

Hill SL, Najafi J, Dunn M, Acheampong P, Kamour A, Grundlingh J, Blain PG, Thomas SHL. [Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMB-CHMICA. A report from the Identification Of Novel psychoActive substances \(IONA\) study.](#) *Clinical Toxicology* 2016, 54(8), 638-643.

**Copyright:**

This is an Accepted Manuscript of an article published by Taylor & Francis in *Clinical Toxicology* on 13-5-16 available online: <http://dx.doi.org/10.1080/15563650.2016.1190980>

**Date deposited:**

05/12/2016

**Embargo release date:**

13 May 2017



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence](https://creativecommons.org/licenses/by-nc-nd/4.0/)

**Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMB-CHMICA. A report from the Identification Of Novel psychoActive substances (IONA) study.**

(UK English Version)

**Authors:** Simon L Hill<sup>1,2</sup>, Javad Najafi<sup>2</sup>, M Dunn<sup>2</sup>, P Acheampong<sup>3</sup>, A Kamour<sup>4</sup>, J Grundlingh<sup>5</sup>, Peter G Blain<sup>1,2</sup>, Simon HL Thomas<sup>1,2</sup>

**Affiliations:**

1. National Institute for Health Research Health Protection Research Unit in Chemical and Radiation Threats and Hazards, Medical Toxicology Centre, Newcastle University, Newcastle NE2 4HH, UK
2. Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle NE1 4LP, UK
3. Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK
4. Acute Medical unit, North Manchester General Hospital, Delaunays Road, Crumpsall, Manchester M8 5RB, UK
5. Emergency Department, Royal London Hospital, Whitechapel, London E1 1BB, UK

**Key terms:** MMB-CHMICA, toxicity, synthetic cannabinoid receptor agonist, methiopropamine

**Corresponding Author:**

Prof Simon HL Thomas  
Medical Toxicology Centre  
Institute of Cellular Medicine, Newcastle University  
Newcastle NE2 7HH, United Kingdom  
Tel: 0191 260 6180  
Fax: 0191 282 0288  
Email [simon.thomas@ncl.ac.uk](mailto:simon.thomas@ncl.ac.uk)

**Sources of Financial Support:** ~~\_\_\_\_\_ National Institute for Health Research~~ None

**Tables :** \_\_\_\_\_ 1

**Figures :** \_\_\_\_\_ 1

**Word Count (text only):** \_\_\_\_\_ 2,5973,129

Formatted: Font: Not Bold

## ABSTRACT

**Context:** Recreational use of Synthetic Cannabinoid Receptors Agonists (SCRAs) has become increasingly common in many countries and may cause severe toxic effects.

**Objective:** To describe the clinical features of toxicity in 7 men after analytically confirmed exposure to ~~use of~~ MDMB-CHMICA, a recently described indole-based SCRA.

**Materials and methods:** Clinical information and biological samples (blood, urine) were collected from patients with severe toxicity after suspected use of novel psychoactive substances. Samples were analysed by ~~High Performance Liquid Chromatography (HPLC) data-independent liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis coupled to a TripleTOF® 5600+ mass spectrometer and data independent liquid chromatography-mass spectrometry (LC-MS/MS) analysis performed using MS/MSALL with SWATH Acquisition.~~

Formatted: Not Highlight

**Case reports:** All 7 cases were men who presented to hospitals in England between July and October 2015; ~~6~~ 6 reported smoking 'legal high' products. In all cases MDMB-CHMICA was identified in blood samples taken on admission to hospital. Other substances were identified in 4 cases (methadone 1, methiopropamine 1, other SCRAs 2). Clinical features in all 7 cases and in the 3 exposed to MDMB-CHMICA alone included acidosis (7/7 and 3/3) which was respiratory (3/7 and 3/3), metabolic (3/7 and 0/3) or mixed (1/7, 0/3), reduced level of consciousness (6/7 and 3/3), mydriasis (5/7 and 3/3), tachycardia (5/7 and 2/3), bradycardia (~~2~~ 2 and 1/3), tonic-clonic convulsions (2/7 and 1/3) and agitation (3/7 and 1/3). Recovery occurred within 24 hours in all cases except one male also exposed to methiopropamine.

**Conclusions:** Analytically confirmed exposure to MDMB-CHMICA was associated with acidosis (often of respiratory origin), reduced level of consciousness, mydriasis, heart rate disturbances and convulsions.



## INTRODUCTION

Presentations to emergency departments involving novel psychoactive substances (NPS) have become common in many countries and a large number of different substances compounds have been implicated. The *Identification Of Novel psychoActive Substances* (IONA) study began collecting biological samples and clinical data from patients presenting to participating hospitals in the United Kingdom with suspected severe toxicity after NPS use in March 2015. The study aims to identify the substances involved in these episodes of toxicity by analysis of samples taken from affected patients and to link these with the clinical effects reported.

Synthetic cannabinoid receptor agonists (SCRA) are one group of NPS that have been increasingly encountered internationally as causes of severe toxic effects in users. As well as being agonists at cannabinoid receptors (CB1 and CB2), they may have other biological actions and these may explain differences in severity and features of toxicity reported in SCRA users compared to those using cannabis. The increasing international use of SCRA may reflect their uncontrolled legal status in many countries and the fact that they are not detected by routine urine drug screens. [1. Trecki et al, 2015; 2. Tait et al 2016; 3. Waugh et al 2016].<sup>1-3</sup> Here

Formatted: Highlight

Formatted: Superscript

In this paper we report clinical details of 7 males presenting to 4 English hospitals with clinical toxicity associated with analytically confirmed exposure to the indole-based SCRA termed MDMB-CHMICA (IUPAC name 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate, sometimes also called MMB-CHMINACA), a substance first detected in Europe in 2014.<sup>4</sup> Its chemical structure is shown in the figure. Six of these gave a history of using branded 'legal high' smoking products. These data are being reported to document the clinical features observed in patients with severe toxicity after confirmed exposure to MDMB-CHMICA.

## METHODS

The IONA study is based in the United Kingdom and open to participation by hospitals that assess patients presenting with acute recreational drug toxicity. By February 2016 there were 11 hospitals recruiting or ready to recruit participants, with a further 16 hospitals expressing interest or in the set up phase.

The study is recruiting suspected NPS users who are at least 16 years of age presenting to participating hospitals with at least one defined feature of severe toxicity. These include fever ( $> 38.5\text{ }^{\circ}\text{C}$ ), clinically important hypothermia, reduced level of consciousness (Glasgow Coma Scale  $< 8$ ), critical care or high dependency unit admission, respiratory insufficiency, requirement for intubation and ventilation, seizure, hallucinations or psychosis, extreme agitation, severe or prolonged ( $> 24\text{ h}$ ) behavioural disturbance, arrhythmia, chest pain or ECG evidence of cardiac ischemia or myocardial infarction, acidosis (arterial or venous pH  $< 7.35$  or bicarbonate  $< 20\text{ mmol/l}$ ), severe electrolyte or fluid disturbances, hypoglycaemia ( $< 1.7\text{ mmol/l}$ ), methaemoglobinaemia ( $> 50\%$ ), tachycardia  $> 140\text{ /min}$ , systolic hypertension or hypotension ( $> 180$  or  $< 80\text{ mmHg}$ ), acute kidney injury, elevated creatine kinase ( $> 1000\text{ IU/l}$ ), alanine or aspartate transaminase (ALT or AST  $> 300\text{ IU/L}$ ), prothrombin time (PT  $> 15\text{ s}$ ) or International Normalised Ratio (INR  $> 1.3$ ), or a Poisons Severity Score of 3 (severe) or 4 (fatal), or any other severe manifestation of toxicity as determined and justified by the investigator.

The IONA study has ethical and research governance approval in England & Wales and separately in Scotland because of differences in the law concerning adults with incapacity. All potential participants are asked to give fully informed written consent for provision of clinical data and samples for toxicological analysis, where they are judged by their clinicians to have the mental capacity to do this. Those who do not have capacity to make a decision about participation, for example those with severe confusion or who are unconscious or intubated can be included on the advice of a

personal (usually a family member) or professional (a health professional independent of the study) representative. These are termed ‘consultees’ in England and Wales and ‘appropriate persons with relevant powers’ in Scotland. Those included on the basis of such advice are asked to consent if and when they regain capacity.

Following consent (or on the advice of a consultee/person with relevant powers), residual blood from samples previously taken for clinical reasons can be used for the study and further samples of blood and urine can also be taken at clinically appropriate intervals until recovery from toxicity. These samples are provided to the Health Protection Research Unit at Newcastle University, together with summary information about the patient including basic demographic details, details of the exposure, clinical and laboratory features observed and clinical outcome. These data are provided in linked anonymized format, identified by a specific code number that can only be linked with the participant’s identity by the clinicians at the participating hospital.

### Laboratory Analysis

Samples were analysed by liquid chromatography–tandem mass spectrometry (LC-MS/MS), consisting of a Sciex TripleTOF® 5600+ high-resolution QqTOF mass spectrometer with a DuoSpray ion source operated in positive electrospray (ESI+) mode, coupled with an Eksigent Nano LC 420 system, using non-targeted data independent LC-MS/MS techniques. The particular data independent analysis method employed was Sequential Window Acquisition of all Theoretical fragment-ion spectra (SWATH) mass spectrometry (MS), which utilises the very fast scanning speeds of quadrupole time-of-flight (QTOF) mass spectrometers. SWATH MS is a form of data independent analysis that repeatedly cycles through consecutive pre-set precursor ion isolation windows, detecting all fragment ion spectra from all the precursor ions contained in a specific window at a given time, providing highly selective MS/MS mass spectra of all analytes. Protonated molecular ions were detected via a time-of-flight (TOF) MS scan covering the 100 to 700 Da mass range. SWATH MS/MS data were acquired in high sensitivity mode,

Formatted: Font: Not Bold

Formatted: Font: Not Bold

Formatted: Font: Not Bold

Formatted: Font: Not Bold

at a mass resolution of at least 20,000, with a collision energy spread of 30±15V over a mass range of 30 to 725 Da, and a 20 Da SWATH isolation window. Mass calibration was performed every second sample by injection of a calibration solution through the LC-MS/MS system.

Chromatographic separation was performed with an ACE C<sub>18</sub> capillary LC column – 100mm x 300µm x 3µm. The column oven and autosampler were maintained at 30 °C and 8 °C respectively. Gradient elution was performed with (A) 0.1 % formic acid in water and (B) 0.1%formic acid in acetonitrile at a flow rate of 5µL/min. Initial gradient conditions were 5 % B, held for 1min; then increased to 95 % B over 20 min, held until 25 min; and returned to 5 % B at 25.1 min and held until 30.0 min.

Formatted: Highlight

Psychoactive substances were extracted from 250µL of plasma or 1mL of urine using solid supported liquid/liquid extraction. Samples were diluted with an equal volume of de-ionised water and centrifuged at 15,000g for 5 minutes. Samples were then transferred onto supported liquid extraction (SLE) columns and gently driven onto the column phase with a short pulse of vacuum. After equilibration at ambient pressure for 5 min, analytes were eluted with 500µL of ethylacetate into polypropylene tubes. A further aliquot of 500µL of ethylacetate was applied and allowed to flow for another 5 minutes before the application of vacuum for 10–20 seconds to elute any remaining extraction solvent. The combined sample eluates were evaporated to dryness under a stream of nitrogen at 45 °C in a Zymark TurboVap. Samples were reconstituted in 25 µL mobile phase A/B 90:10 (v/v), vortexed and centrifugated at 4,000g for 5 min, and transferred to amber autosampler vials containing 300-µL glass inserts. A 1µL aliquot was used per analysis.

Psychoactive substances are extracted from 250µL of plasma or 1mL of urine using solid supported liquid/liquid extraction. Samples are analysed by High Performance Liquid Chromatography (HPLC) coupled to a TripleTOF® 5600+ mass spectrometer. Data

~~independent liquid chromatography–mass spectrometry (LC–MS/MS) analysis is~~  
LC-MS/MS data were processed using MasterView software version 2.2 with SWATH  
MicroApp version 2.0. Compounds were identified by software-assisted library  
searching against reference spectra. Library searching and analyte identification were  
performed on MS-MS data with LibraryView version 1.0 and ChemSpider Library version  
2.0 integrated within the MasterView software. The intensity factor determining impact  
of spectral intensity differences between the acquired and the reference spectrum on  
the purity percentage was adjusted to 3. The intensity threshold utilized to remove  
small peaks under a specific intensity was set to 5. Identification criteria were a library  
match with a purity score greater than 65% and the presence of the molecular ion and  
three characteristic MS-MS fragment ions. Positive matches obtained from this search  
are checked by manual review.

~~, Library View version 1.1 and ChemSpider Library version 2.0 (AB Sciex). For compound  
identification, extracted ion chromatograms (XICs) of precursor ions are generated with  
the peak finding algorithm integrated in MasterView and MS/MS spectra are submitted  
to Library View and ChemSpider. Positive matches obtained from this search are  
checked by manual review.~~

## RESULTS

### Case series

Laboratory analysis of samples from 49 early participants in the IONA study identified MDMB-CHMICA ~~was identified~~ in biological samples from seven male ~~patients~~ ~~presenting who had presented with severe toxicity after use of a NPS~~ to participating hospitals in Liverpool (1), London (1), Manchester (1) and Newcastle (4) ~~with severe toxicity after use of a NPS. All of these patients presented~~ between July and October 2015. Clinical details are summarized in ~~Table 1~~ the table. For cases 1-3 no other substances were identified. Full blood count, urea, electrolytes, creatinine, liver function tests and creatine kinase were normal on admission unless otherwise stated.

Case 1 was a 41 year old man with a history of frequent NPS use including uneventful SCRA use. He was found collapsed outside with a reduced level of consciousness after smoking a product called 'Sweet Leaf'. On arrival in hospital he was drowsy with a Glasgow Coma Scale (GCS) of 11 ~~with and had~~ a bradycardia. Venous blood showed hypercapnia and acidosis (~~Table 1~~ Table) ~~but normal renal and liver function. MDMB-CHMICA was identified in blood taken at the time of admission; no other controlled or recreational substances were detected.~~ He made an uneventful recovery without specific treatment and was discharged 22h after admission. MDMB-CHMICA was identified in plasma taken at the time of admission; no other controlled or recreational substances were detected.

Case 2, a 16 year old male with a past history of Attention Deficit Hyperactivity Disorder for which he was prescribed methylphenidate, was found unconscious at a bus station after smoking 'Sweet Leaf'. On arrival at hospital his GCS was 13 and arterial blood gases revealed a mild respiratory acidosis (Table 1). ~~He had a normal full blood count, coagulation, urea, electrolytes, liver function and creatine kinase.~~ His conscious level gradually improved and he was discharged 18h after admission. MDMB-CHMICA was

identified in blood plasma taken at the time of admission but no other controlled or recreational substances were identified.

Case 3 was a 33 year old male who was found collapsed on the street with a witnessed tonic-clonic seizure. On arrival of the paramedics he had a heart rate of 120 bpm, ~~BP of 145/59 mmHg~~ and GCS of 3/15. He was treated with intravenous diazepam 10 mg for seizures and transferred to hospital. His GCS improved to 9/15 on route and was 14/15 on arrival at the hospital. In the Emergency Department he was agitated, paranoid and violent towards staff, requiring physical restraint. Intravenous access was established and was given IV fluids. Blood tests revealed increases in creatine kinase (CK, 525 IU/L), alanine transaminase (~~ALT~~, 81 IU/L) and bilirubin (41 IU/L). Venous blood gases, taken 1 hour after the diazepam administration, showed a predominantly respiratory acidosis with a high lactate (Table 1). The electrocardiogram was normal. The patient improved over the next few hours and he denied any substance use. He took his own discharge against medical advice 5 ½ h after arriving at the hospital. Analysis of a blood sample taken 1 hour after admission revealed MDMB-CHMICA, but no other recreational substances.

Case 4 was a 16 year old male who collapsed in his home after smoking a product called 'Pandora Reborn'. He was found by his parents with generalized shaking consistent with a tonic-clonic seizure, which terminated without specific treatment. On arrival in hospital he was drowsy but the ~~Glasgow Coma Scale (GCS)~~ was 15/15. Bradycardia, mydriasis, hypercapnia and a mixed acidosis were recorded (Table 1). ~~Otherwise routine blood tests including renal and liver function were normal.~~ An electrocardiogram (ECG) ~~G~~ showed incomplete right bundle branch block. He made an uneventful recovery without specific treatment and was discharged 24h after admission. ~~He made an uneventful recovery and was discharged the following day.~~ MDMB-CHMICA was identified in blood plasma taken at the time of admission. Methadone was also

identified, but no other controlled or recreational drugs were detected. MDMB-CHMICA was also identified in a urine sample provided 10h after admission. He made an

Case 5 was a 23 year old male with a history of daily recreational drug use including various 'legal highs', cannabis and diazepam who was also prescribed quetiapine. He presented with a 3 day history of abnormal behavior with increasing auditory and visual hallucinations, unsteadiness, falls, sweating, agitation, aggression, insomnia and self-injuring (including head banging). On arrival in hospital he was aggressive and uncooperative with pyrexia, tachycardia, dilated pupils and a mild metabolic acidosis (Table 1). Urine screen was positive for benzodiazepines but no other recreational substances. Lorazepam 3mg was administered intravenously before he could be formally assessed. He became increasingly agitated in spite of this with a marked tachycardia (150 beats/min) and required physical restraint. He was intubated and ventilated. Venous blood samples demonstrated increases in white cell count ( $28.03 \times 10^9/L$ ), Urea-urea (15.1 mmol/L), lactate (3.0 mmol/L) and creatine kinase (13,764 IU/L). CA-omputed tomography (CT) brain scan of the brain, and an ECG, Chest X-ray and Lumbar-lumbar puncture were all normal. Urine screen was positive for benzodiazepines but no other recreational substances. PInitially phenylephrine and subsequently noradrenaline were needed to maintain his blood pressure but he was gradually weaned off inotropic support and ventilation and was extubated the day after admission. He remained agitated and aggressive for several days requiring large doses of benzodiazepines and haloperidol but was subsequently discharged 9 days after admission with no sequelae. On recovery he gave a history of smoking a product called 'Vertex'. MDMB-CHMICA and methiopropamine were detected in blood-plasma samples taken on admission, as well as the lorazepam that had been administered in hospital, but no other substances were identified.

Case 6 was a 42 year old man a past history of schizophrenia found naked and confused at a bus stop after smoking 'Black Mamba'. Initial assessment by paramedics reported a

GCS of 13 with unequal pupils, cyanosis, tachycardia and tachypnea. Venous blood gases on admission revealed a metabolic acidosis with hyperlactataemia which rapidly normalized within 6 hours of admission. Other blood tests showed raised total white cell count of  $15.6 \times 10^9/l$  (Neutrophils  $13.3 \times 10^9/l$ ) and potassium of  $5.6 \text{ mmol/l}$  ~~but no other changes from previous samples~~. He was treated with intravenous fluids and sedation, his recovery was uncomplicated and he was discharged 18 hours after admission. MDMA-CHMICA and 5F-ADB-PINACA ~~-(IUPAC name N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide-)~~ were identified in ~~blood plasma~~ taken on admission and also in a urine sample taken 15h after admission.

Case 7, a previously healthy 57 year old male, collapsed after drinking 4-6 cans of “strong lager” and smoking a preparation called “Old Spice”. On arrival in the Emergency Department he was significantly hypothermic (Core temperature  $31^\circ\text{C}$ ) ~~with a lactate of  $2.9 \text{ mmol/L}$~~ . His GCS was 14/15, pulse 89 /min and systolic blood pressure 50 mmHg. This quickly improved to normal with intravenous fluids. Venous blood gases showed ~~pH 7.28, pCO<sub>2</sub> 6.30 and base excess  $-4.1 \text{ mmol/L}$~~  mild acidosis, a base deficit and an elevated lactate. Routine biochemistry analysis ~~did not demonstrate any abnormalities~~. ~~And a CT brain scan of his head was normal. Blood ethanol concentration was not measured~~. He rapidly recovered and discharged himself against medical advice eight hours after admission. MDMA-CHMICA was identified in ~~blood plasma~~ samples and in a urine sample taken 5 hours after admission, together with 5F-ADB-PINACA and AB-PINACA ~~-(IUPAC name N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide-)~~.

## DISCUSSION

MDMA-CHMICA (derived from ~~methyl dimethyl butanoate cyclohexyl methyl indol-carboxamide~~) was first notified to the European Monitoring Centre for Drugs and Drug

Addiction (EMCDDA) following a seizure of product in Hungary in August 2014.<sup>4</sup> Franz  
Here In this paper we have described the clinical features of seven male patients  
presenting to hospital with toxicity associated with analytically confirmed exposure to  
MDMB-CHMICA.

~~Three of these cases had isolated MDMB-CHMICA exposure. In this case series,~~  
~~documented features may be contributed to by other substances also identified in 4~~  
~~cases, but there were 3 cases who had isolated MDMB exposure. Common features~~  
~~described were~~ Common clinical features described in all of these were a reduced level  
of consciousness, respiratory acidosis ~~which was respiratory in origin in all 3 cases with~~  
~~isolated exposure~~, mydriasis and heart rate disturbances. ~~Confusion~~ Seizures and ~~or~~  
behavioral disturbances were also documented ~~and convulsions were recorded in 2~~ one  
case ~~eachs, one exposed to MDMB-CHMICA alone.~~

In the other 4 cases, documented exposure to other substances may have contributed  
to the clinical features observed. The

Formatted: Font color: Red

Formatted: Font color: Red

MDMB-CHMICA (derived from methyl dimethylbutanoate cyclohexylmethylindol-  
carboxamide) was first notified to the European Monitoring Centre for Drugs and Drug  
Addiction (EMCDDA) following a seizure of product in Hungary in August 2014.<sup>4</sup> There  
was a further substantial seizure of 40 kg MDMB-CHMICA in Luxembourg in December  
2014.<sup>5</sup> An EMCDDA alert that was subsequently published by Police Scotland stated that  
as of 20<sup>th</sup> January 2016, 13 reports had been received describing fatalities, including 8  
cases where it was considered that the drug caused or contributed to death, as well as  
23 non-fatal intoxications associated with MDMB-CHMICA.<sup>6</sup> A published report from  
Norway described the sudden cardiac death of a 22 year old male after smoking a  
brown powder, where samples of serum and powder were found to contain MDMB-  
CHMICA.<sup>7</sup> Loss of consciousness and asystole were reported in a 25 year old Polish man  
after smoking a legal high product. Although initially resuscitated, he died a few days

later from multi-organ failure; MDMB-CHMICA was detected in antemortem blood samples.<sup>8</sup> An alert from Wales described a young male who developed dizziness, nausea, breathlessness, chest pains, irregular heart beat and convulsions after inhaling from a rolled cigarette found to contain MDMB-CHMICA.<sup>9</sup>

Most of the clinical features recorded here after exposure to MDMB-CHMICA, including seizures and acidosis, have been previously reported with other SCRA<sup>s</sup> [2. Tait et al 2016].<sup>2</sup> Mydriasis, tachycardia, nausea and vomiting, paranoia, hallucinations, confusion, agitation, breathlessness, drowsiness, unconsciousness or coma, severe motor impairment and loss of sphincter control have been reported following MDMB-CHMICA exposure.<sup>6</sup> [6. Police Scotland 2016].—Respiratory depression evidenced by hypercapnia, however, has not been well documented after SCRA use but was observed in all 3 of our patients with isolated MDMB-CHMICA exposure. This is-may be a plausible effect of SCRA<sup>s</sup>; in rats, cisternal injection of the SCRA WIN55212-2 produced reductions in minute volume and respiratory rate that were prevented by CB1 receptor antagonism.<sup>10</sup> [10. Pfizer et al, 2004] It should be acknowledged, however, that these effects may depend on the mode of administration and the dose used and that there are differences in chemical structure and effects between WIN55212-2 and MDMB-CHMICA.

Like other so-called 'third generation' SCRA<sup>s</sup>, MDMB-CHMICA is not currently controlled in the UK,<sup>11</sup> [11. ACMD 2014] although it is a scheduled/controlled substance in some countries including Germany, Austria, China, Switzerland, as well as the State of Louisiana. The UK situation reflects the increasing difficulty in defining controls for SCRA<sup>s</sup> based on chemical structures because of the diversity involved. The Psychoactive Substances Act 2016-2016 soon coming into force in the UK in April 2016 will make it an offence to produce, supply or possess with intent to supply any non-exempted substance capable of producing a psychoactive effect, including SCRA<sup>s</sup>.<sup>12</sup> [12. National

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

~~Archives 2016]~~ The impact of this legislation on the patterns of toxicity observed with substances requires careful monitoring.

~~Clinical toxicologists and Poisons Centers should be aware of the potential toxicity of SCRA~~s such as MDMB-CHMICA. In conclusion, these analytically confirmed cases suggest that MDMB-CHMICA can cause a reduction in level of consciousness associated with hypercapnia, confusion, ~~tachycardia or bradycardia~~ heart rate disturbances, mydriasis and in some cases convulsions and behavioural disturbances. Clinical toxicologists and Poisons Centers should be aware of the potential effects of SCRAs including MDMB-CHMICA to inform recommendations on appropriate patient monitoring and treatment.

## **Acknowledgements**

The authors are grateful to the clinicians and research nurses in hospitals enrolled in the IONA study for their essential contribution in recruiting patients and collecting samples and clinical data.

This research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Chemical and Radiation Threats and Hazards in partnership with Public Health England (PHE). The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, the Department of Health or Public Health England.

**Declaration of interest:** The authors report no declarations of interest.

## REFERENCES

1. Trecki J, Gerona RR, Schwartz MD. Synthetic cannabinoid related illnesses and deaths. *NEJM*. 2015; 373: 103–107.

Formatted: Font color: Auto

2. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin Toxicol (Phila)*. 2016 Jan; 54(1): 1-13

~~doi: 10.3109/15563650.2015.1110590. Epub 2015 Nov 15.~~

3. Waugh J, Najafi J, Hawkins L, Hill S, Eddleston M, Vale JA, Thompson JP, Thomas SHL. Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists. A report from the United Kingdom National Poison Information Service. *Clin Toxicol (Phila)* 2016; Published online 19<sup>th</sup> April 2016. *Clin Tox* 2016; in press

Formatted: Superscript

4. Franz F, Schwörer N, Angerer V, Moosmann B, Auwärter V. Metabolism and urine analysis of the new synthetic cannabinoid MDMB-CHMICA. *Toxichem Krimtech*. 2015; 82: 192–8

5. United National Office on Drugs and Crime (UNODC). Global smart update. Volume 13, March 2015.

[https://www.unodc.org/documents/scientific/Global\\_SMART\\_Update\\_13\\_web.pdf](https://www.unodc.org/documents/scientific/Global_SMART_Update_13_web.pdf)

Accessed 23rd February 2016 (last accessed ~~24th March~~<sup>5<sup>th</sup> May</sup> 2016)

Formatted: Superscript

6. Police Scotland. Serious adverse events associated with MDMB-CHMICA in Europe.

<http://www.lanarkshirehivandhepatitis.org/news-and-events/news/2016/02/09/police-scotland-serious-adverse-events-associated-with-mdmb-chmica-in-europe/> (last

accessed ~~24th March 2016~~<sup>5<sup>th</sup> May 2016</sup>)

7. Westin Andreas AA, Frost Joachim, Brede Wenche R, Gundersen PO, Einvik S, Aarset H, Slørdal L. ~~et al.~~ Sudden Cardiac Death Following Use of the Synthetic Cannabinoid MDMB-CHMICA. ~~Journal of Analytical Toxicology~~ J Anal Toxicol 2016; 40: 86-7
8. Adamowicz P. Fatal intoxication with synthetic cannabinoid MDMB-CHMICA. Forensic Sci Int 2016; 261: e5-e10
9. WEDINOS working group. Hospitalisation from synthetic cannabinoid MMB CHMINACA. <http://asfacarduf.org/wp-content/uploads/2015/07/MMB-CHMINACA-MDMB-CHMICA-alert.pdf> (last accessed ~~5<sup>th</sup> May~~ 24<sup>th</sup> March 2016)
10. Pfitzer T, Niederhoffer N, Szabo B. Central effects of the cannabinoid receptor agonist WIN55212-2 on respiratory and cardiovascular regulation in anaesthetised rats. Br J Pharmacol. 2004; 142: 943-52
11. Advisory Council on the Misuse of Drugs. 'Third Generation' synthetic cannabinoids. November 2014. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/380161/CannabinoidsReport.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/380161/CannabinoidsReport.pdf) (last accessed ~~5<sup>th</sup> May~~ 24<sup>th</sup> March 2016)
12. National Archives 2016. Psychoactive Substances Act 2016. [http://www.legislation.gov.uk/ukpga/2016/2/pdfs/ukpga\\_20160002\\_en.pdf](http://www.legislation.gov.uk/ukpga/2016/2/pdfs/ukpga_20160002_en.pdf) (last accessed ~~5<sup>th</sup> May~~ 24<sup>th</sup> March 2016)

**Table-1.** Clinical features of 7 males exposed to MDMA-CHMICA, with observations as recorded on admission to hospital.

No	Age	Reported exposures	Route	Analytical confirmation	Features	Temp	GCS	HR	SBP	DBP	RR	Mydriasis	pH	pCO2	pO2	BE	Lactate	LOS
	(y)					°C		/min	mmHg	mmHg	/min	-		kPa	kPa	mMol/L	mMol/L	h
					Lower limit of normal*	36.1	15	50	100	60	12	-	7.35	4.7	12	-3		
					Upper limit of normal*	37.2	15	90	140	90	20	-	7.45	6	15	3	1.9	
1	41	Sweet Leaf', Black mamba	Smoked	MDMB-CHMICA	Reduced level of consciousness, bradycardia	36.4	11	44	96	60	12	Yes	7.29	9.25	VG	4.2	0.6	24
2	16	Sweet Leaf'. Prescribed methylphenidate	Smoked	MDMB-CHMICA	Reduced level of consciousness, tachycardia	36.7	13	120	116	57	19	Yes	7.31	7.47	11.57	0.2	0.7	18
3	33	Not known	NK	MDMB-CHMICA	Reduced level of consciousness, tonic-clonic convulsion, tachycardia, acidosis, behavioural disturbance	36.7	14	120	145	59	14	Yes	7.22	10.4	VG	1.2	4.6	5.5
4	16	Pandora Reborn'	Smoked	MDMB-CHMICA, methadone	Collapse, tonic-clonic convulsion, bradycardia, mydriasis	35.1	10	49	113	53	16	Yes	7.33	7.5	11.3	-5.0	1.2	22
5	23	Vertex'. Frequent use of cannabis and diazepam. Prescribed quetiapine	NK	MDMB-CHMICA methiopropamine Lorazepam**	Aural and visual hallucinations, ataxia with falls, sweating, agitation, aggression, insomnia, self-injuring	38.1	15	100	110	64	n/a	Yes	7.31	4.32	30.5	-9.2	1.13	189
6	42	Black mamba'	Smoked	MDMB-CHMICA, 5F-ADB-PINACA	Reduced level of consciousness, confusion, tachycardia, tachypnoea, acidosis	35.5	13	123	114	91	60	No	7.2	3.97	19.35	-15.0	>20	11.5
7	57	Old Spice', Alcohol	Smoked	MDMB-CHMICA, 5F-ADB-PINACA, AB-PINACA	Collapse, hypothermia, hypotension, acidosis	34.8	14	96	50	-	15	No	7.28	6.3	VG	-4.1	2.9	8.5

\*Upper and lower limits of normal used may vary between hospitals. \*\*Administered in hospital.

GCS = Glasgow Coma Scale; HR = heart rate; SBP = Systolic blood pressure; DBP = diastolic blood pressure; RR = Respiratory Rate; BE = base excess; LOS = Length of hospital stay; VG = Venous blood gases; NK = not known;

FIGURES

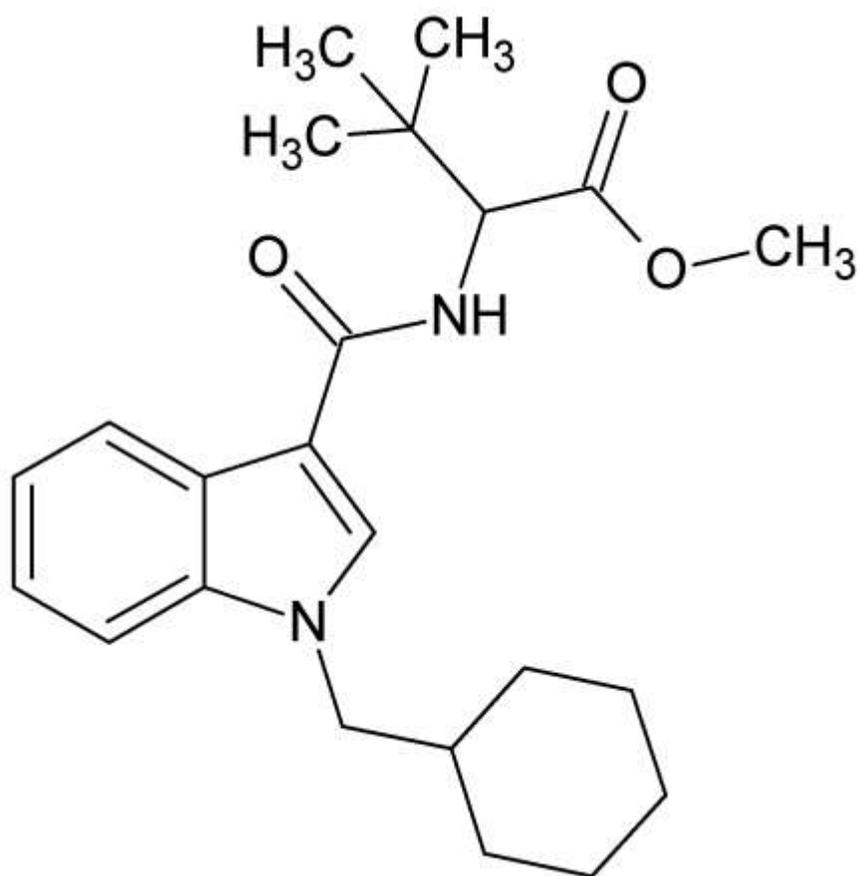


Figure 1: Chemical structure of MDMB-CHMICA