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# Identification and characterization of 4-chloromethamphetamine (4-CMA) in seized ecstacy — a risk to public health

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ABSTRACT

This paper reports the structure elucidation and full characterization of 4-chloromethamphetamine (4-CMA), a compound which was never reported previously outside of laboratory settings in seized drug samples, or samples actively being used at large dance festivals.

Identification of 4-CMA was obtained by liquid chromatography with diode array detector (HPLC-PDA) and gas chromatography mass spectrometry (GC–MS). Further structure elucidation was performed by fragment pattern analysis of the trimethylsilyl and trifluoroacetyl derivatives with GC–MS. The region-isomeric form was confirmed by $^{1}$H nuclear magnetic resonance spectroscopy ($^{1}$H NMR). HPLC-PDA was used for quantitation of 4-CMA in the seized tablet to obtain an indication of the potency.

A literature review of the toxic effects of 4-CMA was performed, and mechanisms for serotonin neurotoxicity were proposed and discussed. Finally the risks for potential widespread harm to the public in events where similar substances or tablets start appearing and circulating on a larger scale in the general population is discussed.



## 1. Introduction

Large changes have occurred in the recreational drug market in Europe over the last decade, which can be roughly divided in two general phenomena: high dose ecstasy, and, perhaps more important, the arrival of new psychoactive substances (NPS). Since the end of the '90s and the beginning of 2000, a plethora of new psychoactive substances specifically designed to evade current international drug legislation. Examples include the advent of mephedrone around 2010, and synthetic cannabinoids (also called "Spice") where a large increase in detected number of substances was recently observed as well. In addition, in the same period, average ecstasy/MDMA quality was low because of precursor shortages a.o. due to increased seizures and competition amongst ecstasy manufacturers. Moreover, ecstasy tablets were often contaminated with other substances such as piperazines (e.g. mCPP). The combination of this historically low ecstasy quality with the emergence of a novel phenomenon, the wide availability of legal psychoactive NPS, resulted in a drastic increase in the number of NPS that were found every year, also in Belgium (Fig. 1).

NPS are originally derivatives of illicit drugs (such as amphetamine) that were designed with similar but not identical chemical structure, resulting in compounds that retained the psychoactive properties of the original molecule but remained legal to manufacture and sell. Most of these substances are sold in smart shops or online as "bath salts", "carpet cleaner", "plant food", "legal highs", or "research chemicals", and pretend not to be intended for human consumption. NPS encompass a wide range of psychoactive compounds, including synthetic phenethylamines, cathinones and synthetic cannabinoids. By the end of 2016 more than 500 unique NPS compounds had been identified by the Early Warning System of the European Centre for Drugs and Drug Addiction (EMCDDA) [1]. Since most of these substances have never been studied formally, and (toxic) effects in humans are mostly unknown, NPS constitute a real danger to public health, especially in the last three years when derivatives of fentanyl ("fentalogs") have started to appear on the market. Also, due to the lack of analytical reference standards, identification and general analysis of these substances poses a significant challenge in forensic toxicology.

In some cases, NPS "cross-over" from the online scene and enter the market for classic illicit drugs where they are being sold by the same illicit dealers; for example, 4-fluoroamphetamine (4-FA) is frequently

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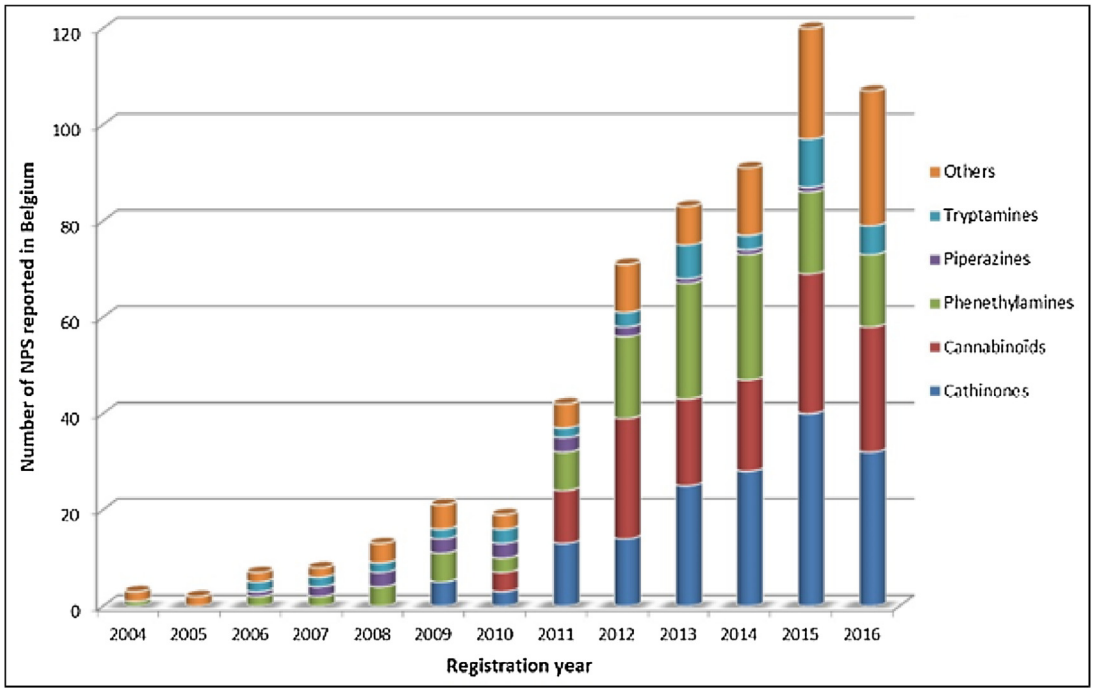


**Fig. 1.** Evolution of number of NPS detected in Belgium each year (2004–2016).

encountered in this fashion. Other NPS have been found in ecstasy tablets, in powders sold as heroin and amphetamine, etc. In almost all cases the user is unaware of their presence, thinking instead he or she received a "weak" batch of the wanted drug. This carries great risk; one example in Belgium and The Netherlands was the contamination of amphetamine/speed with 4-methylamphetamine (4-MA), a NPS with strong serotonergic action. At least six people have died in Belgium as a result of the consumption of this amphetamine mixture [2]. Another widespread example is the presence of PMA and PMMA in ecstasy tablets (Fig. 2), which has led to dozens of deaths worldwide.

During the summer of 2015 (and in the framework of the Tomorrowland dance festival which was on-going during the research discussed below) an ecstasy tablet was submitted to the laboratory for identification. In this paper, firstly we present the identification and structure elucidation of the unknown molecule in the confiscated tablet using GC–MS, HPLC-PDA and $^{1}$H NMR data, a.o. using scarce information available in scientific literature. Secondly, we will report on potential (neuro)toxic effects and potential widespread harm to the public in events where similar substances or tablets start appearing and circulating on a larger scale in the general population.

## 2. Materials and methods

### 2.1. Samples and case histories

During a drug check in the framework of an international electronic music festival in Belgium, several (presumed) ecstasy tablets were confiscated by federal police, and the samples were submitted to the laboratory (Eurofins Forensics, Bruges, Belgium). Based on physical properties eight different tablets could be distinguished. After analysis in our lab, the following substances were found to be present in the tablets: MDMA, MDMA, sildenafil/tadalafil, MDMA, MDMA, DOB and MDMA. One tablet (characterised by a "Durex" tablet logo) contained an initially unknown substance.

### 2.2. Materials

Certified reference components and general chemical reagents were obtained from Cayman Chemical (Michigan, USA). Solvents used for GC–MS and HPLC-PDA were of analytical grade. Methanol, acetonitrile and hydrochloric acid (37%) were obtained from Fisher Chemical (Fisher Bioblock, Belgium). Water was purified by a Milli-Q system obtained from Merck Millipore (Darmstadt, Germany). Triethylammonium (TEA) phosphate 1 M was purchased from Sigma (Zwijndrecht, Belgium) and was diluted 1/40 immediately before use. The external standard diphenylamine was obtained from VWR International (Leuven, Belgium). *N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide (MSTFA) and *N*-methyl-bis(trifluoroacetamide) (MBTFA) were purchased from Machery-Nagel (Germany). NMR analysis and associated sample preparation: deuterated solvents for NMR were purchased from Euriso Top (St. Aubain, France). Tetramethylsilane was of NMR grade and was acquired from Acros Organics (Geel, Belgium). Dichloromethane

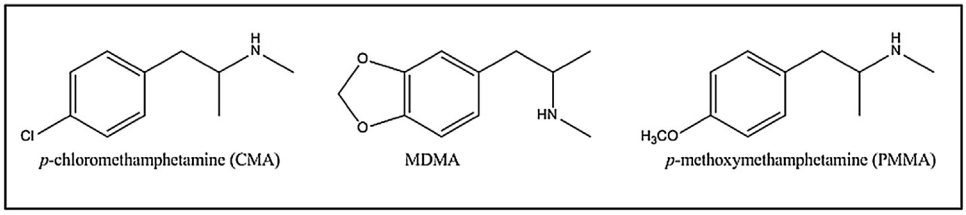


**Fig. 2.** Chemical structure of MDMA, 4-methylamphetamine and p-methoxymethamphetamine.

was purchased from Sigma-Aldrich and was of HPLC grade. Hydrochloric acid and sodium hydroxide were purchased from Acros Organics (Geel, Belgium) and were of ACS grade. Ultrapure water was obtained from a Millipore Synergy UV apparatus (Billerica MA, USA).

### 2.3. Sample preparation and instrumentation

#### 2.3.1. Gas chromatography–mass spectrometry (GC–MS)

A fresh sample solution of 4-CMA in methanol (containing 200 μg/ml diphenylamine as external standard) was prepared. A mass spectrum was recorded by injecting a sample aliquot on an Agilent 6890 N gas chromatograph in combination with an Agilent 7683 injector and an Agilent 5973 inert mass selective detector (Agilent Technologies, California, USA). Mass spectra were recorded using a Varian CP-SIL 8 CB low bleed capillary column (30 m × 0.25 mm, 0.25 μm film thickness) connected to a fused silica retention gap (2.5 m × 0.25 mm). The used carrier gas was helium at a constant flow of 1.1 ml/min. The temperature gradient was applied: starting at 70 °C with 2 min holding time; increase to 310 °C at 8 °C/min with a 9 min holding time. Total runtime was 41 min. Injection port and detector temperatures were set at 300 °C and 230 °C respectively; transfer line temperature was set at 280 °C. An injection volume of 1 μl was used in split less injection mode. Mass spectra were recorded in the range $m/z$ 40–550.

For further structure elucidation, trimethylsilyl—(TMS) and trifluoroacetyl—(TFA) derivatives were prepared by evaporation of the methanolic extract at 40 °C under a gentle stream of nitrogen and subsequent heating in a sealed glass vial at 70 °C for 30 min in the presence of 100 μl MSTFA or MBTFA. Obtained derivatives were evaporated to dryness and reconstituted in acetonitrile. Subsequent analysis was performed using the procedures and protocols outlined in the GC–MS methods mentioned above.

#### 2.3.2. Liquid chromatography with photo-diode array detection (HPLC-PDA)

The “Durex” tablet had the following physical characteristics: rectangular shape (length:12.5 mm; width: 4.3 mm; height: 8.4 mm), yellow/brown (non-uniform) colour, Logo “Durex” on one side and scored on the other side. Tablet weight was 427.1 mg.

The tablet was extracted with methanol, and the methanol solution was subsequent evaporated under a gentle nitrogen stream, taking care not to let temperature rise higher than 40° C. A 50 μl aliquot was also evaporated to dryness at 40 °C under nitrogen, and the resulting powder was reconstituted in 1.0 ml of mobile phase A. Mobile phases consisted of 25 mM TEA-phosphate buffer (A) and 100% acetonitrile (B). The gradient used during elution consisted of 95% A at time 0, changing to 30% A in 30 min and held there for another 5 min.

HPLC-PDA analysis was performed using a Varian Prostar solvent delivery module in combination with a Varian Prostar 410 autosampler and Varian Prostar photodiode array detector. Data acquisition and analysis were performed with the Varian Star and Polyview software. A LiChrospher® 100 RP-18 (5 μm) (Merck, Darmstadt, Germany) was used as saturation column. Separation of compounds was performed in gradient mode using a Microsorb C18 column (150 mm × 4.6 mm, 5 μm particle size, Agilent, California, USA) connected to a C18 guard column (4 mm × 3.0 mm, 3.5 μm particle size). Oven temperature was set at 35 °C. Scan range was 220–340 nm and the chromatogram was monitored at 220 nm and 254 nm for 35 min. The injection volume was 50 μl.

For quantitative analysis a stock solution of 1 mg/ml in methanol was prepared immediately prior to use. 30 mg aliquot of the homogenized powder of the tablet was weighed into a 10 ml volumetric flask and made up to volume with methanol.

For the quantitative analyses, methanolic extract samples (methanol solution volumes used were 25 μl, 50 μl and 75 μl respectively) were sonicated for 30 min and were transferred into an auto sampler vial after homogenizing and centrifuging. After acidifying the samples by addition of 50 μl 10% hydrochloric acid in methanol, samples were dried under a stream of nitrogen and were finally reconstituted in 1 ml initial mobile phase containing an additional 20 μg/ml diphenylamine as external standard. Quantification relative to the internal standard was performed by comparison of surface area/AUC, as calculated on the obtained chromatograms for reference products and the unknowns. A calibration series was used by transferring 10 μl, 20 μl, 50 μl, 75 μl and 100 μl of stock solution into an auto sampler vial, which were subsequently dried under a stream of nitrogen (after addition of 50 μl 10% hydrochloric acid in methanol) and reconstituted in 1.0 ml initial mobile phase containing 20 μg/ml diphenylamine as external standard.

#### 2.3.3. $^{1}H$ nuclear magnetic resonance spectroscopy (NMR)

For the NMR analysis, the active component needed to be isolated from the yellow tablet. Since amphetamines are amines with a pKa of approximately 10, an acid/base extraction procedure was estimated to be suitable. To this end, a fragment of the tablet was placed in a glass test tube to which 10 ml water was added. The tube was sealed with a polypropylene cap and agitated until the material was mostly dissolved and only minor amounts of precipitate persisted. This suspension was transferred to a separatory funnel. The tube was rinsed thoroughly with 2 ml water. The pH of the solution in the separatory funnel was adjusted to 2–3 (Merck indicator paper) using 2.0 M HCl. The remaining solids of the suspension did not go into solution upon the addition of HCl. The aqueous suspension was extracted with dichloromethane (3 × 20 ml). These dichloromethane fractions were discarded. The pH of the (acidic) aqueous fraction was adjusted to 12–13 by the drop wise addition of 4.0 M NaOH. At this pH the amine group in the amphetamine is expected to be in the free base form, which allows extraction into an organic solvent. The aqueous layer was thoroughly extracted with dichloromethane (5 × 20 ml). The dichloromethane fractions were pooled, dried using $Na_2SO_4$, filtered and concentrated *in vacuo*. A minimal amount of an oily residue was obtained. This material was stored under vacuum (~1 mBar) in an attempt to remove all volatile impurities. The residue was dissolved in 1 ml $CDCl_3$ (+0.5% v/v TMS (tetramethylsilane)). From this solution 750 μl was transferred to an NMR tube which was closed with a polypropylene cap.

All NMR spectra were recorded at 25 °C on a Varian Mercury-300BB (300/75 MHz) and processed using the Varian VNMRJ 3.2 software package.2.3. A solution of the material (±20 mg) in $CDCl_3$ + 0.5% v/v TMS (750 μl) was prepared in an NMR tube (5 mm diameter, VWR-300 MHz grade) and sealed using a polypropylene cap. The spectrum was recorded at 300 MHz using 32 scans and was referenced to the signal of TMS at 0 ppm.

## 3. Results

### 3.1. GC–MS

A methanolic sample solution of the tablet was analyzed by GC–MS and the major peak was identified as 4-chloromethamphetamine (4-CMA) by means of computer-based library search and matching with the SWGDRUG Mass Spectral Library (Version 3.1). The mass spectra are shown in Fig. 3.

Fragment pattern analysis of 4-CMA, TMS and TFA derivatives confirmed the presence of a chloromethamphetamine regioisomer. Proposed fragmentation patterns of 4-CMA, TMS and TFA derivatives are given in Fig. 4.

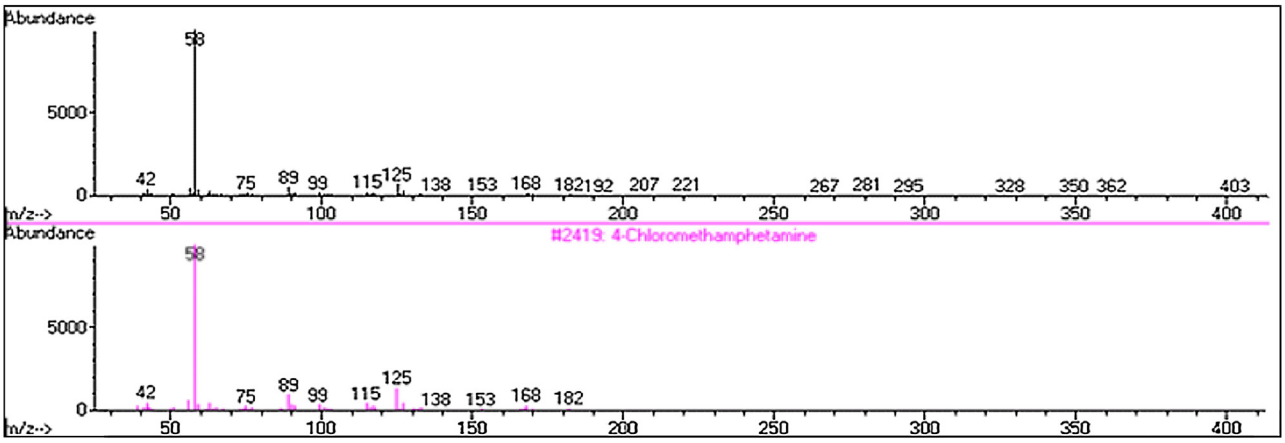


**Fig. 3.** Mass spectrum of 4-CMA in the chromatogram from the tablet (upper) and reference mass spectrum of 4-CMA present in the SWGDRUG library (lower).

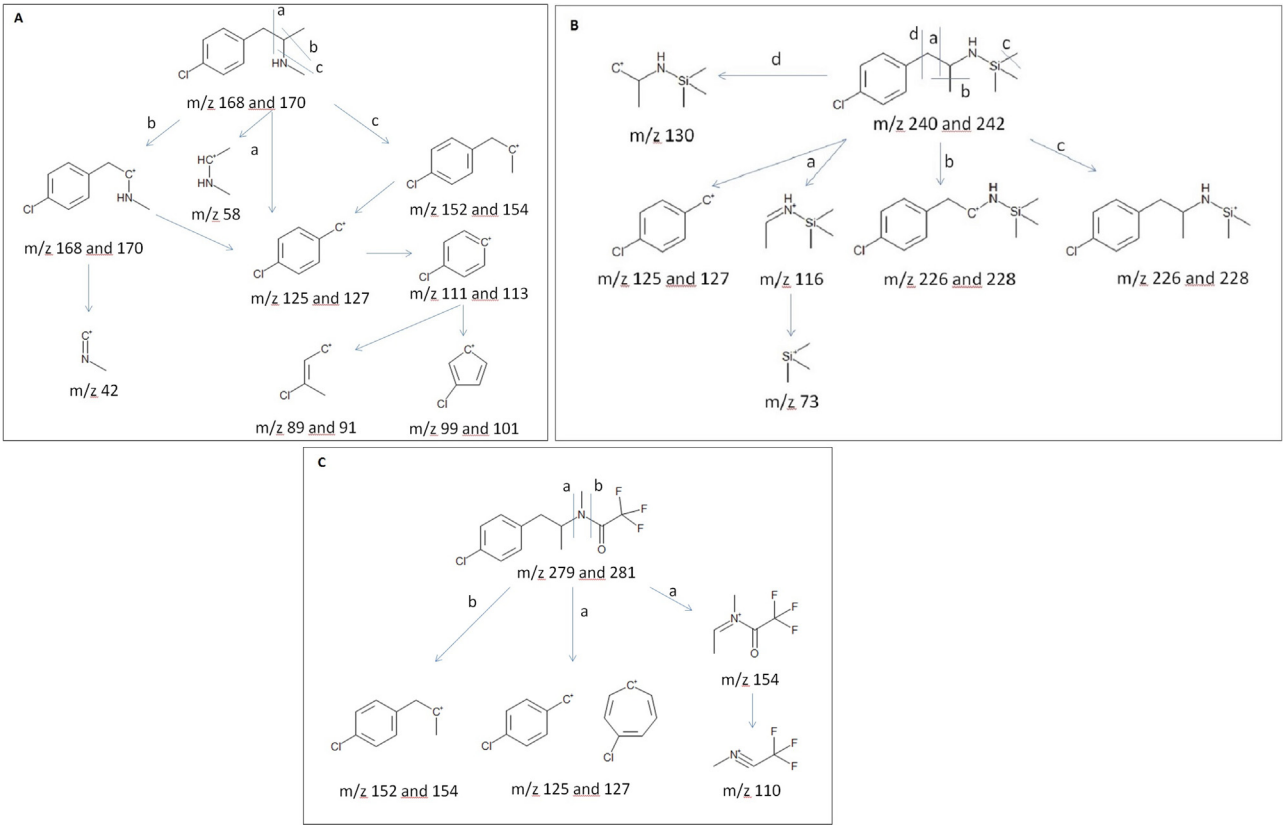


**Fig. 4.** Proposed fragmentation pattern of 4-CMA (A), 4-CMA TMS derivate (B) and 4-CMA TFA derivate (C).

### 3.2. HPLC-PDA

In the chromatograms of the HPLC-PDA analysis, a peak was observed with the same retention time (±2%) and UV spectrum (similarity index > 0.995) as 4-CMA. The HPLC-PDA chromatogram of the tablet with UV spectrum of 4-CMA is shown in Fig. 5. Calibrators and sample extracts were analyzed in one batch.

A six-point calibration curve was made by plotting the ratio of the observed peak area of 4-CMA to that of the external standard diphenylamine to the amount of 4-CMA in the autosampler vial. The calibration curve was linear over the concentration range investigated (r: 0.9969). Residual plots were evaluated, confirming that the used calibration model was appropriate (criteria: 10%). Two aliquots were extracted. All results were within the calibration range and concentrations were calculated from the linear regression equation, taking in account the amount of aliquot extracted. The following mean concentration was measured: 98 mg 4-CMA (as base)/tablet (n = 6; range: 86–106 mg/tablet). A blank was analysed before every sample. No carry-over was observed.

### 3.3. $^{1}H$ NMR

For chloromethamphetamine, with respect to the position of the chlorine atom, three region-isomers are possible, respectively 2-chloromethamphetamine, 3-chloromethamphetamine and 4-chloromethamphetamine (Fig. 6) [4,5].

The signals for the protons of the phenyl group can be found in the area between 6.5–8.0 ppm in the $^{1}H$ NMR spectrum. The peaks are

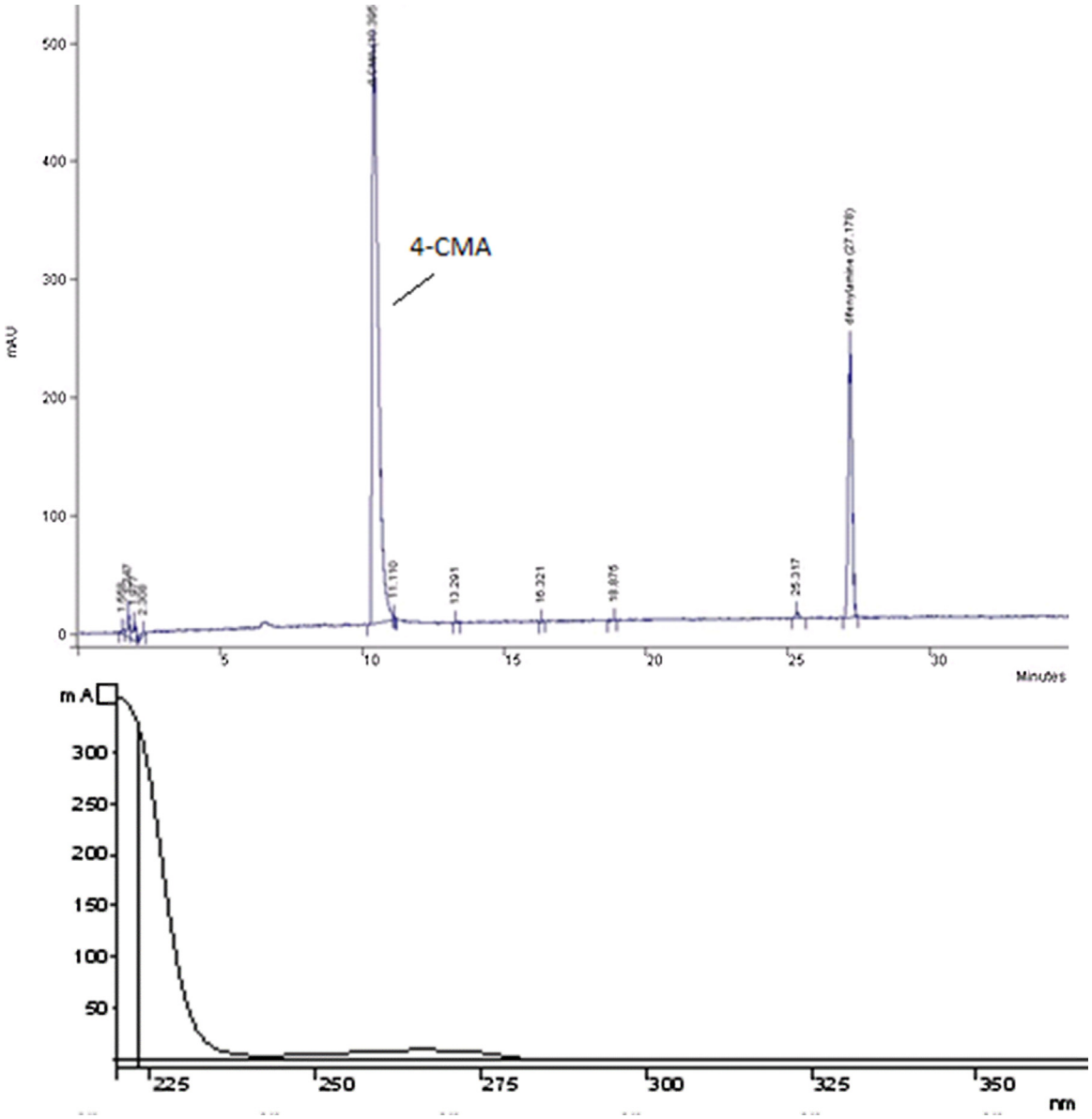


**Fig. 5.** HPLC-PDA chromatogram of the tablet (upper) with UV-spectrum of 4-CMA (lower).

shown to be two doublets, each with an integral of approximately 2, indicating the presence of a clear para-substitution. A full assignment of all the peaks of the 4-CMA structure can be found in Fig. 7.

## 4. Discussion

The combination of all applied techniques HPLD-PDA, GC–MS and $^{1}$H NMR allowed to unequivocally identify the unknown substance as 4-CMA in a tablet confiscated at an international music festival. Since this seizure, which happened in August of 2015 (Fig. 8A), several other instances were reported in the EU where 4-CMA was identified in seized drug samples: in November and December of 2015, light yellow tablets with a turtle logo containing 4-CMA were identified in respectively Romania and Austria (Fig. 8B). Finally, in March 2016 a larger quantity of these tablets with turtle logo was identified by police services in Croatia.

To have an indication of the potency of the tablet, a quantitative assessment of the 4-CMA concentration was performed with HPLC-PDA and was found to be approximately 98 mg 4-CMA (expressed as mg base per tablet).

4-CMA is the para-chlorinated *N*-methylated derivative of amphetamine and was researched in the 1960s as an appetite suppressant or antidepressant [6,7]. During these studies, decreased levels of 5-hydroxytryptamine (serotonin, 5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were observed after the administration of *p*-chloroamphetamine and 4-CMA [4]. Other authors [4,5] found that the substance differed from other amphetamines by exhibiting only a slight central stimulant effect in both animals and humans, and that they acted like an antidepressant rather than a central stimulant. It was also reported that 4-CMA was a potent and long-lasting depleter of brain serotonin. Further investigation into the long-term effects of chloroamphetamines revealed that administration of 4-CMA caused a prolonged reduction in the levels of 5-HT and the activity of tryptophan hydroxylase in the brain. Ultimately it was discovered that 4-CMA was neurotoxic, specifically acting at the serotonergic neurotransmission system [8–11]. By the 1970's it

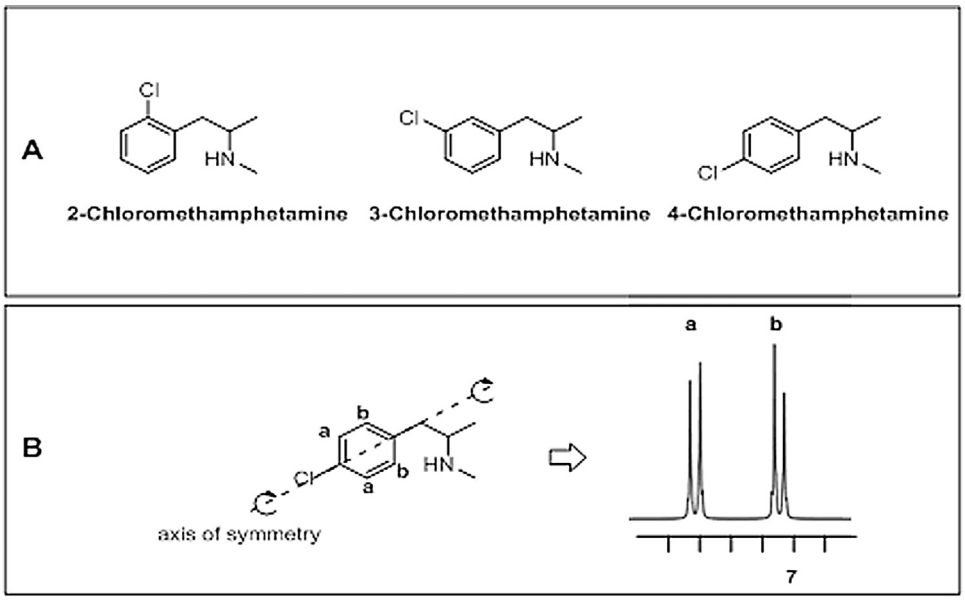


**Fig. 6.** A: Three regioisomeric forms of chloroamphetamine B: Only 4-CMA has the required symmetry to yield the two doublets at 6.6–8.0 ppm.

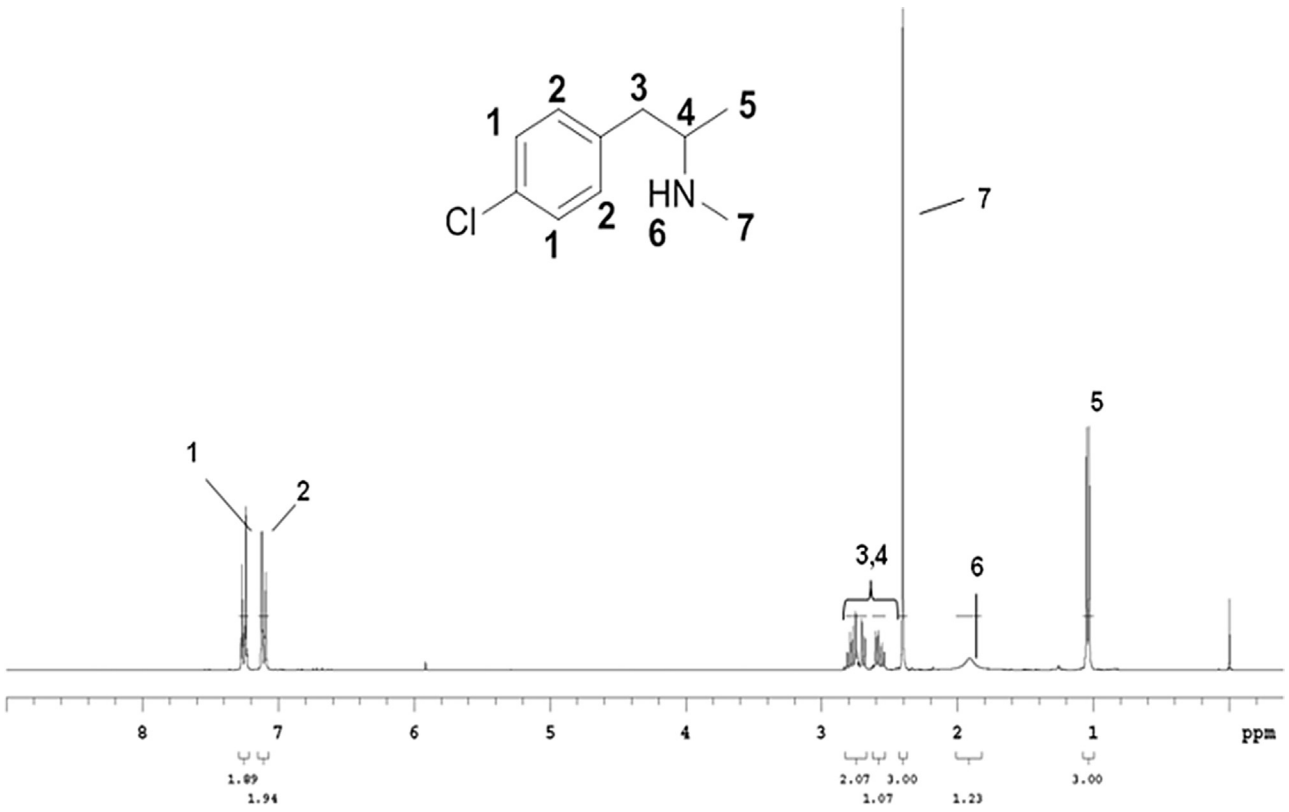


**Fig. 7.** $^{1}$H NMR spectrum of 4-CMA with full structural assignment.

became evident that some ring-halogen-substituted phenethylamines including 4-CMA demonstrated neurotoxic properties mostly resulting in the loss of serotonin neurons [12–15]. Hence, clinical research in humans was halted.

In practice, in the absence of empirical experimental clinical evidence, prof. David Nichols would predict 4-CMA to be a stimulant and hyperthermic agent with a psychopharmacology like MDMA, but more potent, and also neurotoxic. 4-CMA might have a longer duration of action compared to MDMA (which lasts 4–5 h) because it is less susceptible to metabolism. Acute toxicity (hyperthermia, dehydration) was the first concern of Dr. Nichols. Psychoactive effects of 4-CMA and 4-CA were evaluated in humans while researching both compounds as antidepressants. In the dosages used (80–90 mg daily, in 3 doses), no significant acute psychoactive effects were noticed; adverse effects were also low, although an effect on sleep and nausea was mentioned [7].

Regarding potency in humans, very few data, if any, are available. However, data for the *N*-demethylated derivative 4-chloroamphetamine (4-CA) are available. For example, using a MDMA-trained rat drug discrimination study, an effective dose

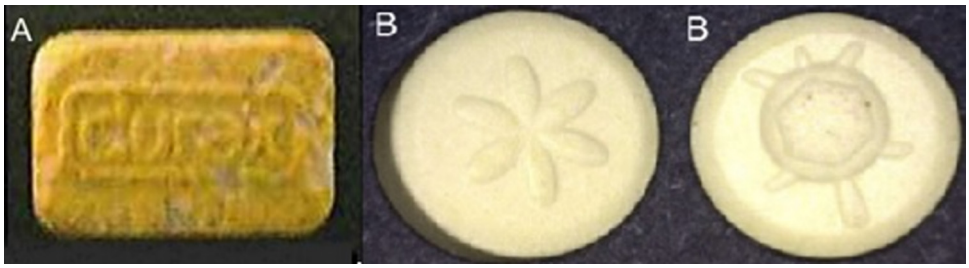


**Fig. 8.** Ecstasy tablets containing 4-CMA, found in 2015 in Belgium (A) and elsewhere in Europe (B).

(ED50) of 0.17 mg/kg was reported for 4-CA, whereas the ED50 of MDMA is 0.78 mg/kg [16]. Based on these *in vivo* rat data one might expect 4-CA to have about four times the potency of MDMA. Also, in a study performed in 1995 it was demonstrated that 4-CA is a more potent 5-HT uptake inhibitor than amphetamine or 4-fluoroamphetamine, although less potent at dopamine and norepinephrine reuptake sites [17]. 4-CMA is the *N*-methylated derivative of 4-CA and will be more lipophilic and hence more likely to penetrate the blood–brain barrier and potentially more potent *in vivo* than 4-CA itself.

None were noted by the authors. Dosages used in lab animals were 1–2 mg/kg. Human clinical dosages of 4-CMA used during the research as an antidepressant amounted to 80 mg daily (divided into three doses) without major physiological side effects [18], a dosage comparable to what was found in the 4-CMA tablet in Belgium (approximately 98 mg/tablet). Since a specific antidote is lacking treatment of overdoses would be symptomatic. *In vivo* metabolism of 4-CMA to 4-chloroamphetamine (4-CA) implicates that at least part of the harm observed in 4-CA trials will also occur after consumption of 4-CMA. Moreover, authors such as Fuller et al. [12] demonstrated in pre-clinical studies with animals with 4-CA that only low dosages of the substance needed to be consumed to already result in long-term loss of serotonergic neuronal function.

Summarizing the receptor actions of 4-CMA, we estimate that clinical effects of 4-CMA will be a combined result of motor activating effects mediated by NA potentiation, and mood-improving effects caused largely by 5-HT potentiation. In practice, these include the typical amphetamine effects (such as increased energy and stimulation, euphoria) and possibly empathogenic effects comparable to those of MDMA [7]. Based on rodent data it is believed that 4-CMA will be more potent than MDMA and will likely have a longer duration of action, with a psychopharmacology similar to MDMA including dose-dependent effects.

From available literature data and expert discussion, we estimate that the health risks for this substance include both acute and more prolonged, long-term effects. Theoretically acute health risks would be comparable to those observed for MDMA, PMMA and 4-MA, and would be mainly due to serotonin release, combined with noradrenergic stimulation. Severe, possibly malignant hyperthermia is a real risk resulting from an induced serotonin syndrome.In addition, 4-CMA shows neurotoxic properties resulting in permanent destruction of serotonergic neurons. Currently the clinical or biological implications of this neurotoxicity remain unknown. Serotonergic neurotransmission being implicated, it stands to reason that long-term exposure and/or damage could potentially include depression or exacerbation thereof, with perhaps an increased incidence in predisposed people. In addition, no information is available about the time of manifestation of these symptoms; late onset of symptoms of induced neurotoxicity is a possibility.

To the author's knowledge, this is the first report confirming the presence of 4-CMA in a seized ecstasy tablet. No intoxications or fatalities involving the use of 4-CMA were found in literature and consultation of the EMCDDA revealed that, other than the tablets reported above, no other events involving 4-CMA were reported in Europe either.

## 5. Conclusions

In this paper, we discuss the first reported case of 4-CMA in seized ecstasy. Conclusive identification and analytical characterization were performed using HPLC-PDA, GC–MS (including TMS and TFA derivatives) and $^{1}$H NMR. After consultation of the scare information available in literature and discussion with experts it became clear that 4-CMA has neurotoxic properties, the effects of which on the human body are currently unknown. Considering that after this initial detection several other tablets containing 4-CMA were found in different parts of Europe, it stands to reason that some people will have consumed these tablets. In clinical cases with observed neurotoxicity after (prolonged) drug abuse, especially ecstasy, and in the absence of other contributing factors, professionals could consider the potential (past) consumption of tablets containing 4-CMA when assessing patient and case history.

It seems reassuring that after March 2016 no tablets containing 4-CMA were ever reported again; we estimate that these tablets may have been present on the European market for about half a year, starting in summer 2015. Perhaps luckily, from spring 2016 onwards, the substance together with its potentially devastating effect on public health, seems to have disappeared from the international market.

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