FACT SHEET

4-chloromethamphetamine (4-CMA)

September 2015

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The information contained in this document is also available on the BEWSD-website (with corresponding pdf-files and analytical data). This part of the website is not accessible for the general public. A login can be requested by contacting ews.drugs@wiv-isp.be.
A. General information

Recent seized sample in Belgium

Substance: 4-chloromethamphetamine
Date of collection: July 2015
Date of analysis: August 2015
Product type: tablet
Colour: Yellow/brown
Region: Antwerpen

Type
Psychotropic substances

Group
Phenethylamines

Name
4-chloromethamphetamine

Nature of substance
4-Chloromethamphetamine (CMA) is a stimulant derivative of amphetamine, that was investigated in the past as an antidepressant. Compared to methamphetamine, noradrenergic effects are less pronounced, and CMA demonstrates considerable influence on serotonin neurotransmission. It has also been established that CMA is a serotonergic neurotoxin.

It is metabolized in vivo to 4-chloro-amphetamine, which is also a known neurotoxic compound.

Other names
4-CMA; p-CMA; CMA

B. Alerts

Alerts
Belgium, September 2015

The BEWSD was informed by Eurofins NV about the analysis of an ecstasy tablet containing chloromethamphetamine. After extensive further analysis (a.o. NMR was necessary), the substance was positively identified as 4-chloromethamphetamine.

The tablet was a brown/yellow rectangle, with imprint/logo “Durex” (photos available further in this document). Tablet characteristics: 430mg weight, dimensions 12.5 x 8.4mm, thickness 3.8mm.

Reports to EMCDDA
No reports, this is the first time this substance is reported.
CMA was found to be a potent and long-lasting depleter of brain serotonin. It has been compared to methamphetamine in normal subjects, and was evaluated clinically as an antidepressant(Kits and van Praag 365-73; van Praag et al. 66-76; van et al. 313-15).

Typical dosages used were 60-90mg daily, divided into three doses. No major physiological side effects were noted.

Later, it was discovered that CMA was a neurotoxic substance, specifically acting at the serotonergic neurotransmission system(Sanders-Bush, Bushing, and Sulser 33-41). Hence, clinical research in humans was halted.

C. Pictures

D. Clinical information

Usage

Subjective effects in man:
Very little information regarding this substance is available.

In the absence of empirical experimental clinical evidence, prof. David Nichols would predict 4-chloromethamphetamine to be a stimulant/hyperthermic agent with a psychopharmacology similar to MDMA, but more potent, and also more neurotoxic. CMA might have a longer duration of action compared to MDMA (which lasts 4-5 hours), because it is less susceptible to metabolism. Acute toxicity of this compound (hyperthermia, dehydration, etc.) was the first concern of dr. Nichols(Nichols 1-3).

The (desired) effects of amphetamines and MDMA have been well described in literature. Psychoactive effects of CMA and 4-CA were evaluated in humans while researching both compounds as antidepressants. In the dosages used (80-90mg daily, in 3 doses), no significant acute psychoactivity was noticed; side effects were also low, although an effect on sleep and nausea was mentioned(van Praag et al. 66-76).

Summarizing the receptor actions of CMA, we estimate that clinical effects of 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 (e.g. increased energy and stimulation, euphoria), and feelings of wellbeing and possibly empathogenic effects comparable to those of MDMA, attributable to the serotonergic properties of CMA(van Praag et al. 66-76). Based on rodent data, it is believed that CMA will be more potent than MDMA and will likely have a longer duration of action, with a psychopharmacology that would be similar to MDMA(Nichols 1-3).
Of course effects will be dose-dependent. More information is available in the section “Dosage”.

**Dosage:**

Regarding potency in humans, very few data, if any, are available. However, data for the N-demethylated derivative 4-CA do exist. For example, Johnson et al found in a MDMA-trained rat drug discrimination study that the ED50 of 4-CA was 0.17 mg/kg, whereas the ED50 of MDMA was 0.78 mg/kg (Johnson et al. 1-10). Thus, from 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 (Marona-Lewicka et al. 105-13). The N-methyl derivative of 4-CA, CMA, will be more lipophilic and hence, more likely to penetrate the blood-brain barrier and potentially more potent *in vivo* than 4-CA itself (Nichols 1-3).

**Table 3. Potencies of halogenated amphetamines at different neurotransmitter systems.** Adapted from (Marona-Lewicka et al. 105-13).

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM) to inhibit monoamine uptake</th>
<th>Ratio of 1/IC50 values</th>
<th>Norepinephrine uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[3H]HT</td>
<td>[3H]Dopamine</td>
<td>[3H]Norepinephrine</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>3769 ± 356</td>
<td>172 ± 23</td>
<td>148 ± 16</td>
</tr>
<tr>
<td>p-Fluoroamphetamine</td>
<td>2352 ± 290</td>
<td>270 ± 33</td>
<td>356 ± 15</td>
</tr>
<tr>
<td>p-Chloroamphetamine</td>
<td>187 ± 25</td>
<td>551 ± 73</td>
<td>257 ± 8</td>
</tr>
<tr>
<td>p-Iodoamphetamine</td>
<td>46 ± 3</td>
<td>1955 ± 135</td>
<td>690 ± 7</td>
</tr>
<tr>
<td>(+)-MDDB</td>
<td>784 ab</td>
<td>7825 ab</td>
<td>1233 ab</td>
</tr>
<tr>
<td>MMAI</td>
<td>212 ab</td>
<td>19795 ab</td>
<td>11618 ab</td>
</tr>
</tbody>
</table>

The IC50 values represent the means ± S.E.M. of three separate experiments. Each experiment utilized five concentrations, run in triplicate. The IC50 values were determined from the linear portion of graded dose-response curves, according to the procedure of Tallarida and Murray (1981). * Significantly different from (+)-amphetamine IC50 (P < 0.001, Student's *t*-test). † Taken from reference Nichols et al. (1991).

Dosages used in lab animals were 1-2mg/kg. Human clinical dosages of CMA used during the research as an antidepressant in the 1970’s amounted to 80mg daily (divided into three doses), comparable to what was found in the CMA tablet in Belgium (van Praag et al. 145-60).

It is important to realize that the dosage used in clinical studies (~80mg daily) was administered divided into 3 doses. So each dose consisted of 25-30mg of CMA. No studies were found where higher dosages were administered to humans.

**Health risks**

A thorough discussion is outside of the scope of this document. However, it is clear that the health risks for this substance include an acute, and a later “stadium”
Acute health risks are comparable to those observed with MDMA, PMMA and 4-MA, and are mainly due to serotonin release, combined with stimulation. Severe hyperthermia is a possibility, possibly resulting from an induced serotonin syndrome.

On top of these acute effects, there is the demonstrated neurotoxicity of CMA, which results in permanent brain damage from destruction of serotonergic neurons. At the moment, it is unknown what clinical results will be observed due to the neurotoxicity of this compound in humans. Long-term damage could, for example, include chronic depression. Time of manifestation of these symptoms is unknown. Treatment of overdoses is symptomatic.

E. Legal status

Uncontrolled

F. Chemistry

Systematic chemical name
[1-(4-chlorophenyl)propan-2-yl](methyl)amine; 4-chloro-N,α-dimethyl-benzeneethanamine

Other chemical names and variants
4-chloromethamphetamine, p-CMA, 4-CMA, CMA

Chemical Abstracts Service (CAS) registry number
1199-85-5 (base); 30572-91-9 (HCl salt)

Molecular information

Molecular structure:

![Molecular structure of CMA]

Molecular formula: \( \text{C}_{10}\text{H}_{14}\text{ClN} \)

Molecular weight: 183.68

Exact mass: 183.0814772

Identification and analytical profile can be found at the end of this document. Analytical spectra were kindly provided by the University of Ghent (prof. dr. Van Calenbergh) and Eurofins Forensics Brugge (dr. apr. Cordonnier).
G. References


Library Searched: C:\DATABASE\SWGDRJG.L
Quality: 52
If: 4-Chloromethamphetamine

Scan 1180 (10.950 min): 816H15-G.D

#2064: 4-Chloromethamphetamine
UV spectra by Eurofins Forensics
Dr. J. Cordonnier
Brugge, Belgium

Scan Rate: 10,000 Hz  Bunch: 4  Data Rate: 2,500 Hz
Detector Range: 220.000->367.000 nm  Valid Range: 220.000->367.000 nm
Spectrum Type: Within  Correction Type: Baseline

Within at 10.240 min  PuP = 223.10 nm

nm  mAU  nm  mAU  nm  mAU  nm  mAU  nm  mAU  nm  mAU

220.00  361.13  221.00  359.35  222.00  351.49  223.00  335.68  224.00  312.36  225.00  276.80
226.00  232.24  227.00  184.05  228.00  137.01  229.00  97.325  230.00  66.320  231.00  43.961
232.00  29.655  233.00  20.049  234.00  14.082  235.00  10.390  236.00  7.9720  237.00  6.4397
238.00  5.3927  239.00  4.8044  240.00  4.3368  241.00  4.0921  242.00  3.9278  243.00  3.9147
244.00  4.0222  245.00  4.1783  246.00  4.4805  247.00  4.6639  248.00  4.9460  249.00  5.2165
250.00  5.9304  251.00  5.9859  252.00  6.3979  253.00  6.7425  254.00  7.0923  255.00  7.3714
256.00  7.6926  257.00  8.1676  258.00  8.6075  259.00  8.9787  260.00  9.2929  261.00  9.4842
262.00  9.7504  263.00  10.028  264.00  10.310  265.00  10.607  266.00  10.703  267.00  10.606
268.00  10.244  269.00  9.6436  270.00  8.9925  271.00  8.4466  272.00  8.0642  273.00  7.8484
274.00  7.6570  275.00  7.2075  276.00  6.5070  277.00  5.4405  278.00  4.2393  279.00  3.1105
280.00  2.2244  281.00  1.6164  282.00  1.2329  283.00  0.9931  284.00  0.8029  285.00  0.7363
286.00  0.6886  287.00  0.6311  288.00  0.6124  289.00  0.5093  290.00  0.4343  291.00  0.4005
292.00  0.3938  293.00  0.3134  294.00  0.2364  295.00  0.2534  296.00  0.3096  297.00  0.3771
298.00  0.3829  299.00  0.3590  300.00  0.2740  301.00  0.2101  302.00  0.2137  303.00  0.1819
304.00  0.2062  305.00  0.1779  306.00  0.1487  307.00  0.1116  308.00  0.0965  309.00  0.1528
310.00  0.1747  311.00  0.1901  312.00  0.1418  313.00  0.0706  314.00  0.0132  315.00  0.0235
316.00  0.0597  317.00  0.1016  318.00  0.1454  319.00  0.1544  320.00  0.1281  321.00  0.1586
322.00  0.1346  323.00  0.1178  324.00  0.1315  325.00  0.0929  326.00  0.1492  327.00  0.1847
328.00  0.1967  329.00  0.1696  330.00  0.1374  331.00  0.1182  332.00  0.1926  333.00  0.2691
334.00  0.3286  335.00  0.3512  336.00  0.2594  337.00  0.2414  338.00  0.1663  339.00  0.1520
340.00  0.1902  341.00  0.1942  342.00  0.2219  343.00  0.2960  344.00  0.2978  345.00  0.2789
346.00  0.2597  347.00  0.2285  348.00  0.1833  349.00  0.1855  350.00  0.1304  351.00  0.1022
352.00  0.1310  353.00  0.1625  354.00  0.2299  355.00  0.2212  356.00  0.1720  357.00  0.1058
358.00  0.0827  359.00  0.1198  360.00  0.1167  361.00  0.1339  362.00  0.1491  363.00  0.1190
364.00  0.1401  365.00  0.1486  366.00  0.1509  367.00  0.2011
chloroamphetamine extracted from tablet

Sample Name: C1Amf
Data Collected on: linux300-mercury300
Archive directory: /home/data/Martijn
Sample directory: C1Amf
File: C1Amf_PROTON_28Aug2015_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdc13
Data collected on: Aug 28 2015

Temp. 25.0 °C / 298.1 K
Operator: Martijn

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
Width 4798.5 Hz
32 repetitions
OBSERVE H1 300.0100342 MHz
DATA PROCESSING
PT size 131072
Total time 3 min 25 sec

ppm
8 7 6 5 4 3 2 1
1.89 1.94 2.07 3.00 1.07 1.23 3.00