WASIMP

Chemical Profiling of Waste from Clandestine Synthetic Drug Production.

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Introduction

The large profits that can be realized by the trading of clandestine drugs have attracted the attention of organized crime and caused its proliferation in the domain. Both national and international judicial and police intelligence departments are confronted with this problem and are trying to find a fitting answer to the issue, sometimes with the assistance of science. More specific for the clandestine synthesis of so-called designer drugs, this is usually translated as the chemical profiling of confiscated drugs, synthetic precursors and chemical waste. Such analyses may assist law enforcement agencies to interconnect drugs sold on the street with manufacturing and dumping sites, and hence may result in the dismantlement of a criminal organization.

Objective

The WASIMP project attempted to find reliable chemical parameters that allow interconnection of chemical ditching sites, and/or permit to interlink dumping sites with underground drug laboratories. Research was focused on MDMA (XTC) and amphetamine (Speed), the two most popular clandestine designer drugs in Belgium.

Most of the confiscated amphetamine has been manufactured *via* the Leuckart reductive amination, while MDMA is often synthesized using PtO_2-catalyzed reductive amination or the so-called “cold method” with $NaBH_4$. Accordingly, synthesis impurities derived from these synthesis routes were emphasized.

This research tries to find an answer on the following questions:

- Does chemical analysis of clandestinely ditched synthesis waste allow to interconnect ditching sites and/or to interlink dumping sites with underground drug laboratories?
- Which parameters are reliable to make these links and how can their automatization be achieved?
- What is the added value of chemical waste analysis for the Justice Department?

Methodology

Sampling

In a first stage, samples from ditching sites and clandestine laboratories were collected in cooperation with Federal Police. Most samples were collected at a processing company. Samples of one production site were collected at the Federal Police. Unfortunately, sampling at the ditching sites or in the clandestine laboratory itself was not possible because of safety reasons. Therefore, sampling of soil samples and reconstruction of the ditching conditions were not applicable.
In total, samples of 9 dumping sites and 5 laboratories were collected.

Analysis

The analysis is subdivided into two segments, *viz.* (a) the chemical analysis of samples within the relevance of the project, and (b) research of the genesis of certain synthesis impurities. The two research aspects stand interdependent, not independent.

(a) Chemical analysis

Protocols used in this research were based on the described methods used in the European Project on Collaborative Harmonisation of Methods for Profiling of Amphetamine Type Stimulants (CHAMP) [1-6].

- Performing *direct injection* on GC/MS, sample purification was needed in a first step using *solid-phase extraction* (SPE). Hereby, in order to analyse a broad spectrum of substances, 4 types of columns were used: reversed phase, normal phase, cation exchange and anion exchange. Nonadecane (100 µg/ml) was added as an internal standard. The eluens of this purification was directly injected into the GC/MS.
- *Headspace solid-phase microextraction (HSPME)* was used as sample preparation to concentrate volatiles before indirect injection on GC/MS. In this technique, a fiber coated with an absorbing substance was used in order to concentrate volatile solvents. Polydimethylsiloxane (PDMS), a non polar coating was found to be the most stable one. Eventually this coating was used in all sample analysis.

(b) Impurity libraries

Impurity libraries were designed and synthesized *via* combinatorial chemistry. By using this new and innovative method, we tried to achieve a higher efficiency than conventional techniques allow and attempt to find a way that enables us to anticipate on changes in the *modus operandi* of clandestine drug manufacturing sites. This approach allows a high degree of automatization.

Results

Samples were statistically compared using the Pearson correlation coefficient. To avoid the influence of high peaks, the peak surface was normalised to the sum of all peak surfaces and standardised by taking the square root of this normalised value. Practically, the following equation was used:

$$r = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}}$$

A value between -1 and 1 was obtained. -1 indicates a negative correlation, +1 indicates a positive correlation. These values were recalculated to values between 0 (negative correlation) and 100 (positive correlation).

To simplify the comparison of the samples, we divided them into different groups based on the chromatograms:

FL: Intermediate M-formylamphetamine (L= 'like')

S: Solvent waste

P2P: Waste from precursor phenyl-2-propanon

AL: Amphetamine is one of the major compounds (L= 'like')

AL2: Strong diluted AL samples. We choose to put these samples into a different group in order not to have an artificial increase of the Pearson coefficient.

Samples were compared within their group for each SPE column. Pearson coefficients were calculated for each group except S and AL2. In these two, the relevance was to low.

Screening on chemical parameters was automated via the use of retention time locking. Herefore, a massaspectrometric library, containing 190 compounds, was composed.

HSPME results

List I gives an overview of the selected parameters used to perform a automated screening on the analysis results.

RT	List I	sum	% appearance
4,58	toluene	75	85,23
5,50	IS	88	100,00
6,72	mesityloxide	21	23,86
9,30	diacetonalcohol	17	19,32
13,82	p-chlorotoluene	19	21,59
16,12	benzaldehyde	55	62,50
17,00	*trans*-β-methylstyrene	36	40,91
17,27	1,2-methyleendioxybenzene	20	22,73
17,72	benzylchloride	74	84,09
18,05	p-bromotoluene	0	0,00
20,62	acetofenon	75	85,23
21,15	methylbenzoaat	19	21,59
21,42	3,4-methyleendioxytoluene	23	26,14
21,60	2-chloroethylbenzene	58	65,91
22,28	2-phenylethanol	1	1,14
23,00	α,α-dichlorotoluene	12	13,64
23,17	phenyl-2-propanon	45	51,14
23,88	ethylbenzoaat	12	13,64
24,70	benzylcyanide	81	92,05
25,13	2-bromoethylbenzene	20	22,73
25,33	3-chloro-1-phenylpropaan	1	1,14
25,60	α,α,α-trichlorotoluene	0	0,00
45,97	1-(3,4-methyleendioxyphenyl)-2-propanon	18	20,45

Some complications were experienced during analysis. For example strong acidic matrices damaged the fiber. The obtained results were hard to interpret. Thereby, most of the found compounds were not specific for a particular synthesis route. For example mesityloxide and diacetonalcohol both indicate the use of acetone. Nevertheless, their presence is strongly dependent on the presence of acid or base and is time dependent.

Based on the experience we had during this project, we can conclude that GC-HSPME/MS is an interesting technique to gather more information about the identity of the used solvents and produced volatiles during the production process. Nevertheless, this method does not give the possibility to make a full differentiation between different samples and therefore its relevance in police investigation is limited.

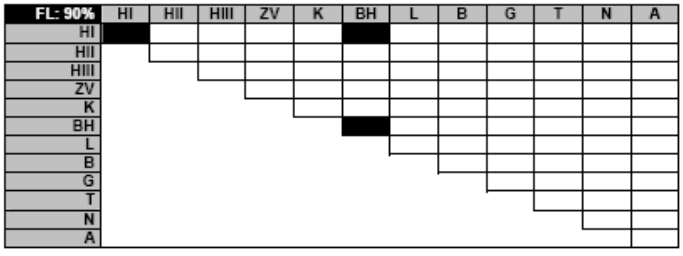
SPE results

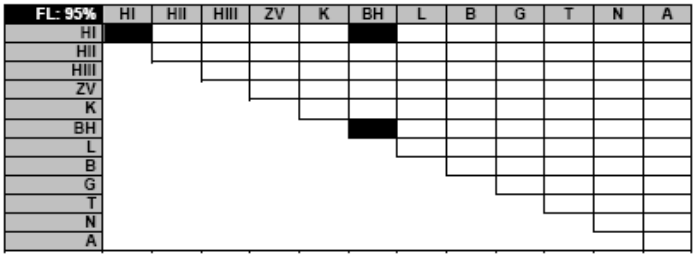
Amphetamine samples

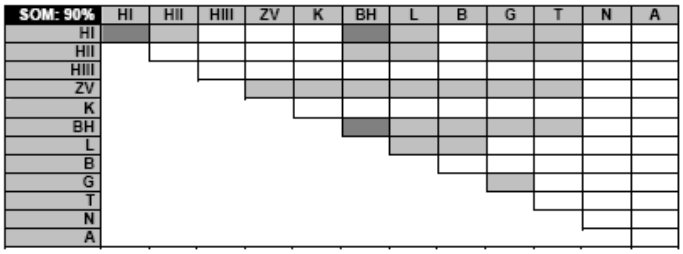
A total amount of 412 analyses were classified as amphetamine related. This was based on the SPE-GC/MS analysis using 36 markers.

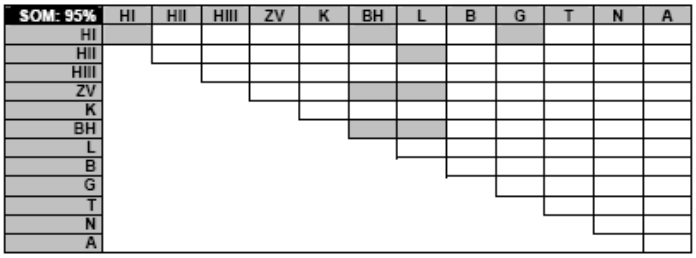
Table I give an example of an overview of the relation found between different samples with a Pearson correlation of respectively 90% and 95%. Black indicates a relation, white = no relation between samples. The “SOM” table gives a comparison for the different groups. Herein, dark gray means there is a relation between two of the three groups while light grey indicates there is only one relation found. Remarkable is the correlation between HI and BH.

Table I







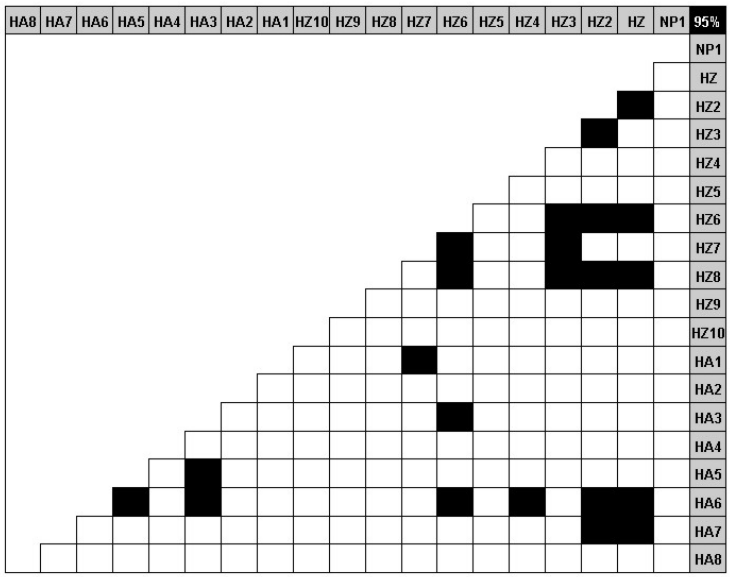


Methamphetamine samples

We investigated three dumping sites that are related to the production of MDMA. In total, 76 analyses were categorised in this group. 28 markers were used in the calculations of possible relations.

An example of the Pearson coefficients of MDMA samples is given. Remarkably, there is a strong correlation found between HA and HZ using the 95% correlation coefficient.

Table II



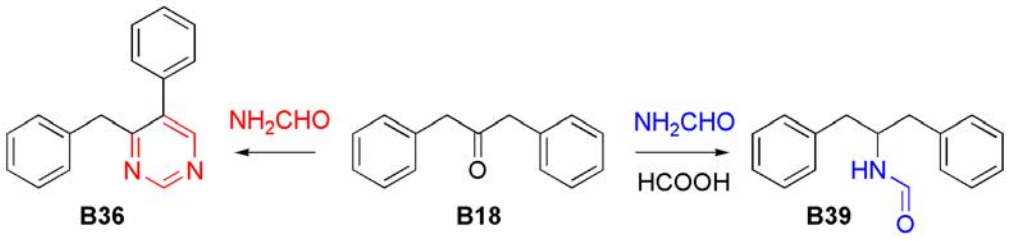
Impurity libraries

Combinatorial chemistry techniques were applied in several trial runs in order to construct mass spectral impurity libraries coupled to a RTL gas chromatographic method. The results have a mixed outcome and indicate that the reagents have to be chosen very carefully based on their expected reactivity. For instance, in one such an experiment, it was attempted to react benzyl amine with a group of carbonyl-containing precursors (deoxybenzoin, propiophenone, acetophenone, benzaldehyde). At room temperature, only the imine from benzyl amine en benzaldehyde was readily formed. Allowing longer reaction times did not appreciatively augment the imine amount of the other carbonyl precursors, yet increased the number of impurities. By increasing the reaction temperature, imine formation was more favourable for all carbonyl precursor compounds. Nevertheless, reaction time appeared to be a crucial factor here as well, since impurity formation increased rapidly. No further attempts have hitherto been made to carry the library beyond the imine stage. Very good results were obtained by reacting a group of benzaldehydes with an amine. In one experiment, a benzaldehyde mixture (2,4-dimethoxybenzaldehyde, asaraldehyde, benzaldehyde, *p*-fluorobenzaldehyde, *m*-anisaldehyde) was reacted with several amines: (A) *n*-butylamine, (B) β-phenethylamine and cyclohexylamine, (C) benzyl amine and piperonyl amine, (D) α-

phenethylamine. The corresponding imines were formed at room temperature with magnetic stirring and molecular sieves (5Å). Analysis of the reaction mixtures was performed using the standard method using *n*-nonadecane as internal standard. The four reaction mixtures A-D consequently resulted in 5 x 6 new compounds, which were identified based on their mass spectrum. Furthermore, retention time data could be incorporated into a RTL-library.

Some rudimentary experiments were carried out to study the formation of impurities derived from 1,3-diphenylacetone under typical Leuckart reductive amination reaction conditions. Several previously not described substances (at least in a forensic context) were detected, leading us to conduct the Leuckart reaction of 1,3-diphenylacetone under well-controlled conditions. As such, the influence of the amination reagent (ammonium formate vs. formamide and formic acid) as well as the presence of varying relative amounts of phenylacetone was examined. At the end of the reaction, a sample was taken from the reaction mixture and analyzed using the default GC/MS method.

Based on our experiments, we identified five hitherto not described substances which might appear as forensically relevant impurities in amphetamine produced from phenyl-2-propanone contaminated with 1,3-diphenylacetone. Two impurities were observed in samples examined during the project, viz. Unknown GM-20070925-1 (B36) and Unknown GM-20070925-2 (B39). Their structures have been tentatively identified based on the Leuckart reaction mechanism and their mass spectra:



Synthesis of these compounds following an independent route could ascertain (or disprove) their structure.

Interpretation of results

An important question is “How do we have to interpret the correlation coefficients?”

The Pearson coefficients are indicative for a causal relation between investigated samples. Nevertheless, the coefficients do not give any information about the nature of the cause of the presence of this link. Causes of the indicated links might be the same synthesis method, the same source of precursor material, the same production site or the correlation might even be just coincidence. In our research, we tried to minimise this coincidence factor by investigating a broad spectrum. This is managed by using four different SPE columns. Nevertheless, a major problem, when searching for links in synthesis waste, is the high variability between samples. This might be caused by collecting all the synthesis waste, probably from different synthesis routes, in one barrel (example NP sample). In this case, comparing Pearson correlations has no relevance. Therefore we can conclude that the predictive character of this analysis of synthesis waste has to be taken into consideration carefully. On the other hand, chromatographic analysis of synthesis waste is certainly not useless. Although it is very difficult to predict certain links, this interesting technique can be useful to put detailed knowledge of a particular case into a scientific context. With this analysis, changes in illegal drug production can be discovered. Therefore, this research might be an added value concerning the illegal drug production in our society.

As a conclusion, we try to give answers on the questions proposed in the beginning of the research project and stated in the objectives.

- Does chemical analysis of clandestinely ditched synthesis waste allow to interconnect ditching sites and/or to interlink dumping sites with underground drug laboratories?

  When information exchange is possible between researchers and police investigators, the chemical profiling of waste from clandestine synthetic drug production can be useful. When evidence already indicates a possible link between laboratory and ditching site, this scientific research can play a supporting role. We advise however not to take the results of the scientific research as isolated evidence without any supporting role of other investigation results.
- Which parameters are reliable to make these links and how can their automatization be achieved?

  Since results of this research are not sufficiently compelling to link ditching sites and/or ditching and production sites with 100% certainty, the above

mentioned question is not relevant anymore. Nevertheless, the parameters used in this research to perform an automated GC/MS screening, are a good reference for further investigation in this research domain.

- What is the added value of chemical waste analysis for the Justice Department?

  The research results cannot stand alone as evidence but need the support of other proof in order to link with certainty different sites. Therefore, we did at the end not appoint a jurist to determine the juridical value.

References

1. Aalberg, L., et al., *Development of a Harmonised Method for the Profiling of Amphetamines I. Synthesis of Standards and Compilation of Analytical Data.* Forensic Sci. Int., 2005. **149**(2-3): p. 219-229.
2. Aalberg, L., et al., *Development of a Harmonised Method for the Profiling of Amphetamines II. Stability of Impurities in Organic Solvents.* Forensic Sci. Int., 2005. **149**(2-3): p. 231-241.
3. Andersson, K., et al., *Development of a Harmonised Method for the Profiling of Amphetamines III. Development of the Gas Chromatographic Method.* Forensic Sci. Int., 2007. **169**(1): p. 50-63.
4. Andersson, K., et al., *Development of a Harmonised Method for the Profiling of Amphetamines IV. Optimisation of Sample Preparation.* Forensic Sci. Int., 2007. **169**(1): p. 64-76.
5. Lock, E., et al., *Development of a Harmonised Method for the Profiling of Amphetamines V. Determination of the Variability of the Optimised Method.* Forensic Sci. Int., 2007. **169**(1): p. 77-85.
6. Andersson, K., et al., *Development of a Harmonised Method for the Profiling of Amphetamines VI. Evaluation of Methods for Comparison of Amphetamine.* Forensic Sci. Int., 2007. **169**(1): p. 86-99.