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# Report on characterisation of New Psychoactive Substances (NPS)

*Identification and characterisation of new drugs including physicochemical properties*

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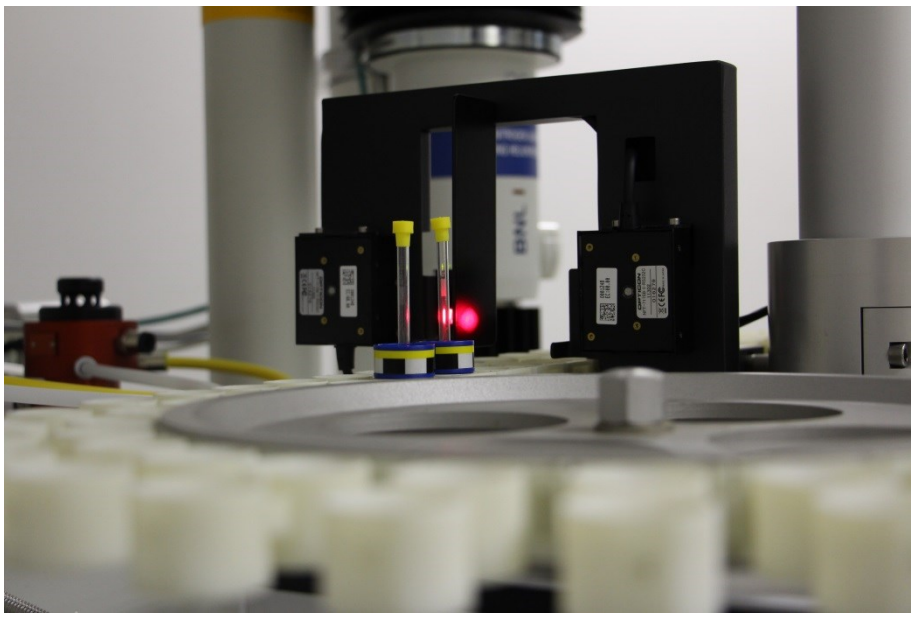

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# 1. EXECUTIVE SUMMARY

The main objective of this report is to give an overview of the analytical strategies and modern laboratory techniques needed to perform a fast unambiguous identification and characterisation of unknown organic chemical substances such as New Psychoactive Substances (NPS). The "routine" analytical methods applied in Member States control laboratories are generally efficient for recognition of already known substances. However, the chemical identification of many unknown substances found by customs and suspected to be NPS requires the use of more sophisticated analytical techniques such as Nuclear Magnetic Resonance (NMR) and High Resolution Mass Spectrometry (HR-MS). These approaches have been tested in the laboratory of the Joint Research Centre (JRC) and the efficiency of the proposed approach has been successfully demonstrated in several study cases.

There is a need for developing methods for fast recognition and identification of New Psychoactive Substances (NPS) and unknown chemicals especially because of the increasing possibility to purchase these substances via internet. Numerous products imported from non-EU countries are often mis-declared as 'bath salts', 'ferilizers', or as 'research chemicals' and may in fact contain so-called 'legal highs', analogues or precursors of known psychoactive substances or of licit or illicit (medical) drugs. The chemical identification of these new substances is a challenge for forensic and customs laboratories. Moreover, physicochemical, toxicological information or psychoactive properties are not known since no data is available for these compounds.

Customs, at the forefront of control of imported products need access and sharing of data on a broader range of new chemicals including eventually NPS or precursors. Electronic platforms such as European Customs Inventory of Chemical Substances (ECICS) or SINAPSE, a free web communication platform provided by the European Commission offering tools to promote expertise in EU policy making (already used by the Customs Laboratories European Network (CLEN)) have been suggested as potential repository of such information for EU customs laboratories. Furthermore, the use of certain seized materials as possible common analytical standards after their appropriate chemical characterisation would help the routine control work of customs laboratories. There remains a need of fine-tuning for harmonisation of proposed Standard Operating Procedures (SOPs) and completion with other analytical methodologies, as well as setting up efficient channels and protocols of communication and sharing of data based on electronic format as already proposed in the present document.

These aspects will be thoroughly examined during the next meeting of the CLEN/TAXUD working group on determination of NPS and unknown substances that will be hosted by EMCDDA in Lisbon on 5 and 6 February 2015. This meeting will also examine the possibilities for a more integrated data based exploitation of NPS uses chemoinformatic format and tools. Computer-aided modelling systems based on the similarity principle of chemical structures can be proposed to facilitate the classification of chemical substances. This will also facilitate the classification of NPS in one of the chemical families (i.e. phenethylamines, tryptamines, and cathinones), to be reported to EMCDDA through the Early Warning System (EWS).

## 2. Background

The emergence of designer drugs as abused substances has seen a dramatic increase over the past few years. More than 70 new psychoactive substances were discovered in 2012 and more than 80 in 2013. Customs and forensic laboratories are faced with a challenge in identifying the chemical structure of these new compounds.

The Member States authorities (customs, forensic, police), the Commission (DG JUST, DG TAXUD), and the European Agencies EMCDDA (European Monitoring Centres for Drugs and Drug Addiction) and EUROPOL (European Union's law enforcement agency) have taken note of this new situation and expressed their worries about the increasing number of new chemical structures reported in the last years. The European Drug Report 2014 published by the EMCDDA notices the rapid emergence of new drugs, chemical or natural substances that are not controlled under international law, and produced with the intention of mimicking the effects of controlled drugs **[1]**. The main trends and characteristics of this new situation can be summarized in the following bullet points:

- Some are produced from precursors in clandestine laboratories in Europe, but most of those chemicals are imported from non-EU countries;
- Products are often mislabelled as 'research chemicals' or 'plant food' with disclaimers such as "not intended for human consumption" with the aim to avoid controls;
- Synthetic cannabinoid receptor agonists, phenethylamines and cathinones, are the main "families" of chemical substances that have been reported in the recent years as most popular illicit drugs;
- An increasing proportion of chemical substances not related to readily recognised chemical groups are now detected;
- Most of the new psychoactive substances, when subjected to control measures, tend to be rapidly replaced. Several new chemical compounds found do not have CAS number or any other chemical registration;
- Physical and chemical properties and spectroscopic data as well as pharmacological and toxicological are often not available for such compounds;
- Substances that have caused problems requiring clinical interventions and fatalities have been recorded in several Member States (e.g. in the documentation presented about the recent case of 4-methylamphetamine) **[2];**

Customs, as the first rampart of the European Union, are responsible for the control of all products entering the EU market. This control applies to chemicals in general, among which are new psychoactive substances (not necessarily controlled under international law), pharmaceutical products and medicines. Efficient tools for the rapid and unambiguous identification of new designer drugs are needed to facilitate rapid decision-making regarding such imported substances. Customs and forensic laboratories generally perform such controls using "routine" analytical methods such as infrared spectroscopy and gas chromatography-mass spectrometry. These techniques allow the recognition of already known substances by comparing the analytical data of samples under investigation with available spectroscopic libraries.

Categorisation of new psychoactive substances by physicochemical characteristics and by their potential action on the central nervous system activity are needed to evaluate whether a substance should be included in international lists of classified and controlled substances. However, the first challenge in the categorisation is to set up a system of robust and efficient approaches for fast identification of these new chemical compounds and for reporting the relevant information to the competent national and European authorities in charge of collecting data on drugs and new psychoactive substances.

The identification of new derivatives as well as new chemical structures requires highly sophisticated analytical techniques such as Nuclear Magnetic Resonance (NMR) and High Resolution Mass Spectrometry (HR-MS). Depending on the case under study this process can also require several kinds of analytical experiments to gather the spectroscopic information necessary for establishing the chemical structure of the molecules or the composition of the product in case of mixture of several compounds. The present report introduces an analytical strategy allowing the characterisation of unknown compounds based on the experience of the JRC in the use of these techniques. These approaches have been successfully tested on a few case studies on samples provided by European customs laboratories. Further to this work, the project CLEN2SAND has been designed and agreed between DG JRC and DG TAXUD to provide scientific and technical support to the Customs Laboratories European Network (CLEN) for the characterisation and chemical identification of new psychoactive substances **[3].**

Through close collaboration between the JRC and CLEN, the project CLEN2SAND will lead to further improvement, harmonisation and dissemination of the analytical methods used for characterisation and reporting of the analytical data of these unknown chemicals supporting the European Commission (DG JUST) proposals for a new Regulation on new psychoactive substances and for a Directive amending Council Framework Decision 2004/757/JHA on illicit drug trafficking (CISNet DG JUST/B3/1004079). These proposals aim at strengthening the EU legal framework regarding new psychoactive substances in line with the EU Drugs Strategy (2013-2020) and the EU Action Plan on Drugs (2013-2016), in particular through its actions 51 & 52 **[4-5]**.

Meanwhile customs and customs laboratories have also considered how to face these problems from their perspective with the support of the SAND project of JRC, the following three main topics could be addressed:

a) **Analytical methods for identification and quantification of designer drugs**

The customs laboratories generally use already established analytical methods and standards allowing rapid identification of banned or controlled substances. The identification of unknown substances requires the use of advanced analytical methods such as Nuclear Magnetic Resonance and High-Resolution Mass-Spectrometry that are available only in a few EU customs laboratories. Moreover such work demands time for integration and interpretation of data from various analytical techniques in order to establish the chemical structure and stereochemistry with sufficient confidence.

b) **Sharing of analytical data among the laboratories**

The rapid access and sharing of analytical data on recently found new substances will be a considerable help for customs laboratories. The data available by EMCDDA or the European Network of Forensic Science Institutes (ENFSI) is not always easily accessible to customs laboratories and focusses on substances already identified as new psychoactive substances by forensic laboratories. Customs, at the forefront of control of imported products, need access and

sharing of data on a broader range of new chemicals including eventually NPS or precursors. Electronic platforms such as European Customs Inventory of Chemical Substances (ECICS) or SINAPSE, a free web communication platform provided by the European Commission offering tools to promote expertise in EU policy making, already used by the CLEN, have been suggested as potential repository of such information for EU customs laboratories. Furthermore, the use of certain seized materials as possible common analytical standards after their appropriate chemical characterisation, would help the routine control work by customs laboratories.

c) **How can customs laboratories support the authorities?**

Customs may contribute to a better communication to the public about health issues of designer drugs and about internet purchase from doubtful suppliers (possible role for decrease of drug demand of the EU Drug action plan), via the EMCDDA.

The scientific expertise involving the JRC is devoted to the scientific and technical support in the confirmation and characterisation of the most difficult cases of chemical structures detected by customs. The customs laboratories should indicate if they can provide aliquots of the latest seized samples in order to assess, through a preliminary study, the technical and scientific challenges faced for the identification of NPS and unknown substances.

# 3. Characterisation of new psychoactive substances

### 3.1 Analytical techniques applied routinely in customs and forensic laboratories

Forensic and customs laboratories have a large experience and competence in the analysis of drugs and illicit substances. The most common techniques routinely used for both qualitative and quantitative analysis of these substances are probably gas chromatography- mass spectrometry (GC-MS) and infrared spectroscopy.

- GC-MS allows the separation of organic molecules that can be made volatile (sometimes further to derivatisation). The retention time and the spectra obtained for the separated analytes are generally compared to libraries of known substances for identification of the molecules. When a good match is found with data found in the library the analyst can then confirm the identity of the chemical compound. Providing information on the molar mass of the compound and of some of its fragments, this technique can also give some hints for the identification of unknown substances not yet registered in available libraries. This can be helpful for suggesting hypothesis of structures especially for analogs. However, generally the GC-MS instruments that are used for control are not high-resolution instruments so the analytical data that can be obtained does not allow a full confirmation of the chemical structure of a new unknown substance. This analytical technique is now rather well disseminated. It is suitable for routine control as the analyses can be performed within a relatively short time (in most cases of the order of a few minutes to one hour), with reasonable running costs and with an investment in analytical equipment affordable by most laboratories. Under appropriate conditions this technique can also perform quantitative determinations.
- Infrared spectroscopy and more recently RAMAN spectroscopy are often used in control for recognition of drugs and illicit substances. Both are based on molecular vibrations. They can be applied directly on samples either in solution or on powders. They are fast and easy to operate and the obtained spectra can be considered as a “kind of fingerprint” of each specific substance. Some patterns of infrared and RAMAN spectra are characteristic of some functional chemical groups and therefore provide information on the chemical structure. However, as for GC-MS this is far to be sufficient for the determination of the chemical structure of a new unknown substances.

Both techniques are increasingly used for controls especially with portable devices.

For routine control it is important to collect and share among laboratories the GC-MS, Infrared and RAMAN spectral data of new psychoactive substances to facilitate and speed-up the control at the borders and by customs laboratories. The improvement and harmonisation of the collection of this data will be considered and implemented in close collaboration with the CLEN within the project CLEN2SAND. A first assessment for a general analytical strategy for this project, involving also the collection and sharing of analytical data within the Customs Laboratories European Network, was discussed during the 1$^{st}$ meeting of the CLEN Project Group on designer drugs and other illicit products hosted by the JRC in Ispra on 6 and 7 of February 2014.

Although very useful, the information obtained by these techniques is not sufficient for the elucidation of the chemical structure of a new unknown substance. Therefore they will not be further discussed in the present report whose main focus is about techniques and analytical strategy for the chemical identification of unknown new psychoactive substances. For this task high-resolution nuclear magnetic resonance (NMR) and high resolution mass spectroscopy (MS)

are the techniques of choice as presented in the next chapters. This analytical strategy has been developed based on the experience of the laboratory of the Joint Research Centre (JRC) in the use of these analytical techniques in different fields. The efficiency of the proposed approach has been successfully demonstrated on several study cases and the general principles of the approach and some results on test compounds have already been presented and discussed, in view of the future implementation of the project CLEN2SAND, on the occasion of meetings of the Customs Laboratories European Network (CLEN). For instance, the latest oral communication giving an overview of the proposed methods and approach was presented at the European Customs Chemists Seminar in Budapest on 7-9 October 2014 and is here attached in Annex 1 (Publication JRC 91976).

### 3.2 Nuclear magnetic resonance analysis of NPS

The present chapter describes the strategy and future development for applying the specific NMR instrumental parameters to be used for the production of NMR spectra of chemical substances for the determination of their identity, purity, structural integrity and stability.

Nuclear magnetic resonance (NMR) spectroscopy is based on a phenomenon called nuclear magnetic resonance which occurs when the nuclei of certain atoms are immersed in a static magnetic field and exposed to a second oscillating magnetic field. Nuclei which are close to one another exert an influence on each other's effective magnetic field. This effect shows up in the NMR spectrum. NMR allows the study of physical, chemical and biological properties of matter.

NMR spectroscopy is an analytical chemistry technique used in quality control and research for determining the content and purity of a sample or chemical as well as its molecular structure. For example, NMR can quantitatively analyse mixtures containing known compounds. For unknown compounds, NMR can either be used to match against spectral libraries or to infer the basic structure directly. Once the basic structure is known, NMR can be used to determine molecular conformation in solution as well as studying physical properties at the molecular level such as conformational exchange, phase changes, solubility, and diffusion. NMR can also be used to provide an independent and intrinsically reliable determination of chemical purity and impurities can be quantified at the 0.1% level when using appropriate analytical settings.

#### 3.2.1 NMR relevant parameters are the chemical shift and the relaxation times

Chemical shifts, generally referred to in terms of ppm, describe the dependence of nuclear magnetic energy levels on the electronic environment in a molecule. For proton the usual range falls between 0 and 12 ppm, as referred to the TMS (tetramethylsilane). Other nuclei such as $^{13}C$, $^{31}P$ and $^{15}N$ have distinct advantages in terms of chemical shifts range in the order of more than 100 ppm, but also disadvantages due to their much weaker sensitivity.

In the NMR spectrum of an organic compound, peaks appear at the positions of absorption, also called the positions of resonance for different nuclei in the molecule.

The exact chemical shift of a particular nucleus in a molecule gives information about how the atom with that nucleus is bonded in the molecule. The **x**-axis of the spectrum is called the delta scale with units of ppm and the **y**-axis is an intensity scale.

From a quantitative point of view, sensitivity depends on the signal-to-noise-ratio, which can be considered acceptable when it is higher than 10. The height of the peaks on the **y**-axis is proportional to the number of nuclei in the molecule with the same chemical shift, so NMR is an ideal analytical method from the linearity point of view since the intensity of resonance is strictly proportional to the number of nuclei resonating at a certain frequency and response factor is not needed for quantification.

### 3.2.2 Strategy to NMR analysis on NPS

The NPS usually are molecules with a molecular weight ranging between 150 and 500, so they are considered as "small molecules".

The amount received from Customs labs of the seized samples is usually several mg. so it is possible to prepare concentrated samples (typical is 10 mg in 600 μL of DMSO-$d_6$ solvent). Due to its ability to dissolve a wide range of compounds and of the simplicity of its own NMR spectrum, deuterated dimethyl sulfoxide (DMSO-$d_6$) is routinely used as a first choice solvent for recording the NMR spectra of such unknown substances. Alternative solvents can be chosen considering i) low solubility in DMSO or ii) overlap of DMSO NMR signals with those of the substance under study. Deuterated chloroform, methanol or water are the other more used NMR solvents. Samples of chemical compounds are generally prepared in DMSO-$d_6$ to a concentration in the range of 0.01M. Other deuterated solvents may be preferred depending on the solubility of the compound in question.

This permits to perform 1 Dimension (1D) and 2 Dimensions (2D) experiments in a relative short time (i.e. 1 min for $^{1}H$ experiment, 15 minutes for COSY experiment).

Determination of the presence of main functional groups (structure fragmentation) is based on 1D experiments ($^{1}H$ and $^{13}C$) determining the chemical shifts, spin multiplicity, integral (peak area), and coupling constants ($^{1}J$, $^{2}J$) of NMR signals.

Successively, the molecular skeleton is built up using 2-dimensional NMR spectroscopy.

The NMR analytical strategy applied in the JRC is based on the following experiments:

1D experiments: $^{1}H$, $^{13}C$, APT

2D experiments: a) homonuclear: COSY, TOCSY, JRES

b) heteronuclear: HSQC $^{1}H$ -$^{13}C$, HMBC $^{1}H$-$^{13}C$, HMBC $^{1}H$ -$^{15}N$

$^{1}H$: $^{1}H$ spectra show three main features: chemical shift, signal intensity, and multiplicity. The information on the molecular structure is based on how many signals (clusters) there are in the spectrum and their chemical shifts, the multiplicity of each signal cluster and how many $^{1}H$ nuclei are present in each cluster (looking at the signals integration). This set of data (with also $^{13}C$ data) permits to easily recognise a molecule if a hypothesis of the structure already exists. In the case the analysed molecule is unknown, it is necessary to proceed with 2D spectra.

$^{13}C$: $^{13}C$ spectrum, with proton decoupling, permits to count (single signals in the spectrum) and to recognise the "type" of carbons (i.e. aliphatic, aromatic, carbonyl groups) present in the molecule. The identification of single signals is facilitated by the fact that the chemical shift range is larger (about 220 ppm in comparison to 15 ppm for the proton spectrum).

APT (attached proton test) : The attached proton test is used as an aid to assignment by separating carbons unattached to protons and $CH_2$ signals from CH and $CH_3$ signals. The APT experiment yields methine (CH) and methyl ($CH_3$) signals positive and quaternary (C) and methylene ($CH_2$) signals negative. It is similar to the classical DEPT experiment (Distortionless Enhancement by Polarization Transfer) but slightly less sensitive: the interesting fact is that a single experiment shows all carbon signals of the analysed substance at once.

$^{1}$H COSY (Correlation Spectroscopy) : COSY spectra show two types of peaks. *Diagonal peaks* have the same frequency coordinate on each axis and appear along the diagonal of the plot, while *cross peaks* have different values for each frequency coordinate and appear off the diagonal. Diagonal peaks correspond to the peaks in a $^{1}$H-NMR experiment, while the cross peaks indicate couplings between pairs of nuclei, permitting to determine which atoms are connected to one another (within a small number of chemical bonds) in the studied molecule.

$^{1}$H TOCSY (Total Correlation Spectroscopy): this experiment is similar to the COSY experiment, in that cross peaks of coupled protons are observed. However, cross peaks are observed not only for nuclei which are directly coupled, but also between nuclei which are connected by a chain of couplings. This makes it useful for identifying the larger interconnected networks of spin couplings.

The JRES (J-resolved) experiment allows to separate the coupling constant and chemical shift information present in the 1H NMR spectrum in separate dimensions of a 2D spectrum. In this way also complicated multiplets in the spectrum can be separated in the single components.

HSQC (Heteronuclear single-quantum correlation spectroscopy) $^{1}$H -$^{13}$C: this experiment detects correlations between $^{1}$H and $^{13}$C nuclei which are separated by one bond. This method gives one peak per pair of coupled nuclei, whose two coordinates are the chemical shifts of the two coupled atoms.

HMQC (Heteronuclear multiple-quantum correlation spectroscopy) $^{1}$H -$^{13}$C experiment gives an identical spectrum as previous HSQC, but it detects correlations over longer ranges of about 2–4 bonds.

Considering that the majority of NPS are molecules containing one or more nitrogen atoms, the JRC strategy of identification uses also the HMQC $^{1}$H – $^{15}$N experiment. The information obtained concerns the number of nitrogen atoms present in the molecule, the distinction of different “types” of nitrogen (i.e. amine, amide groups, nitrogen in indole structure, etc.) based on the $^{15}$N chemical shift and the neighbour $^{1}$H functional groups to the single nitrogen in the molecule.

### 3.2.3 Future developments

*Quantitative $^{1}$H NMR*

Quantitative NMR shows many advantages over other usually used analytical techniques (i.e. chromatographic techniques) with regard to quantification or purity determination of organic substances. The most outstanding attribute of NMR is that it is a relative primary method: the signal intensity is in direct proportionality with the number of protons contributing to the resonance.

The structures of the chemical substances are therefore irrelevant. In addition, no significant empirical factors or unknown biases contribute to the ratio of signals. The signal ratio of two different protons can therefore be measured with high precision and the only significant contribution to the measurement uncertainty is the integration of the signals.

For the calibration of the signal intensities a reference compound of known concentration is usually added. A suitable reference substance must not interact with the sample or with the solvent and the relevant NMR signals which are selected for the measurement must be clearly separated from each other and also from other signals. In addition, for efficient measurements, the NMR relaxation properties of the reference and the sample molecules should be similar.

Appropriate instrument settings are required so that no intensity is lost through incomplete relaxation (use appropriate relaxation delay values).

The weighing of the reference and the sample must be done with utmost accuracy, since this is the essential sample preparation step in NMR analysis.

Concentration determination by NMR can be performed also if an internal reference is avoided and instead an external reference is correlated with the signal strength of the sample of interest. This correlation can be obtained with a calibrated external radio-frequency (r.f.) signal that is irradiated during acquisition (ERETIC signal- **E**lectronic **RE**ference **T**o access In vivo **C**oncentrations).

Recently, an alternative technique was introduced that provides an efficient determination of concentrations of NMR samples, based on the correlation of the absolute intensities in two one-dimensional (1D) NMR spectra measured in different solution conditions based on intrinsic properties of the samples. The method is a direct consequence of the principle of reciprocity and signal intensities in spectra of different samples are correlated by the measurement of a precise 90° r.f. pulse.

*Isotopic NMR*

The potential of isotopic analyses as a tool for origin discrimination is based on the fact that the distribution of isotopes on the different sites of the molecule is not statistical but rather that it depends on the origin of the precursor and on the type of process to which the precursor has been subjected.

Quantitative deuterium nuclear magnetic resonance ($^{2}$H NMR) provides a very powerful tool for distinguishing between different origins (natural, synthetic and different pathways) but is limited by the small range of chemical shift (around 10 ppm like proton) for deuterium. Furthermore, the hydrogen exchange that occurs under certain conditions during organic synthesis can complicate the interpretation of spectra. The carbon skeleton, however, is not susceptible to the same restrictions, and well represents the isotopic content of the starting material.

The site-specific isotopic $^{13}C/^{12}C$ ratios of carbon at natural abundance are accessible by $^{13}$C NMR spectroscopy. This technique is a priori very attractive, also for the large range of chemical shift (about 220 ppm) of $^{13}$C, anyway to obtain a suitable degree of accuracy has proved to be challenging. Nevertheless, the improved technology of modern NMR spectrometers, notably in stability and in the broad-band decoupling ability, is now possible to obtain precise and accurate measurements of specific isotopic molar fractions by $^{13}$C NMR.

## 3.3. High resolution mass spectrometry

This methodology can also be applied to the characterisation of NPS that has been successfully addressed in our laboratory by coupling this with the NMR analysis.

High-resolution time-of-flight (TOF) electrospray (ESI) mass spectroscopy is a powerful and flexible spectroscopic technique that provides information pertaining to the molecular mass, elemental composition (raw formula), and molecular structure of a compound. Accurate mass measurements (TOF MS) are used to determine the exact molecular mass and elemental composition a known or unknown molecule. Tandem mass spectrometry experiments (TOF MS/MS) are used to assist in the structure determination of unknown molecules.

The unknown organic substance is dissolved in an appropriate solvent for performing mass spectrometry experiments. Samples of chemical compounds are generally prepared in a mixture of $CH_3OH$: $H_2O$, 50:50 to a final concentration of 10 µg/ml.

The electrospray ionization (ESI) mode is used for sample introduction in mass spectrometry to produce ions using a spray to which a high voltage is applied to create an aerosol. ESI is a so-called 'soft ionization' technique, since there is very little fragmentation in the source. By default the positive ionization mode is used (ESI+); the negative mode in used when needed (eg. labile molecules). For positive-ion mode, 0.1% HCOOH or acetic acid is usually added into the analyte solution to enhance protonation and increase sensitivity. For negative-ion mode, 0.1% $NH_4OH$ is added into the analyte solution to help de-protonation and increase sensitivity. The ions observed by mass spectrometry may be quasi-molecular ions created by the addition of a hydrogen cation and denoted [M + H]+ or of another cation such as sodium ion [M + Na]+ (possible formation of adducts in the source) (ESI+ mode), or the removal of a hydrogen nucleus, [M − H]− (ESI- mode).MS spectra are recorded for each substance in the TOF MS mode to determine the accurate mass of the molecule and its elemental composition. Depending on the substance, additional TOF MS/MS fragmentation experiments may be required to give information on the fragmentation pattern and elucidate the structure of the molecule. By default, the infusion mode is used. Infusion is for direct infusion meaning that the compound is injected from a syringe pump directly into ion source of the mass spectrometer. A liquid chromatography (LC) separation might be necessary in case of complex mixtures or in the presence of a matrix that may affect the ionization of the compound. The analysis is performed online, by feeding the liquid eluting from the LC column directly to the ESI.

## 4. Data management and data exchange

The elucidation of chemical structures of an unknown compound requires the integration of all analytical and especially spectroscopic data available for the substance under investigation. Gathering of all this data is a challenge for the analytical chemist, especially as the analyses with several analytical techniques and instruments (NMR, LC-MS, GC-MS, IR, RAMAN, etc.) may be performed in different laboratories. This may hamper and slow down considerably the process of determination of the chemical structure of the substance under study.

Spectroscopic data and main features found for a chemical substance can be described in tables and documents reported by the chemists in charge of the analysis with each of the above techniques. For instance a "conventional format" for NMR spectroscopic data is a table of chemical shifts ($\delta$ in ppm), coupling constants (J in Hz), multiplicity (singlet, doublet, triplet, quadruplet,…, multiplet) and relative integrals of the NMR signals. For mass spectrometric data typically a table of masses and intensities of main peaks and fragment ions (for MS/MS experiments) can be produced eventually for the chemical species separated at different retention times (RT) in LC-MS and/or GC-MS analyses. For data obtained from high-resolution MS instruments the isotopic profiles (ratio of signals of each isotope relative to signal of the mono-isotopic mass) could also be considered. Similarly the main absorption peaks typical of specific chemical functions can also be reported in the table of features derived from infrared or RAMAN spectra. These tables summarising the main information from various spectroscopic techniques are useful for other chemists that may encounter the same (or similar) substance. They may also often be included in further edition of monographs regarding the substance. However they require the elaboration of the data by an analyst and therefore may introduce some subjectivity and a loss of information with respect to the transmission of spectroscopic data under electronic format. The modern informatics tools available nowadays enable the management and storage of such analytical data with full traceability and preservation of information and can make available all spectroscopic data collected from various techniques and instruments under a unique processing interface for facilitating the processing and interpretation by the analytical chemist. However this implies the possibility to read the proprietary format of each manufacturer of analytical instrument and eventually convert it into open data format in order to enable the possibility of building up a repository of spectroscopic data and knowledge on chemicals and in particular NPS. The data stored in such a repository could arise from analyses performed on the in several laboratories. Requirements for quality and traceability should then be established and applied by the laboratories participating in the recording and sharing of the data.

The elaboration of hypotheses regarding the possible chemical structure can also be recorded under electronic chemoinformatic formats such as Molfiles and/or SMILES (simplified molecular-input line-entry system) that are readable and can be further used by computer systems and software for further elaboration such as prediction of spectra, matching with similar compounds, prediction of certain physical, chemical or biological properties. These formats and/or unambiguous identifiers such as IUPAC International Chemical Identifier (InChI) and/or its derived InChIKey code can also be used for search within publicly available databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov), ChemSpider (http://www.chemspider.com), DrugBank (http://www.drugbank.ca) and others. Rather that using the conventional CAS numbers or systematic IUPAC name, these chemoinformatic codes and formats should be favoured for the processing and elaboration of data on these unknown substances because they can be generated in an unambiguous and unique manner for any unknown substance once its chemical structure has been established. An extract of the database of substances that have been analysed at the JRC

as case studies to set up the proposed analytical strategy and general approach for collecting analytical data on NPS is presented in a table in Annex 2 of the present report. As an example this table shows some of the chemoinformatic formats and codes discussed above for some of these substances. The actual database also contains the various spectroscopic data that have been recorded on these samples at the JRC (i.e. NMR, MS and in some case Infrared). The database allows an integration of all spectroscopic data to help the chemist with the interpretation, reporting of data and also to search for similarities for chemicals based on spectral characteristics or chemical structure.

GC-MS and infrared spectra recorded on modern analytical instruments can be easily converted in open simple format such as ASCII (text) facilitating thus the exchange and sharing of the corresponding spectroscopic data. The storage of electronic NMR files (FID or transformed spectra) or MS files (e.g. in raw manufacturer format or open format NetCDF or mzXML format) for possible further processing, storage and search in electronic libraries should be considered and further discussed with stakeholders (e.g. Customs and forensic laboratories). The electronic platforms already used by Customs (e.g. European Customs Inventory of Chemical Substances ECICS) could help with the collection and sharing of such data. However this will certainly require development and implementation of new informatics tools and functionalities. The cost/benefit of such developments must therefore be carefully evaluated. These considerations will be taken into account during the next meeting of the CLEN/TAXUD working group on determination of NPS and unknown substances that will be hosted by EMCDDA in Lisbon on 5 and 6 February 2015.

## 5. CONCLUSIONS

The main objective of this document is to present an analytical strategy and approach to facilitate the identification of the chemical structure of new psychoactive substances (NPS). The “routine” analytical methods applied in Member States'control laboratories are generally efficient for recognition of already known substances. However the chemical identification of many unknown substances found by customs and suspected to be new psychoactive substances requires the use of more sophisticated analytical techniques such as NMR and high resolution MS. These approaches have been tested in the laboratory of the Joint Research Centre (JRC) and the efficiency of the proposed analytical strategy has been successfully demonstrated on several unknown substances provided by European Customs laboratories as test cases.

The conclusions that can be formulated from this work are:

- Unlike “classical street drugs”, most samples are generally constituted of one main substance and do not contain cutting agents such as caffeine or glucose;

- A few samples were also found to be mixture of several chemical species (maybe used to mask already known NPS or maybe residue of reagents or by-products);

- The analytical strategy tested at the JRC based on NMR and high resolution MS techniques generally allows the identification of the chemical structure of an unknown substance within 5 working days;

- The case of mixtures may require more effort, however the interest (cost/benefit) of full determination of all major component of such products should also be envisaged and discussed with the various interested parties (i.e. EMCDDA , Customs and Forensic laboratories);

- The approaches tested in this study constitute a first basis for a proposal of harmonised approach and analytical strategy applicable by Customs for quick identification of chemicals.

Based on this initial work initiated in the JRC project SAND, the project CLEN2SAND has been designed to address the needs of European Customs for the fast identification of designer drugs. In this project the JRC will provide scientific and technical support to DG TAXUD and the CLEN for i) establishing a repository of spectroscopic data of NPS and ii) identifying new unknown substances under investigation by Customs authorities.

For establishing this proposal the conclusions formulated in several workshops (Group of Customs Laboratories Workshop on Designer drugs, Berlin, September 2012; Workshop and Webinar organised by the NIST, USA, 1&2 May 2013; Customs Chemists Seminar, Budapest, 7-9 October 2014) have also been taken into account. The project CLEN2SAND has been discussed and formally agreed through an administrative arrangement between DG JRC and DG TAXUD [3]. The work to be conducted in close collaboration with the CLEN Project Group on 'designer drugs' and other illicit products, can build on the preliminary work presented in the current report and in the other deliverables of the project SAND for the year 2014. There is still a need of fine-tuning for harmonisation of proposed SOPs and completion with other analytical methodologies, as well as setting up efficient channels and protocols of communication and sharing of data based on electronic format as already proposed in the present documents. These aspects will be thoroughly examined during the next meeting of the CLEN/TAXUD working group on determination of NPS and unknown substances that will be hosted by EMCDDA in Lisbon on 5 and 6 February 2015. This meeting will also examine the possibilities for a more integrated exploitation of data NPS based of the use of chemoinformatic format and tools. Computer-aided modelling systems based on the similarity principle of chemical structures can be proposed to facilitate the classification of chemical substances. This will also facilitate the classification of NPS in one of the chemical families (i.e. phenethylamines, tryptamines, and cathinones), to be reported to EMCDDA through the Early Warning System (EWS).

## 6. References


1. European Drug report "Trends and developments" 2014 , ISBN: 978-92-9168-694-0, doi:10.2810/32306 , http://www.emcdda.europa.eu/publications/edr/trends-developments/2014

2. Council Decision (2013/129/EU),Official Journal of the European Union L 72/11

3. Administrative Arrangement JRC Nr 33619 CLEN2SAND - DG TAXUD Nr /2014/DE/315

4. EU Drugs Strategy (2013-2020), Official Journal of the European Union (2012/C 402/01) http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012XG1229(01)&from=EN

5. EU Action Plan on Drugs (2013-2016), Official Journal of the European Union (2013/C 351/01) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2012:402:0001:0010:en:PDF

# Chemical identification and detection of new psychoactive substances with spectroscopic analytical techniques

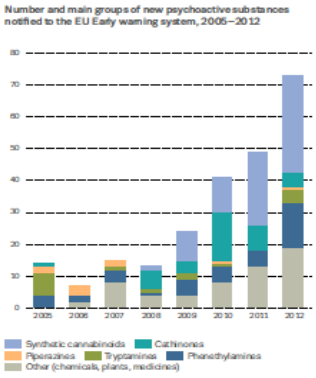
**Customs Chemists Seminar - Budapest, 7-9 October 2014**

Joana Lobo Vicente, Hubert Chassaigne, Fabiano Reniero,
Salvatore Tirendi, Veronica Holland, Kamil Kolar & **Claude Guillou**

**European Commission,**
**Joint Research Centre (JRC)**
**Institute for Health and Consumer Protection (IHCP)**
**Chemical Assessment and Testing Unit**
**via E. Fermi, 2749 - 21027 Ispra (VA) – Italy**
**E-mail: claude.guillou@jrc.ec.europa.eu**

**www.jrc.ec.europa.eu**

# New Psychoactive Substances




During 2012, 73 new psychoactive substances were notified by the Member States for the first time through the EU Early warning system


*Disclaimer: The contents of this presentation are the views of the author and do not necessarily represent an official position of the European Commission*

## JRC Institutional Work Programme

### SAND Scientific Activity on New Drugs

Initially designed for issuing evaluation of risks posed by new substances based on both psychoactive and toxicological properties. EMCDDA and DG JUST (proposal of new regulation)

### CLEN2SAND: Support to DG TAXUD & CLEN

**(Pending Administrative Arrangement between JRC and DG TAXUD)**

Scientific and technical support by the Institute for Health and Consumer Protection (IHCP) of the Joint Research Centre (JRC)
to DG TAXUD and the Customs Laboratories European Network (CLEN) for fast recognition of New Psychoactive Substances (NPS) and identification of unknown chemicals



## New Psychoactive Substances - Designer Drugs

### A European and World Wide issue

Group of Customs Laboratories Workshop on Designer drugs
September 2012 in Berlin

Workshop and Webinar organised by the NIST
1&2 May 2013 in the United States

## Q-TOF Premier Hybrid mass spectrometer

Combining a quadrupole with the time-of-flight technology

**Mass Range**
m/ z 50-3000

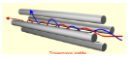
**Resolution**
25,000 at m/ z 400 in W mode

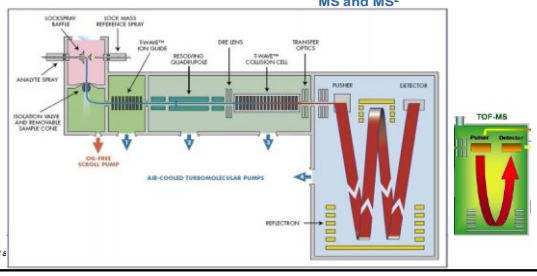
**Accuracy**
5-10 ppm with external calibration

**Sensitivity**
Sub-ng/ mL range for small molecules

**Dynamic Range**
> 4,000 within a single scan

**MS Scan Power**
MS and $MS^2$








## JRC NMR Spectrometers

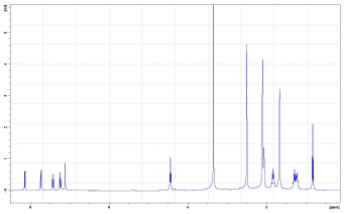
- New Bruker 600 MHz Avance III HD, with cryo-probe for 1H/ 13C/15N/19F nuclei (July 2013)
- New Bruker 400 MHz Avance III, with multi-nuclear probe (July 2014)

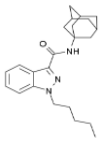
10 mg substance directly in the NMR tube

Dilution with 0.5 mL deuterated solvent

NMR measurement in automation

1H spectrum (2 min.)

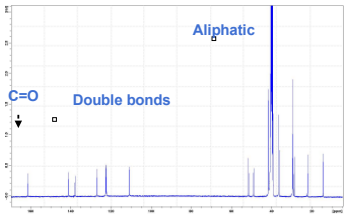




1H NMR mono- and bi-dimensional (COSY, TOCSY)
- 13C NMR mono-dimensional
- 1H/13C HSQC phase sensitive
- 1H/15N HMBC

Total of 6 experiments, performed in automation mode (ICON NMR software)
Total run time 4 hrs

$^{13}$C spectrum (10 min.)



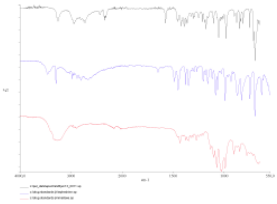

*Disclaimer: The contents of this presentation are the views of the author and do not necessarily represent an official position of the European Commission*

## CONTROL OF "UNKNOWN SUBSTANCES"

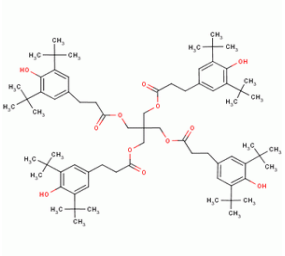
### Antioxidant 1010

**Chemical name** : Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4- hydroxyphenyl) propionate)

**CAS NO.** : **6683-19-8**
**EINECS** : **229-722-6**
**Molecular formula** : **C73H108O12**
**Molecular weight** : **1177.65**
**Chemical structure**



?



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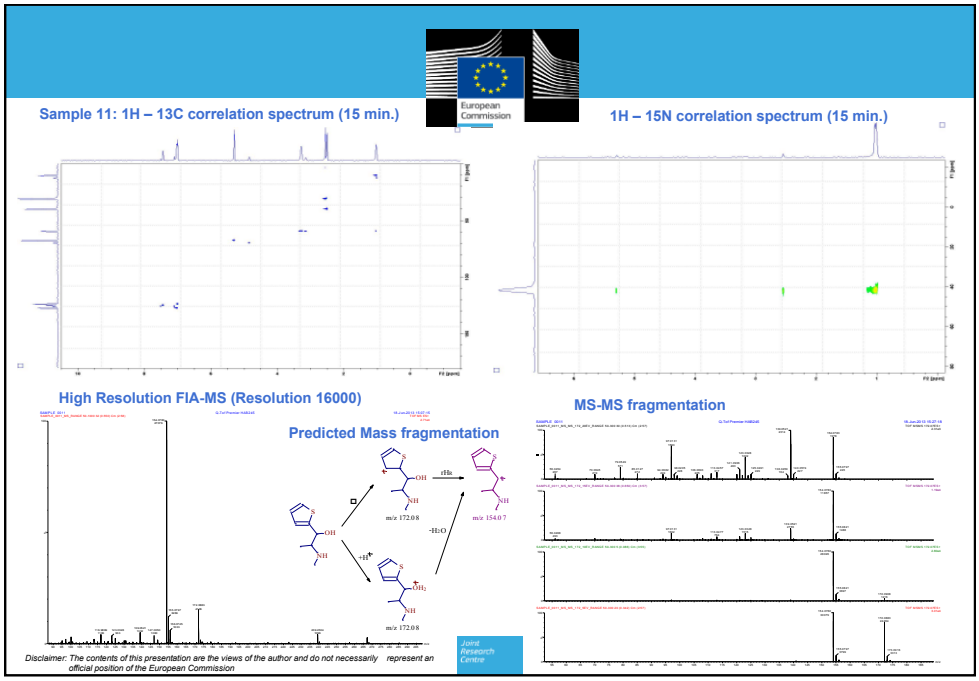
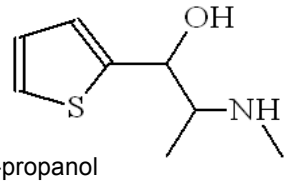



## After NMR and MS this "Antioxidant 1010" was found to be:




**Molecular Formula:** C8H13NOS
**Monoisotopic mass:** 171.071777 Da
**Systematic name:** 2-(Methylamino)-1-(2-thienyl)-1-propanol
**SMILES**: CC(C(c1cccs1)O)NC
**InChI**=1S/C8H13NOS/c1-6(9-2)8(10)7-4-3-5-11-7/h3-6,8-10H,1-2H3
**Std. InChIKey:** PQBXAYQNHATKPC-UHFFFAOYSA-N

SMILES: Simplified Molecular-Input Line-Entry System
InChi: IUPAC International Chemical Identifier

InChiKey: Hashed version of the full standard InChI

CLEN Project Group on designer drugs and other illicit products – 1st meeting – 6 & 7 February 2014

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
TAXATION AND CUSTOMS UNION
Customs Policy, Legislation, Tariff
Combined Nomenclature, Tariff Classification, TARIC and integration of trade measures

**CLEN Action 5**
**Project Group on designer drugs and other illicit products**
**- 1st meeting -**

6 & 7 February 2014 – Ispra, Italy

Minutes of the 1st meeting of the CLEN Action 5 Project Group
on designer drugs and other illicit products
held at the Joint Research Centre premises, Ispra, Italy
on 6 & 7 February 2014, 10:00-17:00 & 9:30-17:00

*Disclaimer: The contents of this presentation are the views of the author and do not necessarily represent an official position of the European Commission*

**Participants: Customs Laboratories**

| | |
|---|---|
| Bulgaria | Boryana DRAGOVA |
| Cyprus | Maria AFXENTIOU |
| Czech Republic | Jiří MAZÁČ |
| France | Catherine LAMOUREUX |
| Germany | Bernd DERING |
| Hungary | Rita KAPILLER-DEZS ŐFI |
| Italy | Francesca Maria FILIPPI |
| Netherlands - *Action 5 leader* | *Ger KOOMEN* |
| Netherlands | Marcel HEERSCHOP |
| Poland | Przemyslaw SOLTYS |

**European Commission - Joint Research Centre**

Pilar Maria AGUAR FERNANDEZ
Pascal CAMPANELLI
Hubert CHASSAIGNE
Claude GUILLOU
Margaret HOLLAND
Kamil KOLAR
Joana LOBO VICENTE
Sazan PAKALIN
Diana REMBGES
Fabiano RENIERO

**European Commission and other European Agencies**

| | | |
|---|---|---|
| DG Justice B3 | Elsa MAIA | |
| DG TAXUD A4 | Alexander PAUL | |
| DG TAXUD A4 | Hervé SCHEPERS | |
| EMCDDA | Ana GALLEGOS | European Monitoring Centre for Drugs and Drugs Addiction |

**Other** Eurofins-CLENTAS Agathe REBOURS

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## NMR for quantification

- NMR is a primary quantitative method: intensity of each signal in the spectrum is directly proportional to the molar concentration of the analyte
- No response factor is needed for quantification
- Chemical purity and impurities can be quantified at 0.1% level



## Interpretation of NMR data

Based on:

- Experience of analyst
- Other pieces of information from other spectroscopic techniques e.g. FT-IR, HR-MS
- Comparison of measured spectra with reference spectra of already known compounds
- Software to assist interpretation

## Validation of chemical structure elucidation

- Based on deduction, reasoning using well-established physics and chemistry knowledge
- Rule of self and full consistency ?
- Lab intercomparison on a few unknown substances ?
- 3 experts with same info, but not exchanging their information on their mode of interpretation ?
- Software based on databases of known compounds or on theoretical considerations ?



## CLEN2SAND Deliverables

1. Electronic data repository collection of spectral (NMR, FT-IR, HR-MS, RAMAN) and chemical data produced by CLEN and the JRC
   TO BE STORED IN ECICS

2. JRC and CLEN internal SOPs for analysis of NPS
   to be eventually adapted and registered in ILIADe after harmonisation

3. Contribution and input for CLEN workshops and trainings especially in the the programme Customs 2020 Project Group CLEN Project Group on “designer drugs and other illicit products” > Docs in SINAPSE platform.

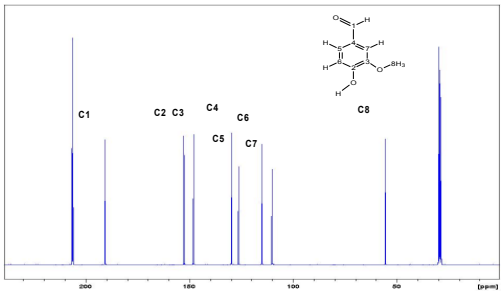
4. Activity reports to DG TAXUD including recommendations regarding the long-term use by DG TAXUD and CLEN. Recorded in SINAPSE platform.

Analytica Chimica Acta
Available online 19 June 2013
In Press, Accepted Manuscript — Note to users

## Isotopic $^{13}C$ NMR

Site-specific $^{13}C$ content by quantitative isotopic $^{13}C$ Nuclear Magnetic Resonance spectrometry: A pilot inter-laboratory study

Alain Chaintreau[a], Wolfgang Fieber[a], Horst Sommer[a], Alexis Gilbert[b], Keita Yamada[b], Naohiro Yoshida[b], Alain Pagelot[c], Detlef Moskau[d], Aitor Moreno[d], Jürgen Schleucher[e], Fabiano Reniero[f], Margaret Holland[f], Claude Guillou[f], Virginie Silvestre[g], Serge Akoka[g], Gérald S. Remaud[g]




## Applications:

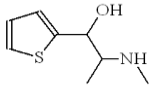
- Precursors
- Counterfeit medicines
- Protection of Intellectual Property Rights



## Identification & confirmation of chemical structure -> "Publication" of spectra – methods - data

NMR

HR-MS




Molecular Formula: C8H13NOS
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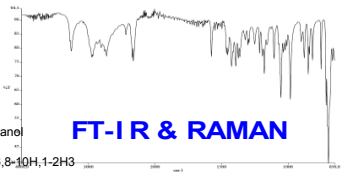
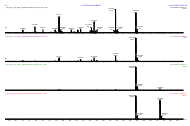
SMILES: CC(C(c1cccs1)O)NC
InChI=1S/C8H13NOS/c1-6(9-2)8(10)7-4-3-5-11-7/h3-6,8-10H,1-2H3
Std. InChIKey: PQBXAYQNHATKPC-UHFFFAOYSA-N

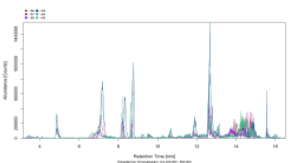


ECI CS

I LI ADe

GC / LC MS method



EMCDDA National Focal Point -REITOX

## NEXT STEPS

- Rapid detection methods can we transfer high resolution FT-IR and RAMAN spectra of new substances fully characterised by NMR and MS in the library of portable devices for fast control at the borders?
- => Calibration transfer: Next lecture by Vincent Baeten (CRAW-Gembloux)
- programme Customs 2020: CLEN Project Group on “designer drugs and other illicit products” – Next meeting beginning 2015?



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## Thank you for your attention

**And Thanks to**

**JRC colleagues**

**the CLEN, DG TAXUD, and DG JUST**

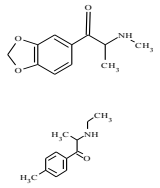
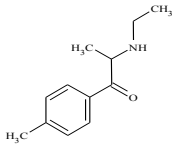
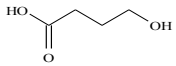
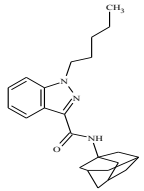
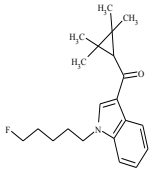
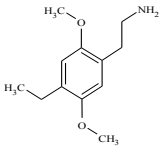
**Joint Research Centre (JRC)**
The European Commission’s in-house science service
**www.jrc.ec.europa.eu**

*Serving society - Stimulating innovation - Supporting legislation*

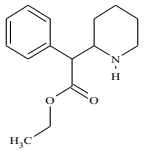
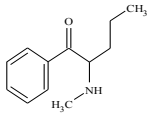
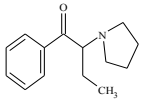
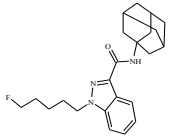
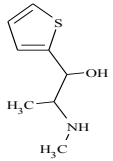


22

# Annex 2

| Eurodat number | Customer's identification | Weight [mg] | NAME | IUPAC Name | Structure | Monoisotopic Mass | Formula | SMILES | InChI Key |
|---|---|---|---|---|---|---|---|---|---|
| 13060001 | 2012 CKP: 1662, 2128-1 | 13.4 | Methylone (*Component 1* )<br>4methylethylcathinone (*Component 2* ) | 1-(2H-1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one (*Component 1* )<br>2-(ethylamino)-1-(4-methylphenyl)propan-1-one (*Component 2* ) |  | 207.0895 (*Component 1* )<br>191.1310 (*Component 2* ) | C11H13NO3 (*Component 1* )<br>C12H17NO (*Component 2* ) | O1COC2=C1C=CC(=C2)C(C(C)NC)=O (*Component 1* )<br>C(C)NC(C(=O)C1=CC=C(C=C1)C)C (*Component 2* ) | VKEQBMCRQDSRET-UHFFFAOYSA-N (*Component 1* )<br>ZOXZWYWOECCBSH-UHFFFAOYSA-N (*Component 2* ) |
| 13060002 | 2012 CKP: 2128-2, 2301, 2013: 0863 smpl B | 31.1 | 4-methylcathinone | 2-(ethylamino)-1-(4-methylphenyl)propan-1-one |  | 191.1310 | C12H17NO | C(C)NC(C(=O)C1=CC=C(C=C1)C)C | ZOXZWYWOECCBSH-UHFFFAOYSA-N |
| 13060003 | 2013 CKP: 0026 | 73.9 | gamma-Hydroxybutyric acid | 4-hydroxybutanoic acid |  | 104.0473 | C4H8O3 | OCCCC(=O)O | SJZRECIVHVDYJC-UHFFFAOYSA-N |
| 13060004 | 2012 CTL: 5396 smpl A | 69 | APINACA | N-(1-adamantyl)-1-pentylindazole-3-carboxamide |  | 365.2467 | C23H31N3O | C12(CC3CC(CC(C1)C3)C2)NC(=O)C2=NN(C3=CC=CC=C23)CCCCC | UCTCCIPCJZKWEZ-UHFFFAOYSA-N |
| 13060005 | 2012 CTL: 5396 smpl F | 45.2 | XLR-11 | [1-(5-fluoropentyl)indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone |  | 329.2155 | C21H28FNO | FCCCCCN1C=C(C2=CC=CC=C12)C(=O)C1C(C1(C)C)(C)C | PXLDPUUMIHVLEC-UHFFFAOYSA-N |
| 13060006 | 2013 CTL: 0863 smpl A | 49.3 | 2C-E | 2-(4-ethyl-2,5-dimethoxyphenyl)ethan-1-amine |  | 209.1416 | C12H19NO2 | C(C)C1=CC(=C(C=C1OC)CCN)OC | VDRGNAMREYBIHA-UHFFFAOYSA-N |

# Annex 2

| Eurodat number | Customer's identification | Weight [mg] | NAME | IUPAC Name | Structure | Monoisotopic Mass | Formula | SMILES | InChI Key |
|---|---|---|---|---|---|---|---|---|---|
| 13060007 | 2013 CTL: 0863 smpl C2 | 172.3 | Ethylphenidate | ethyl phenyl(piperidin-2-yl)acetate |  | 247.1572 | C15H21NO2 | C1(=CC=CC=C1)C(C(=O)OCC)C1NCCCC1 | AIVSIRYZIBXTMM-UHFFFAOYSA-N |
| 13060008 | 2013 CTL: 0863 smpl C3 | 120.74 | Pentedrone | 2-(methylamino)-1-phenylpentan-1-one |  | 191.1310 | C12H17NO | CNC(C(=O)C1=CC=CC=C1)CCC | WLIWIUNEJRETFX-UHFFFAOYSA-N |
| 13060009 | 2013 CTL: 0863 smpl C4 | 74.1 | alpha-Pyrrolidinobutiophenone | 1-phenyl-2-(pyrrolidin-1-yl)butan-1-one |  | 217.1467 | C14H19NO | C1(=CC=CC=C1)C(C(CC)N1CCCC1)=O | GSESDIFGJCCBHN-UHFFFAOYSA-N |
| 13060010 | NA | 176 | 5F-APINACA | N-(1-adamantyl)-1-(5-fluoropentyl)indazole-3-carboxamide |  | 383.2373 | C23H30FN3O | C12(CC3CC(CC(C1)C3)C2)NC(=O)C2=NN(C3=CC=CC=C23)CCCCCF | UCMFSGVIEPXYIV-UHFFFAOYSA-N |
| 13060011 | 2012 CKP: 1817 | 99.3 | 2-(methylamino)-1-(thiophen-2-yl)propan-1-ol | 2-(methylamino)-1-(thiophen-2-yl)propan-1-ol |  | 171.0718 | C8H13NOS | CNC(C(O)C=1SC=CC1)C | PQBXAYQNHATKPC-UHFFFAOYSA-N |

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