FACT SHEET

4-chloromethamphetamine (4-CMA)

September 2015

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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, noradreneric 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).

The inhibition of [^{3}H]5-HT, [^{3}H]dopamine, and [^{3}H]norepinephrine uptake was examined in rat whole brain synaptosomes

	IC_{50} (nM) to inhibit monoamine uptake			Ratio of $1/IC_{50}$ values	
	[^{3}H]5-HT	[^{3}H]Dopamine	[^{3}H]Norepinephrine	Dopamine/5-HT	Norepinephrine/5-HT
Amphetamine	3769 ± 346	172 ± 23	148 ± 16	21.91	25.47
p-Fluoroamphetamine	2352 ± 290	270 ± 33	356 ± 15 [a]	8.71	6.61
p-Chloroamphetamine	187 ± 25 [a]	551 ± 73 [a]	257 ± 8 [a]	0.34	0.73
p-Iodoamphetamine	46 ± 3 [a]	1055 ± 135 [a]	490 ± 7 [a]	0.04	0.09
(+)-MBDB	784 [a,b]	7825 [a,b]	1233 [a,b]	0.10	0.63
MMAI	212 [a,b]	19793 [a,b]	11618 [a,b]	0.01	0.02

The IC_{50} values represent the means ± S.E.M. of three separate experiments. Each experiment utilized five concentrations, run in triplicate. The IC_{50} values were determined from the linear portion of graded dose-response curves, according to the procedure of Tallarida and Murray (1981). [a] Significantly different from (+)-amphetamine IC_{50} ($P < 0.001$, Student's *t*-test). [b] 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 permant 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

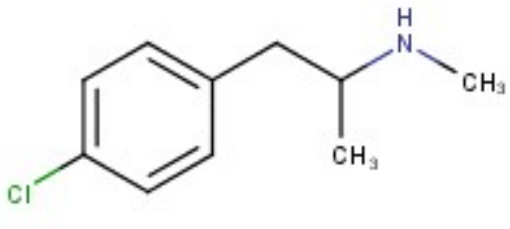
4-chloromethamphetamine, p-CMA, 4-CMA, CMA

Chemical Abstracts Service (CAS) registry number

1199-85-5 (base); 30572-91-9 (HCl salt)

Molecular information

Molecular structure:



Molecular formula: $C_{10}H_{14}ClN$

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).
The Belgian EWS alert is presented here (in Dutch and French).

The Belgian EWS alert that was send to the professional sector and general population can be found below (only in Dutch and French).

NL
Geachte collega's

Het Belgisch Early Warning System Drugs op het Wetenschappelijk Instituut Volksgezondheid (WIV-ISP) werd op de hoogte gebracht van de ontdekking van de nieuwe psychoactieve substantie 4-chloromethamphetamine (CMA).
Deze stof werd eind juli aangetroffen in een ecstasy-tablet, in de regio Antwerpen.

CMA is een derivaat van methamfetamine waarover zeer weinig bekend is. Het is de eerste maal ooit dat deze stof wordt aangetroffen, op dit ogenblik is deze stof nog legaal.
Oorspronkelijk werd CMA onderzocht als antidepressivum, maar na ontdekking van de neurotoxische eigenschappen werd dit onderzoek stopgezet.
De stof is bijzonder toxisch en veroorzaakt blijvende schade aan het serotonerge neurotransmittersysteem.
Daarnaast is ze ook acuut gevaarlijk: zeker in combinatie met bv. MDMA bestaat een risico op een serotonine syndroom en extreme hyperthermie, met mogelijk de dood tot gevolg.
Tot op heden werden geen intoxicaties of overlijdens gemeld gerelateerd aan CMA.

CMA werd in ons land aangetroffen in een rechthoekige gele tablet met logo “Durex”.

Het BEWSD volgt de situatie van nabij op, en zal u op de hoogte brengen van nieuwe ontwikkelingen.

FR

Chers collègues,

Le Belgian Early Warning System Drugs, de l’Institut Scientifique de Santé Publique (WIV-ISP), a été informé de la présence de la nouvelle substance psychoactive 4-chloromethamphétamine (CMA).
Cette substance a été découverte fin juillet dans une tablette d’ecstasy dans la région d’Anvers.

Le CMA est un dérivé de la méthamphétamine pour lequel il existe peu d’information. C’est la toute première fois que cette substance est rapportée. Actuellement cette substance est légale.
A départ, le CMA a été étudié pour ses propriétés antidépresseur, mais après la découverte de propriétés neurotoxiques, les recherches ont été stoppées.
La substance est extrêmement toxique et cause des dommages durables au système neurotransmetteur de sérotonine.
De plus il est également dangereux de manière immédiate : certainement en combinaison avec par exemple la MDMA il existe un risque d’un syndrome sérotoninergique et d’une hyperthermie extrême avec la possibilité de conséquences létales.
Jusqu’à présent il n’y a eu aucune intoxication ou décès liés au CMA qui ont été rapportés.

Le CMA a été découvert chez nous sous la forme d’une tablette rectangulaire avec le logo « Durex ».

Actuellement la tablette “Durex” est la seule tablette connue contenant du CMA. Il ne peut pas être exclu que du CMA soit également présent dans d’autres tablettes d’ecstasy.

Caractéristiques de la tablette :
Longueur : 12,5mm
Largeur: 8,4mm
Epaisseur: 4,3mm
Poids: 430mg
Forme: Rectangulaire
Couleur: Jaune
Logo: Durex
Ceci ne peut être établit qu'après une analyse de laboratoire. En Belgique il est possible de faire usage du service de testage de pilules de Modus Vivendi.

Le BEWSD suit la situation de près et vous tiendra informés lorsque de nouvelles informations seront disponibles.

Cordialement,

Peter
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Information: BEWSD Alert levels

The BEWSD has decided to distinguish its alert messages depending on the severity of the reported information.
The following 4 alert levels are used, and will always be indicated between brackets ([]) in the subject line of the alert message.

G. References

Johnson, M. P., et al. "Behavioral, biochemical and neurotoxicological actions of the alpha-ethyl homologue of p-chloroamphetamine." Eur.J.Pharmacol. 191.1 (1990): 1-10.

Kits, T. P. and H. M. van Praag. "A controlled study of the antidepressant effect of p-Chloro-N-methylamphetamine, a compound with a selective effect on the central 5-hydroxytryptamine metabolism." Acta Psychiatr.Scand. 46.4 (1970): 365-73.

Marona-Lewicka, D., et al. "Psychostimulant-like effects of p-fluoroamphetamine in the rat." Eur.J.Pharmacol. 287.2 (1995): 105-13.

Nichols, D. E. Personal Communication. Blanckaert, P. 1-3. 24-8-2015. 24-8-2015.

Sanders-Bush, E., J. A. Bushing, and F. Sulser. "Long-term effects of p-chloroamphetamine and related drugs on central serotonergic mechanisms." J.Pharmacol.Exp.Ther. 192.1 (1975): 33-41.

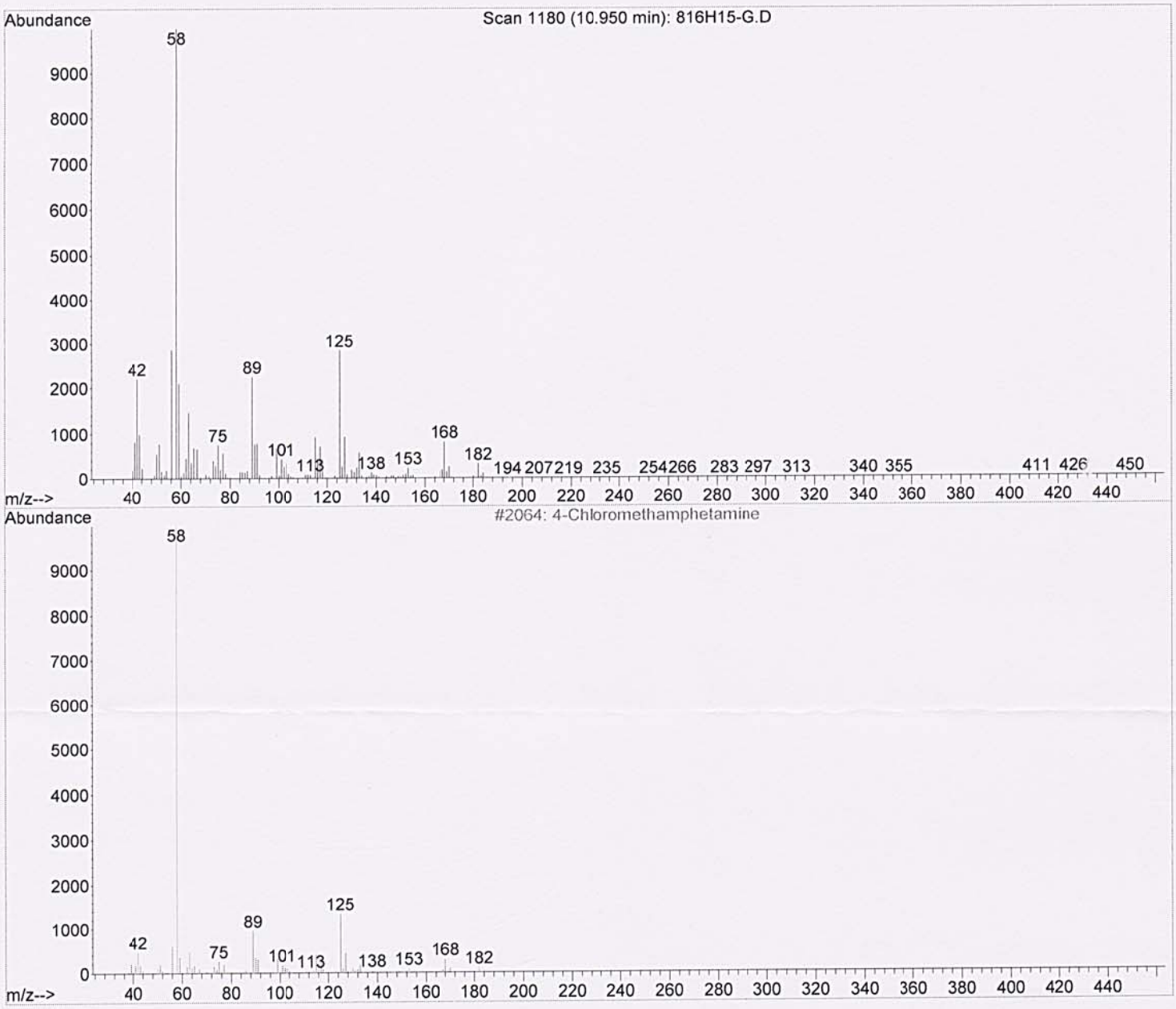
van Praag, H. M., et al. "Influencing the human indoleamine metabolism by means of a chlorinated amphetamine derivative with antidepressive action (p-chloro-N-methylamphetamine)." Psychopharmacologia. 13.2 (1968): 145-60.

van Praag, H. M., et al. "A comparative study of the therapeutic effects of sone 4-chlorinated amphetamine derivatives in depressive patients." Psychopharmacologia. 20.1 (1971): 66-76.

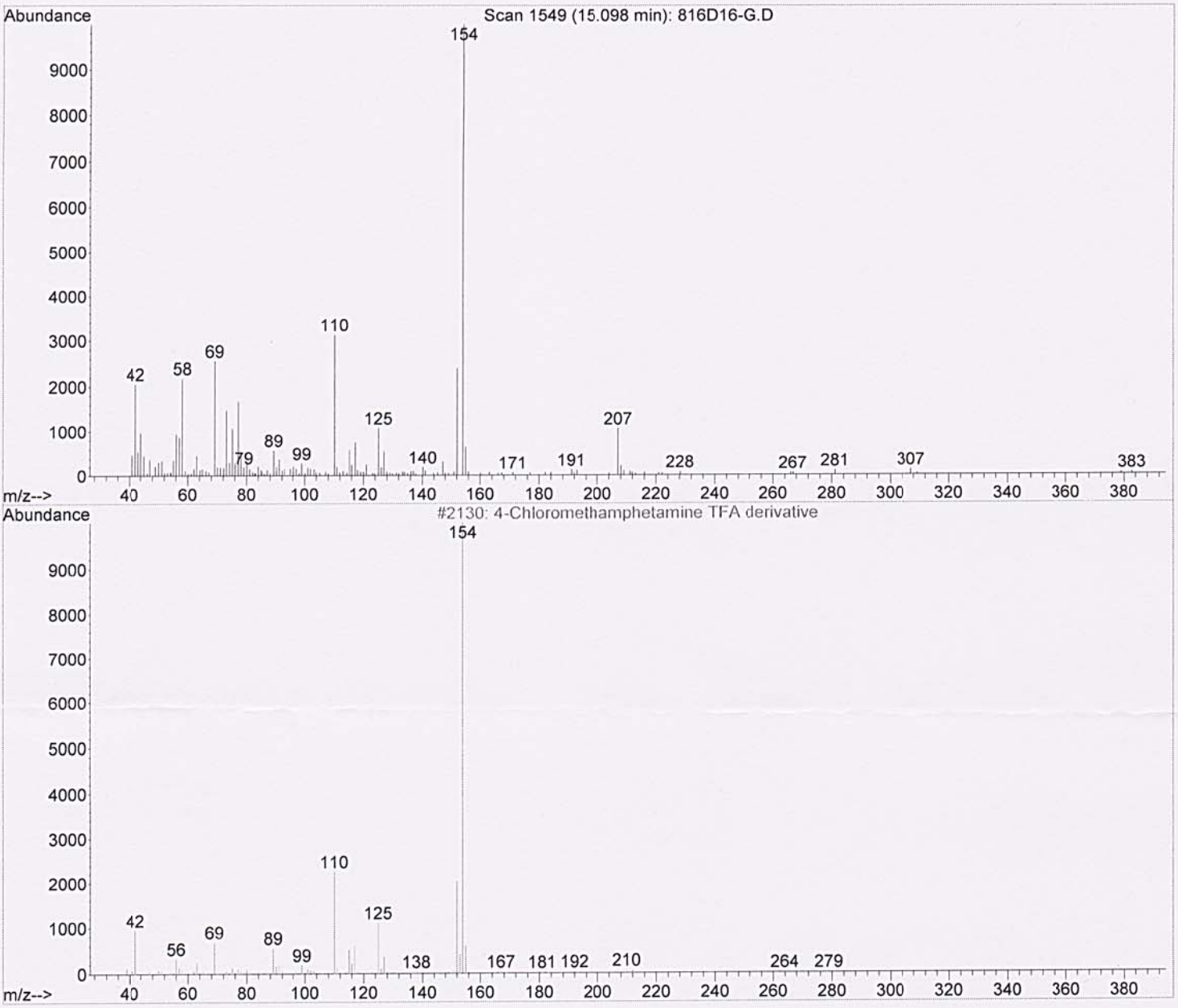
van, Woudenberg F., et al. "Investigation of the influence of p-chloro-N-methamphetamine on the human metabolism of 5-hydroxytryptamine with high voltage electrophoresis and liquid scintillation counting." Clin.Chim.Acta 27.2 (1970): 313-15.

GC/MS spectra by Eurofins Forensics
dr. J. Cordonnier
Brugge, Belgium

Library Searched : C:\DATABASE\SWGDRUG.L
Quality : 52
ID : 4-Chloromethamphetamine



Library Searched : C:\DATABASE\SWGDRUG.L
Quality : 62
ID : 4-Chloromethamphetamine TFA derivative



Title :
Run File : c:\star\data\2015\augustus\f-0816-15-g.run
Method File : c:\star\toxico.mth
Sample ID : F-0816-15-G

UV spectra by Eurofins Forensics
dr. J. Cordonnier
Brugge, Belgium

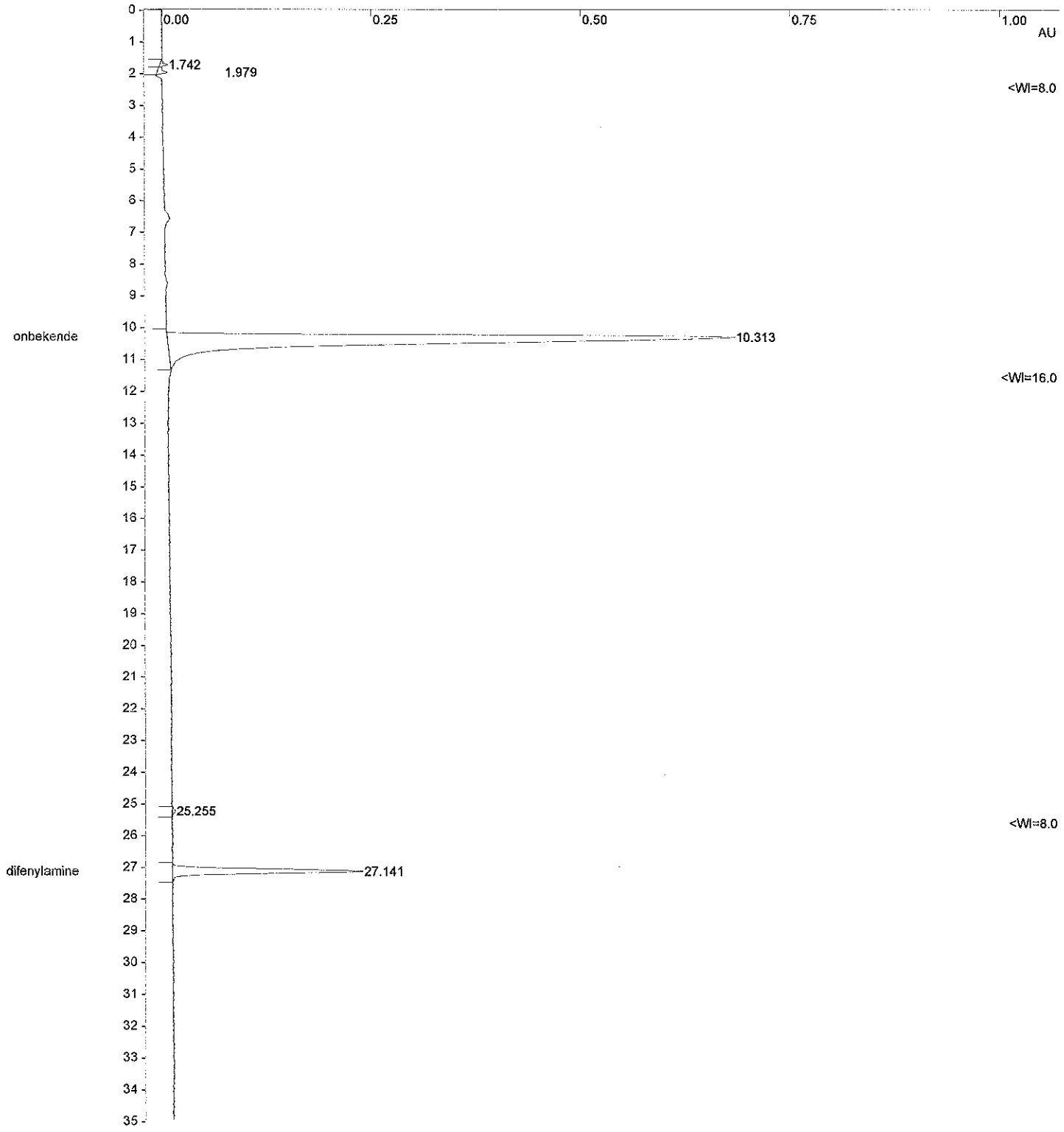
Injection Date: 8/6/2015 10:03 AM Calculation Date: 8/6/2015 11:52 PM

Operator : vc/ab/dd
Workstation: ACER
Instrument : Lc system
Channel : 2 = 220.00 nm

Detector Type: 335 UV-Vis. PDA
Bus Address : 44
Sample Rate : 2.50 Hz
Run Time : 35.000 min

** LC Workstation Multi Instrument Version 6.41 ** 00820-64C8-FAA-20B4 **

Chart Speed = 0.57 cm/min Attenuation = 32 Zero Offset = 2%
Start Time = 0.000 min End Time = 35.000 min Min / Tick = 1.00



Print Date: 06 Aug 2015 23:51:21

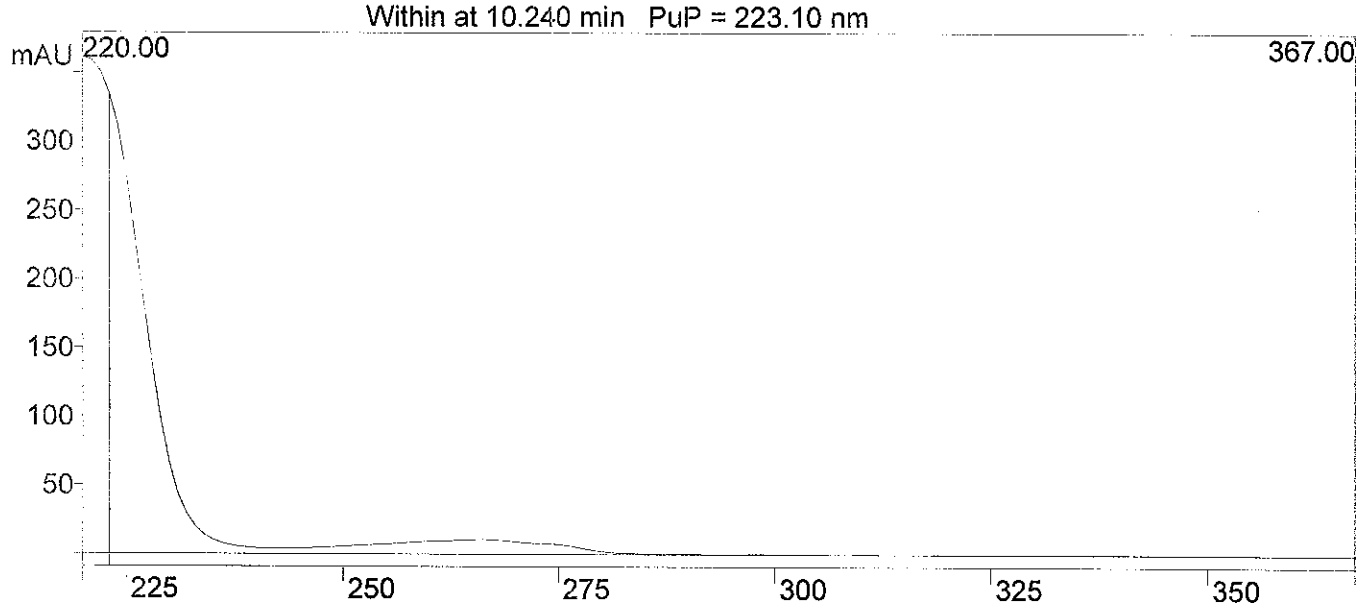
Spectrum Plot Report

Spectrum # 7

File: c:\star\data\2015\augustus\f-0816-15-g.run
tR: 10.240 min PuP (220.000->367.000 nm) = 223.099 nm
Name: F-0816-15-G

Instrument: Lc system
Method: toxico.mth
Operator: vc/ab/dd
Run Date: 8/6/2015 10:03 AM

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



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	5.3827	239.00	4.8044	240.00	4.3348	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	5.5304	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	8.0462	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	0.3348	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	0.2819	343.00	0.2968	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:
ClAmf
Data Collected on:
linux300-mercury300
Archive directory:
/home/data/Martijn
Sample directory:
ClAmf
FidFile: ClAmf_PROTON_28Aug2015_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
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
FT size 131072
Total time 3 min 25 sec