing secondary and tertiary mental-health services across the South London and Maudsley NHS Foundation Trust (SLAM) evidenced that of 1,322 adults detained under Section 136 of the Mental Health Act between 2017 and 2018, 1.9% reported or were suspected of having used SCRA (all men), relative to 19.1% having used cannabis and 11.8% cocaine. New SCRA use (defined as the first recorded use for each patient in the clinical database) increased steeply after 2014 to a maximum in the second quarter of 2016, before a small decline by the end of 2017 [Hobbs et al., 2020].

9.4. Poisons centre referrals

9.4.1. Referrals to poisons centres reflect how commonly healthcare professionals need to seek further information about the substances that their patients may have been exposed to. The UK NPIS reported year-on-year increases in healthcare professional enquiries related to SCRA between 2011 and 2014, with 77% made by those working in acute hospitals. Commonly-reported clinical features in those reporting SCRA use without other substances included tachycardia (17%), reduced level of consciousness (16%), agitation or aggression (10%), vomiting (6.9%), dizziness (6.0%), confusion (4.8%), pupillary dilatation (4.6%) and hallucinations (4.6%). These reported exposures, however, were not analytically confirmed and the precise chemical compounds involved are unknown [Waugh et al., 2016].

9.4.2. Reductions in annual NPIS enquiries related to NPS, of which SCRA and branded products likely to contain SCRA form the majority, have since been reported. These reductions started to occur in the year before the enactment of the PSA in May 2016 [Al-Banaa et al., 2020]. Unpublished information provided by the NPIS (see Annex C) shows that telephone enquiries related to SCRA, and to branded products (likely to contain SCRA), decreased from 108 (6.7% of all enquiries relating to drugs of misuse) and 276 (17.6%) respectively in the financial year 2015/16 to 27 (2.4%) and 16 (1.4%) respectively in 2019/20. TOXBASE® is the poisons information database of the NPIS and reductions were also seen for TOXBASE® accesses by healthcare professionals to SCRA and branded products (likely to contain SCRA) from 5,542 (8.2% of enquiries relating to drugs of misuse) and 8,009 (11.9%) respectively in 2015/16 to 2753 (4.0%) and 1,990 (2.9%) respectively in 2019/20.

9.5. Neurological effects

9.5.1. There have been many reports of seizures induced by SCRA use [Louh and Freeman, 2014]. The onset and frequency of seizures appears variable; there is a report of a seizure within 30 minutes of ingesting JWH-018 [Lapoint et al.,

2011] and another following daily use of PB-22 (QUIPIC) [Gugelmann et al., 2014]. There are also several case reports citing a high seizure frequency from confirmed use of MDMB-CHMICA [Hermanns-Clausen et al., 2018; Hill et al., 2016] or other indazole SCRA [Hill et al., 2018].

9.5.2. Wider clinical review studies have highlighted that SCRA-induced seizures affect a small proportion of users and tend to present as single episode seizures. Of 1,898 SCRA exposures reported to the US poisons centres and recorded on their National Poison Data System between January 2010 and October 2010, 52 (2.25%) seizures were reported; the majority (43) were single episodes, although two patients developed status epilepticus [Hoyte et al., 2012]. In a Centers for Disease Control and Prevention (CDC) case series of ED visits, 14% of visits involved generalised tonic-clonic seizures [White, 2017].

In a systematic review, generalised seizure rates were reported as 3.8% (US poison centre series), 14% (US Emergency Departments) and 15% (paediatric poison centre series). Seizures affected those with analytically confirmed exposure to a wide range of SCRA including JWH-122, JWH-210, JWH-018, PB-22, BB-22, AM-2233 and 5F-PB-22 [Tait et al., 2016].

9.5.3. Acute confusion, agitation, behavioural disturbances, aggression, delirium and hallucinations may also occur and are discussed below under mental health harms. Neurological complications were cited as an underlying cause of death in 3.4% of all SCRA-associated deaths in England reported to the NPSAD (as of August 2020).

9.6. Respiratory effects

Common and clinically important effects of SCRA intoxication include difficulty in breathing and respiratory depression [Weinstein et al., 2017; Akram et al., 2019]. An observational study of analytically confirmed SCRA-related ED presentations reported respiratory depression in 61% of 44 cases of MDMB-CHMICA or AB-CHMINACA toxicity [Hermanns-Clausen et al., 2018]. In a UK study, all three reported cases of isolated MDMB-CHMICA-toxicity developed a reduction in consciousness associated with respiratory depression and type II respiratory failure [Hill et al., 2016]. Pneumonia has also been reported as a consequence of SCRA use [NEPTUNE, 2015; Weinstein et al., 2017]. Respiratory complications were cited as an underlying cause of death in 6.1% of all SCRA-associated deaths in England reported to NPSAD (as of August 2020).

9.7. Cardiovascular effects

9.7.1. Tachycardia (rapid heart rate) and hypertension (high blood pressure) are very common in patients with confirmed SCRA exposure [Tait et al 2016]. In a controlled administration study, increased heart rate occurred within the first hour of inhaling JWH-018 vapour in doses ranging from 2mg to 6.2 mg [Theunissen et al., 2019]. Conversely, there have been some reports of bradycardia (low heart rate) and hypotension (low blood pressure) from SCRA-induced toxicity [Hancox et al., 2020]. Other immediate cardiovascular effects from intoxication include palpitations and chest pain [Cohen et al., 2012; Faircloth et al., 2012; Hermanns-Clausen et al., 2012; NEPTUNE,

2015; Hill et al., 2016; Labay et al., 2016; Weinstein et al., 2017; Hill and Dargan, 2018; Akram et al., 2019; Theunissen et al., 2019; Hancox et al., 2020].

9.7.2. There have also been case reports linking SCRA exposure to prolonged cardiac repolarisation (meaning the heart muscle takes longer than normal to recharge between beats), a condition that increases the risk of a particular form of ventricular tachycardia called '*torsades de pointes'*. Risks are expected to be higher in users who are already taking prescribed drugs that prolong cardiac repolarisation (e.g. some anti-depressants, mood stabilisers, anti-psychotics or methadone) or other illicit substances that affect cardiac repolarisation such as cocaine [Hancox et al., 2020].

9.7.3. More severe cardiovascular events have also been reported from exposure, such as acute myocardial infarction (heart attack), perimesencephalic subarachnoid or intracerebral haemorrhage (bleeding around or in the brain), middle cerebral artery occlusion (stroke), resuscitated cardiac arrest and sudden cardiac death [Tait et al., 2016; Wolff and Jouanjus, 2017; Shanks et al., 2016; Westin et al 2016; Rose et al., 2015]. These severe effects can occur in young people who would not usually be considered at risk of cardiovascular disease. For example, myocardial infarction was described in three males, all aged 16, after smoking the spice product 'K2' [Mir et al., 2011]. Ischaemic stroke was reported in a 25-year-old man with analytically confirmed exposure to ADB-FUBINACA [Moeller et al., 2017] and intracranial haemorrhage was reported in a 31-year-old male and a 25-year-old female [Rose et al., 2015].

9.7.4. Cardiac complications were cited as an underlying cause of death in 6.7% of all SCRA-associated deaths in England reported to NPSAD (as of August 2020) and 23% of the cases described in an international systematic review [Giorgetti et al., 2020a].

9.7.5. CB_1 receptors are widely expressed in both the myocardium and endothelial smooth muscle. The apparent diversity in reported cardiovascular effects from SCRA intoxication may reflect differences in acute versus acute-on-chronic effects, as are reported for THC [Pacher et al., 2017].

9.8. Gastroenterological effects

Nausea and vomiting are common features of SCRA intoxication [NEPTUNE, 2015; Labay et al., 2016; Bhanushali et al., 2013; Hermanns-Clausen et al., 2012, Faircloth et al., 2012; White, 2017; Rowley et al., 2017] and were reported in 13% to 94% of presentations in a systematic review of case series [Tait et al., 2016]. Rare cases of cannabinoid-induced hyperemesis syndrome have been reported from frequent or habitual smoking of SCRA, involving repeated nausea, vomiting and abdominal pain [Hopkins and Gilchrist, 2013; Ukaigwe et al., 2014].

9.9. Genitourinary and renal effects

9.9.1. Acute kidney damage is a widely evidenced feature of SCRA toxicity [NEPTUNE, 2015; Hill and Dargan, 2018; Akram et al., 2019] with many

cases being reported in previously healthy adult males [Bhanushali et al., 2013;Buser et al., 2014; Weinstein et al., 2017; White, 2017]. An investigation conducted by the Wyoming Department of Health (USA) in 2012, identified 16 cases of acute kidney injury associated with SCRA use across six different US states, with no causal link to a single SCRA brand or compound across all the cases. SCRA exposure was confirmed analytically in six of seven cases tested. Renal biopsies were performed in eight patients and findings included acute tubular injury (five patients), acute interstitial nephritis (two patients) or both (one patient); five of the 16 patients were treated with haemodialysis [CDC, 2012].

9.9.2. In addition to direct SCRA-related renal toxicity, there are other potential mechanisms by which SCRA can lead to acute kidney injury. Rhabdomyolysis (rapid breakdown of skeletal muscle) has been seen with SCRA use and this is one assumed mechanism of acute kidney injury [White, 2017], but renal toxicity may occur without elevations in creatine kinase, a key biomarker of rhabdomyolysis [Srisung et al., 2015]. Dehydration associated with vomiting is another likely cause of acute kidney injury in some cases.

9.10. Reproductive effects

Very little information is available on the effects of SCRA use during pregnancy. However, the developing embryo has a functioning endocannabinoid system and may be vulnerable, as cannabinoid signalling is relevant to several reproductive processes, including fertility, preimplantation embryonic development, oviductal embryo transport, implantation, and placentation [Sun and Dey, 2012; Alexandre et al., 2020].

9.11. Haematological effects

Between March and April 2018, more than 150 patients presented to hospitals in Illinois, USA, with coagulopathy associated with elevation of the international normalised ratio after SCRA use. Analysis of serum samples demonstrated the presence of the long acting anticoagulant brodifacoum, thought to be an adulterant of the SCRA products used [Kelkar et al., 2018].

10. Neuropsychiatric health harms

10.1. Intoxication

10.1.1. Many SCRA are full agonists at the CB_1 receptor, some with an extremely high affinity to the receptor binding site, producing intoxicating effects even after exposure to small amounts [Cohen et al., 2012]. The effects of acute intoxication are variable and include euphoria, paranoia, sedation or agitation, with or without disturbance of consciousness (i.e. delirium) [Faircloth et al., 2012; NEPTUNE, 2015; Labay et al., 2016; Abouchedid et al., 2017]. Acute psychotic symptoms (i.e. hallucinations and delusions), are common effects of SCRA use [Weinstein et al., 2017; Hill and Dargan, 2018]. SCRA are five times more likely than THC to be associated with hallucinations. This may occur because their full agonism at the CB_1 receptor inhibits GABA transmission [van Amsterdam et al., 2015], with downstream effects on dopamine [Bossong and Niesink, 2010; Forrester et al., 2012].

10.1.2. Participants in a controlled administration study showed increased levels of confusion, amnesia, dissociation, derealisation, depersonalisation and increased drug liking after taking JWH-018 [Theunissen et al., 2019]. Psychotic symptoms were not observed, however, it was noted much of the active compound settled in the administration pipe and blood levels of participants were very low.

10.1.3. Effect profiles are typically inconsistent between SCRA compounds, due to the variability of affinities to the CB_1 receptor and potential activity at off-target receptors. This inconsistency places people at greater risk of acute toxicity as the compounds and doses involved are commonly unknown so effects cannot be predicted accurately [Peacock et al., 2019]. However, the majority of symptoms reported are self-limiting and of short duration [Abouchedid et al., 2017]. Treatment of agitation and restlessness with benzodiazepines is an acceptable and effective intervention [Cohen et al., 2012; NEPTUNE, 2015] and adjunctive treatment with anti-psychotics such as quetiapine is well-tolerated [Kalk et al., 2016], although clinicians should be mindful of the risk of prolonged cardiac repolarisation in SCRA users [Hancox et al., 2020].

10.1.4. Data from a UK survey on SCRA use showed that users reported a shorter effect and faster time to peak effect than with natural cannabis [Winstock et al., 2013]. Similarly, users presenting for treatment in association with problematic SCRA use in New Zealand reported that SCRA have a short duration of action and quick time to peak onset of action [Macfarlane and Christie, 2015].

10.2. Psychosis

10.2.1. Use of SCRA has been associated with a spectrum of psychotic presentations, from psychotic symptoms in the context of intoxication (see above), to a SCRA-related psychosis that persists for weeks after intoxication [NEPTUNE, 2015; Akram et al., 2019; Weinstein et al., 2017; Faircloth et al., 2012] or months [Hurst et al., 2011]. The quality of evidence is low, comprised mainly of case series and cross-sectional studies, often without toxicological confirmation of SCRA use [Hobbs et al., 2018]. Psychosis is described both in those with and without a preceding history of psychosis [Hobbs et al., 2018; Hobbs et al., 2020]. Early development of psychosis has been described after use of a SCRA only four times, but psychosis may also develop late, e.g. after more than a year of use [Hurst et al., 2011].

10.2.2. Studies of psychiatric in-patients from the USA, Israel, Turkey and Germany have made comparisons of symptoms between psychosis associated with SCRA and cannabis use [Altintas et al., 2016; Bassir et al., 2016; Shalit et al., 2016; Welter et al., 2017]. Common themes are that patients who have used SCRA and experience psychosis are younger and tend to experience more ‘positive symptoms’ of psychosis (e.g. hallucinations and delusions) than cannabis users, whereas cannabis users tend to show more so-called ‘negative symptoms’ (e.g. lack of motivation, social withdrawal). Agitation, aggression and anxiety are reportedly more common in SCRA-related psychosis [Altintas, 2016; Bassir et al., 2016]. Patients who had used SCRA required higher daily doses of antipsychotics (mean equivalent to 11mg

haloperidol) than those who used cannabis (mean equivalent to 6mg haloperidol). Both US and UK studies have found that psychiatric patients with a history of SCRA use need more frequent or prolonged in-patient treatment than patients who do not use SCRA [Bassir et al., 2016; Hobbs et al., 2020]. Case reports indicate that a significant proportion of patients with SCRA-related or precipitated psychosis report suicidal thinking (24% in those without a pre-existing psychotic disorder, 40% in those with a pre-existing psychotic disorder) [Hobbs et al., 2018].

10.3. Mood disorders

There are less data available on mood effects with SCRA use, distinct from changes in effect that accompany psychosis or intoxication. Most data relate to mood changes in intoxication, which can range from a manic-type presentation, excitability, agitation and restlessness, combativeness, irritability to decreased activity. As reported above, suicidal thinking appears common [Cohen et al., 2012; Hermanns-Clausen et al., 2012; Faircloth et al., 2012; NEPTUNE, 2015; Labay et al., 2016; Hill and Dargan, 2018].

10.4. Memory disorders

The controlled administration study described above revealed significantly impaired critical tracking and memory performance in the first hour after inhalation of JWH-018 [Theunissen et al., 2019]. A number of studies have also reported cognitive changes associated with even short or occasional SCRA use, including difficulty in thinking clearly, confusion, sedation and somnolence and memory changes or difficulties [NEPTUNE, 2015; Weinstein et al., 2017]. A study that tested the cognitive functioning of SCRA users at centres in Hungary and Israel found SCRA users to have significantly impaired working and long-term memory and cognitive inhibition compared to cannabis users and non-users [Cohen et al., 2017].

10.5. Anxiety

Panic and anxiety are commonly reported effects of intoxication in user surveys [Faircloth et al., 2012, NEPTUNE, 2015; Weinstein et al., 2017; Akram et al., 2019]. Cohen et al [2017] found significantly higher anxiety scores for SCRA users compared to non-cannabis users.

10.6. Psychological and physiological dependence

10.6.1. In animal studies, prolonged exposure to SCRA results in tolerance to their agonist effects, decreased CB_1 receptor expression and signalling in specific brain regions and withdrawal symptoms upon cessation of drug administration [González et al., 2005]. Approximately 15% of patients report physiological dependence [Vandrey et al., 2012] and often report withdrawal symptoms as the primary reason for continued use. Furthermore, withdrawal symptoms are sometimes reported very soon after exposure and may be difficult to distinguish from acute toxic effects [Rodgman et al., 2014; Cooper, 2016]. As a result of these early symptoms, patients may feel the need to smoke SCRA products at least every hour [González et al., 2005]. Commonly reported withdrawal effects include cravings, headache, anxiety, anger/irritability, depression, insomnia, nausea and vomiting, loss of appetite

and sweating, while abrupt withdrawal may precipitate severe symptoms including tachycardia, chest pain, palpitations, breathlessness and seizures [Vandrey et al., 2012; Weinstein et al., 2017; Klega and Keehbauch, 2018] with the severity of withdrawal features seeming to correspond with the amount of SCRA used each day [Cooper, 2016].

10.6.2. In a qualitative study that interviewed homeless people in Manchester city centre, SCRA were consistently described as more addictive than other substances. Interviewees reported rapid development of tolerance to SCRA that resulted in them using larger quantities each day. Continued use of SCRA was motivated by a desire to avoid the acute and unpleasant symptoms associated with withdrawal, despite being fully aware of the risk of death [Gray et al., 2020]. Symptoms of withdrawal reported by interviewees included hallucinations, paranoia, excessive sweating, severe stomach cramps, diarrhoea, vomiting and loss of appetite.

10.6.3. In a study in New Zealand of patients attending treatment for problematic SCRA use over the course of 2013/14, heavy users reported smoking every one to two hours to avoid withdrawal symptoms. Symptoms reached a maximum at day two and remained at a high level up to day five. Many clients with SCRA withdrawal symptoms required intensive support including medication and admission to an inpatient detoxification unit. Coexisting substance dependence apart from nicotine dependence was low [Macfarlane and Christie, 2015]. The same study reported that SCRA withdrawal symptoms were similar to those of withdrawal from THC but were more severe and did not lessen with the administration of THC. The differences in presentation may reflect the inclusion of extraneous compounds, including amphetamine-like stimulants [Macfarlane and Christie, 2015].

11. Social harms

11.1. Shift in demographic use

11.1.1. While early users of SCRA may often have conformed to Newcombe's (1999) definition of psychonauts, there has been a shift in demographic use of SCRA towards less affluent and vulnerable populations, including homeless people or those in prison [Blackman and Bradley, 2017]. Blackman and Bradley suggest that this is largely because individuals within these groupings tend to experience low self-esteem and minimal self-worth, with negative perceptions of attaining short- or long-term positive outcomes. There is a perception that SCRA have strong intoxicating effects, most notably their perceived propensity to precipitate detachment from reality [Ellsworth, 2019], which therefore drives people to use SCRA as an accessible and affordable way to release themselves from situations that are often unbearable and carry with them a sense of nihilism and despair.

11.2. Harms to individuals who are homeless

11.2.1. There is recognition of the high-risk behaviours precipitated by the use of SCRA and the exacerbation of problems experienced by the homeless individuals who use them. The powerful and rapidly acting psychotropic effects of SCRA coupled with increased accessibility and decrease in price

increases the risks of violence, exploitation and victimisation for the very vulnerable homeless population [Ellsworth, 2019]. Research focussing on use by young people indicated that SCRA were commonly used by the homeless population both to induce sleep and to ease the social and psychological consequences associated with living on the streets [Higgins et al., 2019].

11.2.2. The Homeless Prevention leads for both Bristol, and Bath and the North East Somerset Council, provided anecdotal reports of dealers adopting 'county line' type tactics of coercion to supply the drug into the homeless community. This is where dealers target a network of potential users by pursuing vulnerable individuals who attend recovery groups, dependency units, and areas associated with those in crisis. Once the dealer establishes a relationship with the individual, whether through drug dependency, debt or as part of their 'relationship', they then supply drugs to the users' associated peer group. Councils provided anecdotal reports of dealers with personal accommodation, sleeping rough in the community in an attempt to get housed in hostels to supply the drug ('cuckooing').

11.3. Harms to individuals in custody

11.3.1. The number of prisoners who report that they have developed a drug problem in custody has more than doubled in the last five years and SCRA are highly prevalent and are particularly disruptive in prisons [HM Prison and Probation Service, 2019]. In a study that analysed 354 non-judicial samples seized from Scottish prisons, 41% contained at least 1 SCRA compound. All but one of the SCRA detected in this study belonged to the indole/indazole-3-carboxamide class. The concentrations of individual SCRA detected in these samples were up to 1.17 mg/cm^2 paper. The nature of the substances present and their concentrations varied both between paper samples and across individual sheets.

11.3.2. Social harms in prison resulting from SCRA use include debt, bullying, aggression, violence, and 'spiking for enjoyment purposes' [User Voice, 2016; Blackman and Bradley, 2017; HM Prison and Probation Service, 2019; Higgins et al., 2019; Corazza et al., 2020 Norman et al., 2020]. Regular users can develop tolerance rapidly and this can induce dependence and spiralling debt with dealers within prisons. In addition, bullying behaviours include supply based on certain conditions and targeting individuals to perform certain high-risk tasks. Both bullying behaviours were associated with relieving boredom or expressing dominance [HM Prison and Probation Service, 2019; User Voice, 2016]. A more disturbing aspect of SCRA use highlighted is that spiking individuals with high-dose SCRA has occurred to entertain other prisoners [HM Prison and Probation Service, 2019; Higgins et al., 2019]. Prisoners were provided with SCRA at no cost but were instructed to use an excess amount for the entertainment of other prisoners rather than for testing the effects of the drug for resale purposes within prison.

11.3.3. A striking facet of the discussions of the negative effects of SCRA use in prison was the discourse provided by offenders in a prison-based study by Corazza et al [2020]. The majority of the language used was dark and punctuated with bleak metaphors, for example "going to hell' (a hole in the

floor), a “dark place” (predicting one’s death), “the Devil’s drug”, and “bottom of the barrel” [Corazza et al., 2020].

11.3.4. Scottish prison survey data from 2017 demonstrated that since the enactment of the PSA, there has been a decrease in prisoners reporting NPS use prior to entering prison but an increase of reported NPS use whilst in prison. While these figures are likely to be lower than the actual use of NPS and SCRA in prisons due to response biases, they still demonstrate a shift in the use of NPS in and outside prisons only a year after the enactment of the PSA [Norman et al., 2020].

11.3.5. A smoke-free policy in Scottish prisons was implemented in July 2017, and was fully in effect by the end of 2018, with e-cigarette kits made available to inmates as an alternative. Before the smoking ban, inmates either smoked herbal material mixed with tobacco or would roll up a piece of the SCRA-saturated paper into a cigarette and smoke it. Since the ban, inmates are now known to place pieces of SCRA-infused paper between the heating element and the e-liquid cartridge of the e-cigarette. The potential for differential effects of inhaling SCRA in this way, compared with smoking/pyrolysis, is yet to be explored [Norman et al., 2020].

11.3.6. A shift from SCRA-impregnated herbal materials (64% of submitted samples) to papers and card sprayed with, or soaked in. solutions containing SCRA (14% of submitted samples) has been observed in prisons in England and Wales. This is likely in response to the implementation of prison smoking bans in and to facilitate smuggling [Norman et al., 2020].

11.4. Crime, exploitation and violence

11.4.1. Problematic use of drugs and alcohol may increase the risk of perpetration of interpersonal and acquisitive crimes or exacerbate the risk of falling victim to these offences. Gray et al (2020) identified heavy users who reported spending up to £50 daily, forcing them to commit crimes to fund their habit. Offences to pay for SCRA included low-level acquisitive crime, serious violence and sex work [Gray et al 2020, Higgins et al., 2019; Ralphs et al., 2017a; 2017b].

11.4.2. Likewise, negative or unsafe environments and adverse personal circumstances are strongly connected with an increase in vulnerability to the offences above. The use of SCRA is also specifically associated with vulnerability to low-level acquisitive crime and offences against the person [Gray et al., 2020; Higgins et al., 2019]. According to Ellsworth (2019), one of the negative consequences of SCRA use by people who are homeless includes a significant ‘victimisation-enhancing’ effect. Likewise, Higgins et al (2019) indicated an increased risk of sexual assault experienced by female homeless persons who were under the influence of SCRA. The Homeless Prevention lead for Bristol Council provided anecdotal reports of offenders using spliffs or drinks spiked with SCRA to carry out sexual assaults and robberies. These cases are frequently not reported to the Police because both victim and offender are within the homeless community.

11.4.3. Violence and aggression were also reported in the vulnerable homeless and prison populations because of the impact that SCRA intoxication and withdrawal has on mood. SCRA users reported finding themselves and others agitated, aggressive and violent if they were unable to obtain SCRA, with members of the street homeless community often inciting violence on other members [Gray et al., 2020]. This has also been witnessed in prisons and a reported increase in NPS use in prisons, predominantly SCRA, has been linked to an increase in violence and increased unpredictability in prisoners' behaviour when under the influence of NPS [Norman et al., 2020].

11.4.4. An outbreak of adverse effects related to SCRA use in Mississippi was reported, where 119 patients received care in a single hospital over one weekend in April 2015. Of this group, 32% exhibited aggressive or violent behaviour. SCRA were identified in the serum of 39 of 56 serum samples analysed. The predominant SCRA was MAB-CHMINACA (ADB-CHMINACA), which was found in 33 samples [Kasper et al., 2019].

11.5. Stigma

11.5.1. Research that focused on the pre and post legislative changes in controls of psychoactive drugs in 2010 indicated that some NPS (including SCRA) were often used because they were easily available, less costly and there was less likelihood of stigma linked to a 'drug user identity' [McElrath and O' Neil, 2011; Van Hout and Brennan, 2011]. Recently, the mainstream media has repeatedly highlighted the devastating impact of SCRA use within the homeless population in Manchester. Much of this stigmatising media coverage has ignored the lived experiences and suffering of those whose lives are scarred by poverty and substance abuse [Gray et al., 2020, Alexandrescu, 2019].

11.5.2. In New Zealand, a study of treatment outcomes for SCRA dependency reported that the higher rates of admission to an inpatient setting was linked to the naivety of treatment staff and services about the management of SCRA withdrawal [Macfarlane and Christie, 2015].

11.5.3. The same has been reported in the UK. Evidence submitted by Manchester Metropolitan University highlighted that SCRA users had experienced services that underestimate the support required for this unique drug dependence, causing people using SCRA as their main drug not to present to local drug treatment services.

12. Conclusions

12.1. A large number of SCRA compounds have been prevalent in Europe and in the UK in recent years. Evidence suggests that the main location of synthesis is China.

12.2. SCRA are typically provided as herbal smoking mixtures or sheets of paper sprayed with SCRA solution, which is then smoked by the user. Other methods of administration include vaporising ('vaping') SCRA liquid solutions or ingestion of pills or powders.

12.3. Over the past five years, the most prevalent SCRA compounds identified in the UK are all captured by the current third generation generic control and are therefore classified as Class B drugs under the Misuse of Drugs Act 1971.

12.4. There are examples of ‘fourth-generation’ SCRA that have been encountered in Europe, but these are currently not prevalent in the UK, although continued monitoring for their potential emergence remains important.

12.5. SCRA users are most commonly males and an important minority are under the age of 18 years. There is evidence that the overall prevalence of NPS use, including herbal smoking blends (predominantly SCRA), has declined in the UK since 2016, with consequent reductions in poisons centre referrals. Deaths related to SCRA may be underestimated as these compounds may not be routinely tested for in drug screens. Deaths in which SCRA have been identified analytically increased in frequency up to 2018 and occurred more frequently in winter. Limited data are available after 2018.

12.6. While overall population use of SCRA has declined in recent years use of SCRA is most prevalent in areas of high deprivation and is common in the homeless population and in custodial settings, driven by their 'mind-numbing' effects, low cost and difficulty in analytical detection.

12.7. Since the ACMD last reported on these compounds, further evidence has emerged of the physical, mental health and social harms of SCRA. Adverse effects can include loss of consciousness, sometimes associated with respiratory depression, rapid heart rate, nausea and vomiting, agitation, confusion, behavioural disturbance with aggression and violence, psychosis and seizures. Cardiac dysrhythmias, cardiac arrest, myocardial infarction, stroke and acute kidney failure have also been reported. Longer term effects associated with SCRA use include mood disorders, anxiety, depression and suicidal thoughts, and there is some emerging evidence of adverse impacts on memory and cognition.

12.8. There is also increasing evidence of pharmacological tolerance, dependence and withdrawal effects with SCRA use. SCRA are described by users as more addictive than other substances and users may need to smoke SCRA frequently to avoid withdrawal symptoms. Intensive support including medication and in-patient admission may be needed but drug treatment services may not be available or may not appear suitable to SCRA users.

12.9. Social harms associated with SCRA use include acquisitive crime and sex work to fund purchase of SCRA, violence, exploitation and victimisation. Those under the influence of SCRA may be victims of crime, including sexual assaults. Use in prison may be associated with debt, bullying, aggression, unpredictable behaviour and violence. Prisoners may be exposed to high doses of SCRA, either knowingly or after surreptitious administration ('spiking') for other inmates to be entertained by their effects.

12.10. The ACMD has previously provided advice relevant to populations that have a high prevalence of SCRA use. These reports are ‘Drug-related harms in

homeless populations and how they can be reduced' and 'Custody-Community Transitions (CCT)'. In these reports, recommendations were made by the ACMD for the Government to offer more integrated and targeted services to the homeless with improvements to be made in outreach and peer mentoring programmes in order to engage and retain homeless people in proven treatments. Furthermore, it has been recommended that the services in contact with the homeless should receive better training to obtain skills in dealing with complexity and in retaining homeless drug users in treatment. Further recommendations have also been made to reduce the stigma held by services providers who are employed to support people that are homeless and engaged in substance use.

13. Recommendations

No single approach will be sufficient to reduce SCRA-related harms. Approaches that need to be considered include legal status, surveillance, treatment services, education and training, and research.

Classification under the Misuse of Drugs Act

The ACMD considered different options for classification. In favour of reclassification to Class A, recently encountered examples have been of increasing potency and the severe physical and mental health impacts on users may be comparable to those of some Class A drugs. There have also been increases in SCRA-associated deaths since previous recommendations were made. The compounds have particularly traumatic effects on vulnerable communities and evidence of severe harms may be harder to find because use is now predominantly in marginalised populations, where data collection is more challenging. SCRA use may cause agitated psychosis commonly needing physical restraint and this may be equivalent to the effects of methamphetamine or crack cocaine. SCRA have a significant impact on the general population including young people and reclassification would give further powers to support law enforcement to interrupt supply.

Arguments for maintaining SCRA in Class B are that most of the harms described in this report were covered by previous ACMD reports and there is insufficient good quality evidence of new or more severe harms to warrant a higher classification. While the potential impact on marginalised populations is a clear concern, overall population use and consequently the incidence of many of the harms has decreased in the last few years, suggesting that Class B remains appropriate. This would also prevent increased possession penalties for already beleaguered homeless populations. It was also acknowledged that one motivation for use was the reduced risk of detectability (i.e. in mandatory drug tests), which would not be impacted by reclassification.

Having considered these arguments, the ACMD recommend that SCRA should remain in Class B. There was currently not enough evidence of

variations in harms between different examples to recommend different levels of classification would be appropriate for individual SCRA.

<u>Recommendation 1</u>: The ACMD has reviewed the available evidence of harms from SCRA use and recommends that the current classification of all SCRA controlled by the MDA, either under the synthetic cannabinoid generic definition or listed by individually by name remains appropriate. These substances should therefore continue to be controlled under Class B of the Misuse of Drugs Act 1971.

Lead: The Home Office

Measure of outcome: SCRA continue to be included under Class B of the Misuse of Drugs Act 1971

Scheduling under the Misuse of Drugs Regulations 2001

Synthetic drugs interacting with the cannabinoid system or compounds without cannabimimetic activity that might have been captured by the 'third-generation' generic definition may offer potential therapeutic benefits and the current Schedule 1 status of SCRA might create a barrier to research on such compounds of interest. However, this has largely been addressed by the 2019 legislative changes and the ACMD will provide separate advice on barriers to research related to SCRA. No information is available about compounds captured by the 'third-generation' generic definition in early pharmaceutical development but no examples of SCRA that demonstrate therapeutic value or that are known to be involved in clinical trials were identified in this review.

Research is possible involving compounds in Schedule 1, provided the appropriate Home Office licence is in place. The ACMD is able to review the appropriate schedule of specific named products when evidence has been obtained of therapeutic benefit. In the absence of such evidence, a change to Schedule 2 for the group as a whole or for any individual SCRA does not fit with current scheduling guidance and is therefore not recommended.

<u>Recommendation 2</u>: The ACMD has reviewed potential uses of SCRA and recommends that the current scheduling of all SCRA in the Misuse of Drugs Regulations 2001, either under the synthetic cannabinoid generic definition or listed by individually by name remains appropriate. These substances should therefore, continue to be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 on the grounds that they currently have no recognised medicinal use.

Lead: The Home Office

Measure of outcome: SCRA continue to be included under Schedule 1 of the Misuse of Drugs Regulations 2001.

Surveillance

Currently available user surveys have limited data on NPS and should be updated regularly to ensure that they collect data on emerging substances of misuse.

At any one time, a limited number of SCRA tend to dominate the UK SCRA market. However, the individual types of SCRA in circulation within the UK have changed significantly over time, often in response to legislative changes in other jurisdictions. To ensure that the prevalence of SCRA is monitored, that analytical toxicology facilities are aware of which materials are in circulation and that medical practitioners are informed of which materials are likely to have been used, surveillance should be commissioned to monitor the prevalence and type of SCRA in drug seizures, waste water and in biological samples from users.

There is also a need for analytical surveillance of drug and biological samples for accurate determination of the substances involved in episodes of misuse. This requires sophisticated analysis and suitable reference materials as well as adequate and consistent funding.

Analysis of post mortem samples provides particularly valuable information on the causes of fatal drug intoxication, but the compounds that are tested for are inconsistent and may vary geographically. Comprehensive analysis that includes all possible contributing compounds is expensive and it would be inappropriate for this to be applied universally for all drug related deaths. However, it would, for example, be justified for cases where a clear toxicological cause of death has not been identified. Therefore, it would be beneficial to develop national standards for drug testing by coroners and procurators fiscal to improve consistency. There is also a need for information to be available about the specific compounds currently being misused in the UK to inform analysis in individual cases.

In relation to SCRA specifically, there is an ongoing risk that compounds that evade the current 'third-generation' generic definition may be detected in UK drug markets in the future. The evidence does not currently suggest significant misuse of these 'fourth-generation' SCRA in the UK and those with CB_1 agonist properties are captured by the PSA. Control of any of these compounds via the MDA is therefore not currently warranted, although ongoing monitoring for their appearance remains essential.

To facilitate improved analytical detection, toxicology laboratories require assistance to underpin their ability to detect and identify SCRA. FEWS has previously provided this type of support to forensic drug laboratories, including the provision of reference materials necessary to support identifications in seized materials. SCRA reference materials for toxicology laboratories, including a wide range of metabolites and stable-isotope labelled materials are now available, but there are so many that obtaining a full range to hold as a library would be too expensive for most laboratories.

<u>Recommendation 3:</u> National user surveys should explicitly collect or continue to collect data on emerging substances of misuse. These should include the Crime Survey for England and Wales (CSEW), Scottish Crime and Justice Survey (SCJS), the Northern Ireland Health Survey series, and Smoking, Drinking and Drug use among young people in England (SDD) survey.

Leads: The Home Office, Justice Directorate (Scotland), Department of Health (Northern Ireland), NHS Digital

Measure of outcome: Increased information about use of NPS subtypes (including SCRA) in published reports.

<u>Recommendation 4</u>: Guidance on a UK-wide minimum standard set of post-mortem toxicology tests is developed for apparent drug-related deaths, to include testing for novel psychoactive substances. This would include agreed reporting standards.

Leads: The Chief Coroner's Office for England and Wales, the Coroners Service for Northern Ireland, the Crown Office and Procurator Fiscal Service Scotland, the UK and Ireland Association of Forensic Toxicologists, Faculty of Forensic and Legal Medicine, and local authorities.

Measure of outcome: The development and publication of a national standard that facilitates a consistent approach to post-mortem toxicology testing in apparent drug-related deaths is taken across the UK, where possible.

<u>Recommendation 5;</u>

a) **Toxicology analysis of samples from deaths thought to be drug-related, where there is no obvious toxicological cause, should include prevalent SCRA, including 'fourth-generation' SCRA reported in global drug markets. Where this testing is not possible because of inadequate resources, low sample volume, or another reason, toxicology reports should include a clear statement that a SCRA test has not been carried out. If SCRA testing has been carried out, a list of the compounds included in the test should be included in the toxicology report. Information on prevalent compounds should be available to coroners and forensic toxicologists, who should take this into account when deciding on the substances to be tested for. Forensic toxicologists should discuss important limitations of their analysis in their reports to the coroner.**
b) **Local partnerships undertaking learning reviews of drug related deaths within their populations to be clear about the extent to which SCRA have or have not played a role in the death. Furthermore, to identify any local trends and patterns, and respond accordingly to reduce the future incidence of harm and deaths from SCRA.**

Leads: The Chief Coroner's Office for England and Wales, the Coroners Service for Northern Ireland, the Crown Office and Procurator Fiscal Service Scotland, the UK and Ireland Association of Forensic Toxicologists, the Faculty of Forensic and Legal Medicine, Public Health England (PHE), the

Home Office Forensic Early Warning System (FEWS), and local drug related deaths review partnerships.

Measure of outcome: All post-mortem toxicology drug testing in apparent drug-related deaths where there is no obvious toxicological cause to include testing for prevalent SCRA or a clear statement that testing has not been done. This will enable those monitoring SCRA-related deaths to interpret case numbers as a percentage of those tested for SCRA. Forensic toxicology reports contain a clear statement about the compounds that have been tested for and the limitations of the analysis used should be discussed.

Recommendation 6: The Forensic Early Warning System (FEWS) should provide support to improve analytical capabilities of toxicology laboratories nationally. Toxicology laboratories should have access to:

(a) regularly updated information about SCRA that are currently prevalent in the UK, and reference materials (as provided by FEWS), and/or

(b) a centralised screening service that can offer technical assistance when needed for the accurate identification of the SCRA present in relevant samples they process.

Adequate resource should be made available to FEWS for these functions.

Leads: FEWS, the Home Office

Measure of outcome: Analytical toxicology laboratories to be able to identify and report on the presence or absence of currently prevalent SCRA in post mortem samples.

Recommendation 7: Surveillance should be commissioned to establish improved systematic monitoring of the prevalence of novel psychoactive substances, including SCRA, in relevant samples across the UK. These might include:

a) drug seizures;
b) waste water (including targeted studies); and
c) biological samples from users.

This surveillance should encompass those with non-fatal toxicity, including those attending emergency departments, mainstream drug services and special or vulnerable populations, such as the homeless and prisoners.

Data should be consolidated and made available to those responsible for the investigation of drug-related deaths as well as authorities responsible for advising on clinical management and public health protection.

Leads: Public Health England (PHE), the Home Office, the Ministry of Justice (England and Wales), the Department of Justice (Northern Ireland), the Justice Directorate (Scotland).

Measure of outcome: Regularly published information on the prevalence of NPS including SCRA detected in these populations. Early detection of emerging NPS including SCRA to inform public health policy.

Enhancing local drug treatment services

SCRA users often do not engage with treatment services and there is a need for more assertive outreach to improve access to treatment within a holistic package of care. More assertive outreach was recommended previously by the ACMD in its report **'**Drug-related harms in homeless populations and how they can be reduced'. Opportunities should be taken to identify and refer clients as they present to services including emergency departments. Appropriate drug treatment services should be commissioned and available in areas where SCRA use is prevalent, with local contracts stating that this group is eligible for treatment as currently these services may concentrate on problematic heroin or alcohol use. Services also need to be provided by prison and probation services, providing support for prisoners with problematic drug use, including SCRA, while in custody and after release, as previously recommended in the ACMD report on 'Custody-Community Transitions (CCT)'.

Treatment services should also be aware of the burden of SCRA use amongst their clients. Clear referral and care pathways are needed, including protocols for observation or referral of those with SCRA intoxication as well as for the management of withdrawal, including in prisons. Tailored psychosocial and social care interventions should be developed and assessed and made available, with examples of best practice being shared. Service users who report psychotic symptoms or suicidal thoughts should be reviewed by an appropriately trained mental health professional. The prison and probation services of the UK should develop and extend services that provide face-to-face, individualised support to prisoners who have drug problems in the run-up to release and through the transition to the community.

<u>Recommendation 8</u>: Assertive outreach teams should have the competencies and capacity to allow earlier identification and referral of those with problematic SCRA use. Community, residential and custodial treatment services should be specifically commissioned and appropriately funded to work with SCRA users. Treatment providers should survey existing clients to establish the burden of SCRA use for those already in treatment.

Commissioners and treatment providers should work with other relevant organisations to ensure that SCRA-specific care pathways and structured tools are available. This should include assessment for signs of dependence and physical health harms, management of psychosis and withdrawal, and interventions to minimise the social impact of

SCRA use. Examples of good practice should be shared between services and availability and use of these tools should be audited.

Leads:

England

Public Health England (PHE), the Department of Health and Social Care (DHSC), the Association of Directors of Public Health, Local Government Association (commissioners of community and residential treatment), NHS England (commissioners of custodial treatment), treatment providers (for example through Collective Voice and NHS Addictions provider alliance), Care Quality Commission (auditing body)

Northern Ireland

Public Health Agency, Health and Social Care Board (commissioners of community and residential treatment), South Eastern Health and Social Care Trust, Northern Ireland Prison Service (commissioners of custodial treatment), Treatment providers (through Health and Social Care Trusts), Regulation and Quality Improvement Authority (auditing of treatment providers)

Scotland

Alcohol and Drug Partnerships (commissioners of community and residential treatment; commissioners of treatment providers), NHS Scotland (commissioners of custodial treatment), Care Inspectorate (auditing of treatment providers)

Wales

Area Planning Boards, NHS, Public Health (commissioners of community and residential treatment), Dyfodol (G4S), Police and Crime Commissioners, NHS (commissioners of custodial treatment), Area Planning Boards (commissioners of treatment providers), NHS, third sector providers (such as Barod, Cais, WCADA, Kaleidoscope), Care Inspectorate Wales (auditing of treatment providers)

Measure of outcome: Written management pathways available and practised by all providers.

Training and education:

As these compounds are most prevalent in specific communities, they may not be widely understood by professional staff encountering users. These would include staff in acute and in mental health trusts, prison staff and those working with homeless populations. Users themselves may also be unaware of the harms associated with use of these compounds.

<u>Recommendation 9</u>: Training should be provided to all professional staff who may encounter SCRA users and delivery of this training should be subject to audit. Educational material should also be available that is tailored for SCRA users.

Leads: The Department of Health and Social Care (DHSC), Health Education England, Care Quality Commission (England), the Regulation and Quality Improvement Authority (Ireland), the Care Inspectorate (Scotland), the Care Inspectorate (Wales), the Chief Social Worker for Children and Families and the Chief Social Worker for adults.

Measure of outcome: Care organisations have a training log available to demonstrate that relevant staff have undergone appropriate training. Educational material available for SCRA users.

Research

Although a substantial amount of research has been published since the ACMD last reviewed this group of drugs, there remain areas where further research would be useful to inform policy and the clinical management of acute and longer-term health effects.

<u>Recommendation 10</u>: Research involving SCRA should be commissioned, including (but not limited to) the following areas:

- pharmacology and toxicology of prevalent and emerging SCRA;

- optimum management of acute SCRA intoxication, including evaluation of potential therapies;

- development of accurate field tests for SCRA that can adapt to changes in the drug market;

- longer-term health effects of SCRA use, including effects on memory and cognition and on reproductive and foetal health; and

- development and validation of structured tools for rating intoxication and withdrawal states.

Leads: National Institute for Health Research (NIHR), Public Health England

Measure of outcome: A themed topic to be developed by NIHR and any other relevant bodies in the next 12 months.

Annex A: International legal status of SCRA

Health and Social harms from SCRA use have been witnessed across the world, driving demand for a political and public health response. To date, the response has largely been in the form of prohibition policies aimed at restricting the supply and use of SCRA rather than service reform [Gray et al., 2020].

International controls

At an international level, an increasing number of SCRA are being controlled under Schedule II of the 1971 United Nations (UN) Convention on Psychotropic Substances. Materials controlled under this Convention are set out in the annually-updated 'List of Psychotropic Substances under International Control' (the 'Green List'), issued by the International Narcotics Control Board (INCB). Signatories to the Convention are required to include all listed substances within their national system of control.

Potential new materials for international control are assessed on an individual basis by the World Health Organisation's Expert Committee on Drug Dependence (WHO ECDD). This evaluation requires a firm evidential base and only a limited number of substances are considered each year. When materials are added to the 'Green List', all signatories to the Convention are required to bring them under their national control system within six months of the announcement of the UN decision. This usually corresponds to an announcement by the UN in the spring of each year, requiring national control by the autumn.

The December 2019 'Green List' includes 14 SCRA, of which four (indicated by *) were added during 2019:

AB-CHMINACA;

*ADB-CHMINACA;

5F-MDMB-PINACA (5F-ADB);

AB-PINACA;

AM-2201;

5F-APINACA (5F-AKB-48);

*CUMYL-4CN-BINACA;

*AMB-FUBINACA (FUB-AMB or MMB-FUBINACA);

*ADB-FUBINACA;

JWH-018;

MDMB-CHMICA;

5F-PB-22;

UR-144; and

XLR-11 (5F-UR-144).

The 2020 announcement of new additions to the ‘Green List’ included a further four SCRA, which are required to be under national control systems by autumn 2020:

AB-FUBINACA;

5F-AMB-PINACA (5F-AMB, 5F-MMB-PINACA);

5F-MDMB-PICA; and

4F-MDMB-BINACA.

One other SCRA that was assessed, APINACA (AKB-48), was not added to the list but is being kept under surveillance.

All the UN listed materials are controlled under the UK’s Misuse of Drugs Act 1971.

National controls

In addition to the requirement to control the materials specified by the UN Convention, individual countries can place other materials of national concern under their national control systems. This can be done either by naming individual substances (e.g. China), or by means of broader analogue (e.g. USA) or generic (e.g. UK, Germany) controls. Some relevant national responses are considered below.

China

China is widely acknowledged as the main producer and exporter of SCRA. As a signatory of the UN Drug Conventions, materials under UN controls are controlled within China. In addition, China has brought an extensive range of other NPS, including SCRA, under national control. The impact of these controls on production within China can significantly influence the range of materials encountered in other parts of the world. In October 2015, China placed 116 NPS under control, including the following individually listed SCRA:

5F-ABICA;

5F-AB-PINACA;

5F-ADBICA;

5F-AMB-PINACA (5F-AMB);

5F-APINACA;

5F-PB-22;

5F-UR-144;

A-796,260;

A-834,735;

AB-CHMINACA;

AB-FUBINACA;

AB-PINACA;

ADBICA;

ADB-PINACA;

AM-1220, -1248 and -2233;

APICA;

APINACA;

CB-13;

CUMYL-THPINACA;

EAM-2201;

FUB-JWH-018;

FUB-PB-22;

JWH-007, -015, -019, -081, -122, -203, -210 and -370;

MAM-2201;

MDMB-CHMICA;

MDMB-FUBINACA;

PB-22 (QUPIC);

PX-2 (5F-APP-PINACA);

RCS-4;

STS-135 (5F-APICA); and

UR-144.

All the listed materials are controlled under the UK's Misuse of Drugs Act, with the exception of CB-13, which is reported to have poor CNS penetration.

In August 2018, China added the following 8 SCRA to their nationally-controlled list:

ADB-CHMINACA

ADB-FUBINACA

AMB-CHMICA

AMB-FUBINACA (FUB-AMB)

FUB-APINACA

BIM-2201

NM-2201

5F-MDMB-PINACA (5F-ADB)

USA

The USA's system of drug control is built around two key elements:

- the Controlled Substances Act 1970 (CSA), which individually lists controlled materials, and,
- the Controlled Substance Analogue Enforcement Act 1986 ('the Analogue Act') which extends control to cover materials that are similar both in structure and effect to materials listed in Schedules I or II of the CSA.

The profusion of novel structures encountered as NPS, and particularly as SCRA, and the requirement of the Analogue Act to be able to demonstrate similarity of structure to an already-controlled material, has meant that a series of additions to the CSA have been made which provide points of comparison for the many SCRA variants being identified within the NPS market.

The CSA currently (as of May 2020) lists 42 individual SCRA as Schedule I materials, including 17 of the 18 of the UN 'Green List' materials. The US authorities regard the 18th material, 4F-MDMB-BINACA, as a positional isomer of 5F-AMB (5F-MMB-PINACA) and therefore not requiring a separate entry.

The other materials listed in Schedule I of the CSA are:

FUB-144;

5F-CUMYL PINACA;

ADB-PINACA;

AM-694;

AKB48 (APINACA);

CP-47,497 and its C8 homologue;

5F-EDMB-PINACA;

JWH-019, -073, -081, -122, -200, -203, -250 and -398;

MDMB-FUBINACA;

MMB-CHMICA;

FUB-AKB48;

NM-2201;

PB-22 (QUPIC);

RCS-4 and RCS-8; and

THJ-2201

All the US listed materials are controlled under the UK's Misuse of Drugs Act.

Germany

Germany lists an extensive range of individual SCRA (more than 60) within Schedule II of their Federal Narcotics Act (Betaubungsmittelgesetz, BtMG).

In addition, it has recently adopted generic controls on several types of NPS, including SCRA, as part of its New Psychoactive Substances Act. The German SCRA generic is similar to the UK's, addressing materials made up from the four structural elements of typical SCRA, but is broader in scope, as it reflects some recently reported structural variants that are outside the UK's current generic.

Core structures that are covered by the German generic but not the UK's include carbazole and carbolin-1-one, as well as some additional azaindole and azaindazole positional variants. This extends the scope of its control to cover SCRA recently reported by the EMCDDA such as MDMB-CHMCZCA, EG-018, EG-2201 and Cumyl-PeGaClone.

In addition, a separate section of the German generic covers 3-sulphonylamido benzoate and 3-sulphonamido benzamide-based SCRA such as QMPSB derivatives, a group of materials that is not addressed by the UK generic.

Although the German generic is potentially extremely broad in scope, limitations are placed on the maximum size or mass of some components, which serve to limit the coverage of their control.

Annex B: Summary of most frequently identified SCRA in the UK

Welsh Emerging Drug and Identification of Novel Substances (WEDINOS)

Funded by Public Health Wales, WEDINOS provides laboratory testing of samples volunteered by the community. Samples are received anonymously by post from either individuals or participating organisations such as substance misuse services, housing and hostels, youth clubs and young people's services, education, night clubs and bars, mental health community teams, local authorities, the Ambulance Service and the Police. Test results are then made publicly available online.

Between January 2017 and December 2019 WEDINOS identified 19 SCRA on 623 occasions, from 62 different post code areas. These represent 6.25% of all substance identifications by WEDINOS during this time period. Of these, the most frequently identified compounds were 5F-MDMB-PINACA (5F-ADB, 269), 4F-MDMB-BINACA (142) and AMB-FUBINACA (118).

Since December 2019, there has been a decrease in the number of samples containing AMB-FUBINACA, paralleled by an increase in the prevalence of 4F-MDMB-BINACA. 5F-MDMB-PINACA was the sixth most commonly identified substance within all samples. SCRA were most frequently identified within samples provided by criminal justice (in particular the prison estate) and homelessness services [WEDINOS, 2020].

TICTAC Communications Ltd.

TICTAC is a provider of drug identification and drug information to the criminal justice and healthcare sectors. For this report, TICTAC provided analysis information from herbal, powder and liquid products that had been test-purchased between 2015 and 2017. These purchases were primarily from websites, but some were from shops and most samples purchased were herbal mixtures. Purchased samples typically contained more than one SCRA and the most frequently notified compounds (as a % of total notifications) were 5F-APINACA (35.3%), 5F-PB-22 (18.5%) and 5F-MDMB-PINACA (5F-ADB) (8.2%, first identified in 2016).

TICTAC also submitted analysis results from prison seizures. Many of the samples analysed contained more than one SCRA but the range of compounds identified was limited. In 2017, the most frequent compounds appearing in analysis were (as a percentage of total notifications) were MDMB-CHMICA (30.7%) and 5F-MDMB-PINACA (5F-ADB) (29.4%). By 2018, this had changed to 5F-MDMB-PINACA (5F-ADB) (46.2%) and AMB-FUBINACA (26.3%) and subsequently 5F-MDMB-PINACA (5F-ADB) (63.6%) and AMB-FUBINACA (14.8%) in 2019.

Forensic Early Warning System (FEWS) NPS Collection Plans

As part of the FEWS project, the Defence Science and Technology Laboratory (DSTL) has collected and analysed samples of suspected NPS in non-attributable samples

Prison Collection Plan

DSTL collected and analysed samples of suspected NPS in non-attributable samples recovered from 14 participating prison grounds between March 2018 and February 2019. Of the NPS identifications, 99% were SCRA. The most prevalent NPS in the collection were 5F-MDMB-PINACA and AMB-FUBINACA, which accounted for 83% of the NPS occurrences.

In the following financial year (April 2019 to March 2020) DSTL analysed 1,087 non-attributable samples collected from 8 different prisons in Surrey, Suffolk and Somerset. There were 11 different SCRA identified in these samples and SCRA accounted for 93% of total NPS occurrences. The four most commonly identified SCRA (with frequency represented as percentage of total NPS notifications) were 5F-MDMB-PICA (28%), 5F-PB-22 (23%), 5F-APINACA (5F-AKB-48) (13%) and APINACA (AKB48) (13%).

UK Border Force seizures

This collection was conducted to gather intelligence on the type and number of NPS that are entering the UK via Fast Parcel and postal deliveries. In its first year, the FEWS programme collected and analysed 149 samples from five Fast Parcel and postal hubs between April 2018 and February 2019. From this sample, four different SCRA compounds were identified, the most prevalent being 5F-MDMB-PINACA.

The following year (April 2019 to March 2020) saw a significant reduction in samples received; There were 28 samples collected and analysed from a single UK Border Force location and in this collection three SCRA were identified (ADB-BUTINACA, 5F-MDMB-PICA and MDMB-4en-PINACA).

Vulnerable group collection plan

DSTL collected and analysed samples of suspected NPS samples seized between March 2018 and February 2019 by the police from the homeless community and non-attributable samples found on the premises at three Immigration Removal Centres. From 109 samples recovered, mostly from Immigration Removal Centres, there were 52 NPS notifications, 35 of which were 5F-MDMB-PINACA.

Eurofins

Eurofins is a forensic service provider for the police, law enforcement agencies, solicitors and barristers and corporate organisations in the UK and abroad. In samples from police seizures between July 2019 and June 2020, three compounds have dominated, making up more than 75% of the notifications collectively. These

were 4F-MDMB-BINACA, MDMB-4en-PINACA, and 5F-MDMB-PICA, with MDMB-4en-PINACA making up 33% of all SCRA notifications in this time period.

Manchester Drug Analysis and Knowledge Exchange (MANDRAKE)

MANDRAKE is a fixed Home Office licenced resource, based at Manchester Metropolitan University (MMU, Department of Natural Sciences), working in partnership with the Greater Manchester Police (GMP) to facilitate rapid, robust chemical analysis services to inform intelligence-gathering as opposed to legal action (i.e. prosecutions). During the period between February 2017 and February 2018, they tested 75 suspected SCRA herbal mixtures seized by the GMP. Across the 75 samples, analysis frequently found three distinct SCRA present (5F-MDMB PINACA (5F-ADB), MDMB-CHMICA and AMB-FUBINACA), with the most prevalent SCRA being 5F-MDMB PINACA (appearing in 77% of the samples). These three compounds were largely seen on their own (in 85% of samples), but two compounds were sometimes found in combination (in 11% of samples) – which may be associated with a lack of process control during manufacture and/or blending of samples. Only 4% of samples contained no psychoactive or controlled ingredients.

A wide variation in SCRA concentrations were identified across samples tested. Over the course of the 12-month period, analysis showed a significant decrease in the concentrations of samples seized. For example, of the eight samples of 5F-MDMB PINACA (5F-ADB) identified in seizures (not in combination) in April 2017, the average concentration was approximately 35 mg/g. In contrast, of the four samples of 5F-MDMB-PINACA (5F-ADB) identified in seizures (not in combination) in September 2017, the average concentration was approximately 2.9 mg/g.

LGC Group

The Sport and Specialised Analytical Services laboratory, part of the Standards division of LGC Group, formerly the Laboratory of the Government Chemist, is a laboratory providing specialist toxicology services in the UK. For this report it provided data on NPS and NPS metabolites identified from post-mortem cases with suspected NPS use. Samples originated from various sites across the UK including the Leicester Royal Infirmary Toxicology Unit, Eurofins Forensics and the Great Northern Hospital, Sheffield.

In this data set the most prevalent compounds identified in post mortem cases were 5F-APINACA (5F-AKB-48) and MDMB-CHMICA in 2015/16. From early 2016, this then shifted to 5F-MDMB-PINACA (5F-ADB) and AB-FUBINACA until the start of 2019 where 4F-MDMB-BINACA and 5F-MDMB-PICA became the most frequently identified in analysis. This was then followed by a high prevalence of MDMB-4en-PINACA in late 2019 and early 2020.

It is worth noting that AB-FUBINACA, AMB-FUBINACA and EMB- FUBINACA converts to the same product in the body so is indistinguishable in post-mortem

metabolite analysis. However, due to the higher prevalence of AMB-FUBINACA in seizure data (as evidenced by data provided by WEDINOS, TICTAC, FEWS and MANDRAKE) it has been assumed that these metabolite findings were due to AMB-FUBINACA use.

The Identification of Novel Psychoactive Substances (IONA) study

The NIHR and PHE-funded IONA study has been analysing samples from adults (aged 16 or over) presenting to participating hospitals in England, Scotland and Wales with severe acute toxicity after suspected NPS exposure since March 2015. By April 2020, analytical information was available for 579 study participants with suspected NPS exposure. In this cohort, SCRA were the most common NPS group identified, found in samples from 186 patients (32%). The most common examples identified were 5F-MDMB-PINACA (5F-ADB, 14.7%), MDMB-CHMICA (9.8%) and AMB-FUBINACA (FUB-AMB, 9.7%). The proportion of patients where a SCRA was detected in at least one sample has reduced since 2016, with temporal changes differing between the most commonly identified SCRA. Reductions have been seen for MDMB-CHMICA since 2015, increases followed by early reductions for 5F-NPB-22 and 5F-PB-22 (highest numbers in 2016), and increases followed by later reductions for 5F-ADB and FUB-AMB (highest numbers in 2017). During 2019 and early 2020, increasing numbers of exposures were identified involving FUB PB-22 (QUFUBIC), 4F-MDMB-BUTINACA (4F-MDMB-BINACA), 5F-MDMB-PICA and MDMB-4en-PINACA. Of note, SCRA were usually found in combination with other drugs of misuse, with several separate examples commonly identified in samples from the same person, often alongside other substances.

National Programme on Substance Abuse Deaths (NPSAD)

NPSAD collates information from coroners about deaths related to drugs in addicts and non-addicts in England, Wales and Northern Ireland. To be recorded on the NPSAD database, there must be the presence of one or more psychoactive substance(s) directly implicated in the death, a history of dependence or abuse of drugs or the presence of controlled drugs at post-mortem. NPSAD receives drug-related death reports from over 80% of coroners. Cases are recorded by year of death, so figures are subject to change as more reports are confirmed.

In the years 2016 to 2018, AMB-FUBINACA and 5F-MDMB-PINACA dominated in drug-related-deaths in England where SCRA were detected at post mortem (see Table 1). This was particularly true in 2018 where these compounds made up 24% and 64% of the SCRA identifications in SCRA-associated deaths reported to NPSAD (where SCRA was either detected at post-mortem and/or implicated in cause of death).

Appearance of these two substances dropped in 2019, where toxicology reports identified two new compounds, 5F-MDMB-PICA and 4F-MDMB-BINACA, as the most

prevalent SCRA found at post mortem; each accounting for 24% of the SCRA identifications in SCRA-associated deaths reported to NPSAD.

Table 1: SCRA compounds detected at post-mortem and/or implicated in cause of death, in drug-related deaths in UK.

	2015				2016				2017				2018				2019			**TOTALS***
	NI	S	E		NI	S	E		NI	S	E		NI	S	E		NI	S	E	
APINACA (AKB-48)						1	1													2
BB-22			1																	1
AB-CHMINACA			2		1															3
5F-APINACA (5F-AKB-48)			3		1		1								1					6
5F-PB-22	1		3				1								2				1	8
MDMB-CHMICA			4		1	1	1		2		4				1					14
AMB-FUBINACA** (FUB-AMB or MMB-FUBINACA)							3				18			2	18				2	43
5F-MDMB-PINACA (5F-ADB)							7		1		32		1	1	48		1		3	94
AB-PINACA							1													1
MMB-CHMICA							1				1									2
5F-MDMB-PICA															2				7	9
4F-MDMB-BINACA															2				7	9
APP-BINACA															1					1
5F-MMB-PICA																			2	2
4F-MDMB-PICA																			3	3
5F-AMB PINACA (5F-AMB or 5F-MMB-PINACA)																			3	3
MDMB-4en-PINACA																			1	1

Notes for Table 1:

*Figures represent the number of detections of SCRA at post mortem. Figures do not represent the total number of SCRA-associated deaths as there are examples of multiple SCRA being detected post mortem.

** AMB-FUBINACA may also include notifications for AB- and EMB-FUBINACA as post-mortem metabolite analysis has limited capability in differentiating between these compounds.

(NI) Northern Ireland
SCRA detected at post-mortem and/or implicated in cause of death in cases reported to the Northern Ireland Statistics Research Agency (NISRA) up until August 2020. Years correspond to the date the death was registered.

(S) Scotland
SCRA detected at post-mortem and/or implicated in cause of death in deaths registered in Scotland between 2008 to 2018. Data provided by NRS. Years correspond to the date of death registration.

(E) England and Wales
SCRA detected at post-mortem and/or implicated in cause of death in cases reported to NPSAD up until September 2020. Years correspond to the date the death occurred. A further 10 detections have been reported in 2020: four detections of 4F-MDMB-BINACA, two detections of MDMB-4en-PINACA and four detections of 5F-MDMB-PICA.

NPSAD reported a single case occurring in Wales where a SCRA was detected at post-mortem. This was the detection of 5F-MDMB-PICA in a death occurring in February 2020, and as such has not been represented in the table above.

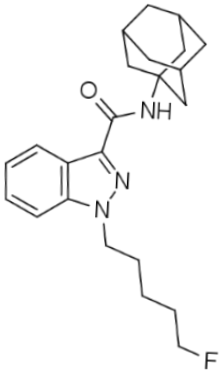
Annex C: National Poisons Information Service (NPIS) telephone enquiries and TOXBASE® accesses concerning SCRA

The NPIS provides the healthcare profession in the UK with information and advice on the diagnosis, treatment and management of suspected poisonings in humans. Support is provided by the online poisons information database TOXBASE®, or by a 24-hour national telephone service. The NPIS can provide information on the number of accesses to TOXBASE® and the numbers and details of telephone enquiries made to the service by health professionals. These numbers reflect (but do not measure directly) the frequency of contacts between health professionals and patients presenting following specific suspected exposures.

Table 2: Number (and % of all drug of misuse related activity) of telephone enquiries to NPIS and TOXBASE® online accesses relating to SCRA and branded products (likely to contain SCRA) from 2015/16 to 2019/20 inclusive

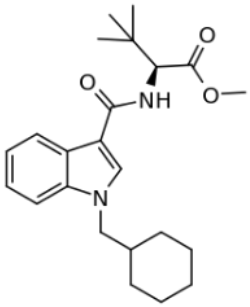
		2015/16	2016/17	2017/18	2018/19	2019/20
Telephone enquiries	SCRA	108 (6.7%)	52 (4.8%)	59 (4.7%)	47 (3.9%)	27 (2.4%)
	Branded products (likely to contain SCRA)	276 (17.1%)	74 (6.1%)	36 (2.9%)	31 (2.5%)	16 (1.4%)
	NPIS telephone enquiries for all drugs of abuse	1,613	1,210	1,245	1,220	1,112
TOXBASE® accesses	SCRA	5,542 (8.2%)	3,343 (5.2%)	3,532 (5.6%)	3,330 (5.0%)	2,753 (4.0%)
	Branded products (likely to contain SCRA)	8,009 (11.9%)	2,025 (3.1%)	1,689 (2.7%)	2,045 (3.0%)	1,990 (2.9%)
	TOXBASE® Accesses for all drugs of abuse	67,228	64,015	63,373	66,227	68,195

Annex D: Compound chemical structures (recently prevalent SCRA)



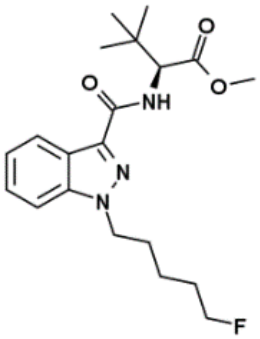
5F-APINACA (also known as 5F-AKB48 or 5F-AKB-48)

Core:	Indazole
Secondary group:	adamantyl
Linking group:	carboxamide
Tail:	pentyl
Substituents:	fluoro group on pentyl tail



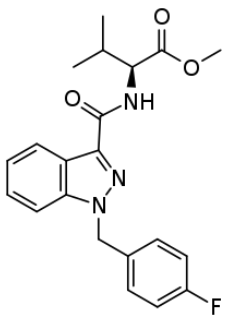
MDMB-CHMICA

Core:	Indole
Secondary group:	an ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	cycloalkylmethyl
Substituents:	2 methyl groups on secondary structure



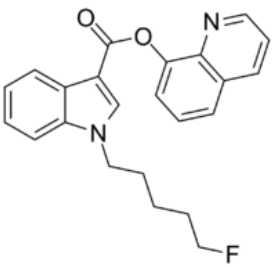
5F-MDMB-PINACA (also known as 5F-ADB or 5F-ADB-PINACA)

Core:	Indazole
Secondary structure:	ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	pentyl
Substituents:	fluoro substituent on pentyl tail 2 methyl groups on secondary structure



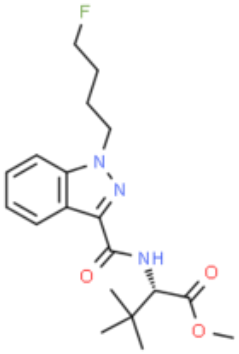
AMB-FUBINACA (also known as FUB-AMB and MMB-FUBINACA)

Core:	Indazole
Secondary structure:	ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	benzyl
Substituents:	fluoro substituent on benzyl tail methyl group on secondary structure



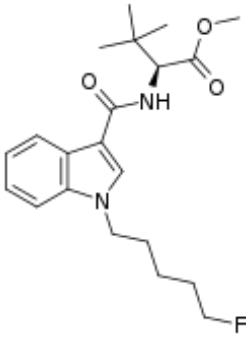
5F-PB-22 (5F-QUPIC or quinolin-8-yl 1-pentyfluoro-1H-indole-3-8-carboxylate)

Core:	Indole
Secondary structure:	quinolinyl
Linking group:	carboxylate
Tail:	pentyl
Substituents:	fluoro substituent on pentyl tail



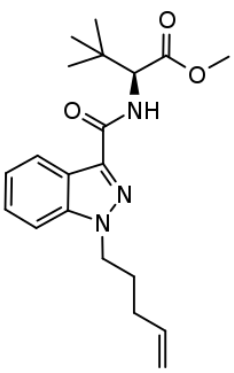
4F-MDMB-BINACA (also known as 4F-MDMB-BUTINACA)

Core:	Indazole
Secondary structure:	ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	butyl
Substituents:	fluoro substituent on butyl tail
	2 methyl groups on secondary structure



5F-MDMB-PICA

Core:	Indole
Secondary group:	ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	pentyl
Substituents:	fluoro substituent on pentyl tail
	2 methyl groups on secondary structure



MDMB-4en-PINACA

Core:	Indazole
Secondary group:	ester of 1-hydroxy-1-oxopropan-2-yl
Linking group:	carboxamide
Tail:	alkenyl
Substituents:	2 methyl groups on secondary structure

Annex E: Quality of evidence

Range of evidence

Evidence gathered was considered in line with the ACMD's 'Standard Operating Procedure (SOP) for using evidence in ACMD reports' [ACMD, 2020].

This report mainly draws on evidence from peer-reviewed literature (UK and international publications) and government reports. To evidence the prevalence of specific SCRA compounds identified in the UK, the ACMD's NPS Committee wrote to stakeholders requesting data on their most frequently identified SCRA since 2015. Responses were received from the following (which include submissions of 'data not available').

External agencies:

- Eurofins
- IONA study
- LGC Group
- MANDRAKE
- NPSAD
- TICTAC Communications Ltd
- WEDINOS
- NPIS

In addition to the above, the ACMD's NPS Committee consulted with the appropriate Government departments and sponsored agencies, such as MHRA, Ministry of Justice, the National Crime Agency (NCA) and DSTL to inform sections of the report.

In order to identify the rates of SCRA associated-fatalities that have been recorded in the UK, the ACMD's NPS Committee used a distinct list of compounds as presented in Table 1. The following reporting agencies for each administration were then approached for data on these substances: NPSAD (England and Wales), NISRA (Northern Ireland), NRS (Scotland).

Quality of evidence (design, limitations, bias)

When collating the evidence for this report, the ACMD's NPS Committee identified a distinct number of limitations on the evidence identified. Retrospective analysis and clinical presentations frequently relied on either self-reporting of the patient or clinical interpretation of patient reported exposures, which mean reporting will be heavily influenced by the knowledge held.

Forensic analysis on seizure materials will be limited by access to complex and expensive equipment, and further still by access to the appropriate reference material.

It was noted that there was a distinct lack of longitudinal studies on the impact of SCRA use to make quality assessments on its harm difficult.

Annex F: List of abbreviations used in this report

ACMD	Advisory Council on the Misuse of Drugs
CB_1	Cannabinoid Receptors Type 1
CB_2	Cannabinoid Receptors Type 2
CCT	Custody-Community Transitions
CDC	Centers for Disease Control and prevention
CSA	Controlled Substances Act 1970
CSEW	Crime Survey for England and Wales
DHSC	Department of Health and Social Care
DSTL	Defence Science and Technology Laboratory
ED	Emergency Department
EMC	Electronic Medicines Compendium
EMCDDA	European Monitoring Centre for Drug and Drug Addiction
EU	European Union
FEWS	Forensic Early Warning System
GMP	Greater Manchester Police
INCB	International Narcotics Control Board
IONA	Identification of Novel Psychoactive Substances study
IUPAC	International Union of Pure and Applied Chemistry
MANDRAKE	Manchester Drug Analysis and Knowledge Exchange
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Crime Agency
NDTMS	National Drug Treatment Monitoring System
NEPTUNE	Novel Psychoactive Treatment: UK Network
NHS	National Health Service
NIHR	National Institute for Health Research
NISRA	Northern Ireland Statistics and Research Agency
NPIS	National Poisons Information Service
NPS	Novel Psychoactive Substances
NPSAD	National Programme on Substance Abuse Deaths
NRS	National Records of Scotland
ONS	Office for National Statistics
PHE	Public Health England
PSA	Psychoactive Substances Act 2016
SCJS	Scottish Crime and Justice Survey
SCRA	Synthetic Cannabinoid Receptor Agonists
SDD	Smoking, Drinking and Drug use among young people in England survey
SLAM	South London and Maudsley NHS Foundation Trust
SOP	Standard Operating Procedure
THC	Tetrahydrocannabinol

UK	United Kingdom
UN	United Nations
US	The United States of America
WEDINOS	Welsh Emerging Drug and Identification of Novel Substances
WHO ECDD	World Health Organisation Expert Committee on Drug Dependence

Annex G: ACMD membership, at time of publication

ACMD membership, at time of publication	
Professor Judith Aldridge	Professor of Criminology, University of Manchester
Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live Southwark
Professor Owen Bowden-Jones	Chair of ACMD, Consultant psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Lecturer in social work, Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Professor Sarah Galvani	Professor of Social Research and Substance Use, Manchester Metropolitan University
Lawrence Gibbons	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Professor Graeme Henderson	Professor of Pharmacology, University of Bristol
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services, NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate professor in clinical pharmacy practice, University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead, University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Harry Shapiro	Director, DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Reader in Mood Disorders and Psychopharmacology, King's College London
Dr Ann Sullivan	Consultant physician in HIV and Sexual health and National co-lead for HIV Surveillance, PHE
Professor Matthew Sutton	Chair in Health Economics, University of Manchester
Professor David Taylor	Professor of Psychopharmacology, King's College, London and Director of Pharmacy and Pathology, South London and Maudsley NHS Foundation Trust

ACMD membership, at time of publication	
Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Consultant Psychiatrist and Clinical Director, Oxleas NHS Foundation Trust
Ms Rosalie Weetman	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust

Annex H: ACMD NPS Committee membership, at time of publication

ACMD NPS Committee membership, at time of publication	
Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live Southwark
Mr Paul Bunt	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Mr Peter Cain	Drugs Scientific Advisor Eurofins Forensic Services
Dr Anne Campbell	Lecturer in social work, Queens University Belfast
Mr John Corkery	Senior Lecturer in Pharmacy Practice at University of Hertfordshire
Dr Amir Englund	Research Fellow at the Addictions Department of the Institute of Psychiatry, Psychology and Neuroscience, at King's College London.
Lawrence Gibbons	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Professor Graeme Henderson	Professor of Pharmacology, University of Bristol
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Dr Nicola Kalk	Clinical lecturer in Addiction, King's College London
Professor Roger Knaggs	Associate professor in clinical pharmacy practice, University of Nottingham
Professor Fiona Measham	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Harry Shapiro	Director, DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan	Consultant physician in HIV and Sexual health and National co-lead for HIV Surveillance, PHE
Professor Simon Thomas	NPS Committee Chair, Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble	Former Forensic chemist, Laboratory of the Government Chemist (LGC)

ACMD NPS Committee membership, at time of publication	
Dr Mike White	Former Forensic Intelligence Adviser
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust

In addition to members of the NPS committee listed, significant contributions were made by NPSAD and the NPIS and a special mention would like to be extended to both organisations.

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