Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: A Dutch perspective

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HIGHLIGHTS
- Enantiomeric profiling with chiral chromatography was undertaken.
- Enantiomeric profiling is a useful tool for source apportionment of aberrant drug loads in sewage water.
- A distinction was made between consumption and disposal of un-used drugs.
- In the case of MDMA a distinction could be made whereas for amphetamine no distinction could be made yet.

GRAPHICAL ABSTRACT

Abstract
Analysis of wastewater with an aim of community-wide estimation of drug use is a new and very promising approach. Until now it was very difficult to determine if mass loads of studied drugs were actually originating from consumption, or disposal of unused drugs or production waste. This uncertainty in the estimation of community wide drugs use should not be underestimated. This paper aims to apply for the first time enantiomeric profiling in verifying sources of the presence of MDMA and amphetamine in wastewater based on a case study in two Dutch cities: Utrecht and Eindhoven. The results showed that MDMA is usually present in wastewater due to its consumption (MDMA enriched with R(-)-enantiomer). Excessively high mass loads of MDMA during a sampling campaign in Utrecht in 2011 proved to be racemic indicating direct disposal of unused MDMA possibly as a result of a police raid at a nearby illegal production facility. Enantiomeric profiling was also undertaken in order to verify the origin of unexpectedly high mass loads of amphetamine in the city of Eindhoven in 2011. Unfortunately, a distinction between consumption and direct disposal of unused amphetamine in Dutch wastewater could not be achieved. Further work will have to be undertaken to fully understand sources of amphetamine in Dutch wastewaters.

1. Introduction
Analysis of wastewater with an aim of community wide estimation of drug use is a new and very promising approach. It was first proposed by Daughton in 2001 (Daughton, 2001), implemented by Zuccato et al. in
2. Experimental

2.1. Chemicals and materials

Reference standards: \( R/S(\pm)-\)amphetamine and \( R/S(\pm)-3,4\)-methylenedioxyamphetamine (MDMA), were purchased from Lipomed AG (Arlesheim, Switzerland) as solutions in methanol (MeOH) at a concentration of 1 g/L. Internal standards (IS): \( R/S(\pm)-\)amphetamine-d11 and \( R/S(\pm)-\)MDMA-d5 were purchased from Lipomed AG. The internal standards were added prior to the sample treatment.

2.2. Sampling and sample treatment

Two one-week monitoring programmes were undertaken in 2010 and 2011. In 2010, influents from five Dutch sewage treatment plants (STPs) were collected in weeks 7–8 from the cities of Amsterdam, Utrecht, Eindhoven, Apeldoorn and the Schiphol airport (Bijlsma et al., 2012). In 2011, influents from the same STPs in the cities of Amsterdam, Utrecht and Eindhoven were collected in weeks 10–11 as part of a study to compare loads of drugs of abuse in 19 European cities (Thomas et al., 2012). From these two campaigns we will take a closer look at two STPs. The first is the STP of the city of Utrecht which has a catchment area covering the city and the maximum distance to the STP is 8 km. The efficient of this STP is partly recirculated into the influent. The second STP is that of the city of Eindhoven which has a catchment area covering the city but also neighbouring villages and has a maximum distance to the STP of 27 km (see Fig. 1). Both sampling weeks happened to be immediately after the Carnival week of the corresponding year.

All samples were taken in high density polyethylene sample bottles by volume proportional sampling during a twenty four hour cycle. The sampling equipment was setup to take a discrete sample of 50 mL every 400 m³ for Utrecht and every 800 m³ for Eindhoven. In this way the average sampling frequency was for Utrecht 5.5 min in 2010 and 6.8 min in 2011 and for Eindhoven every 8.2 min in 2010 and every 7.2 min in 2011 which are all well below the considered minimal sampling frequency for flow proportional sampling of 15 min (Ort et al., 2010). For each city samples were collected on 7 consecutive days accordingly. After collection of the samples they were immediately stored at \( -18 \) °C. Before extraction the samples were transferred to storage at 4 °C to allow the frozen sample to be defrosted. The samples were then adjusted to pH 7 and a mixed solution of deuterated internal standards was added. The samples were then filtered through a 1.0 μm glass fibre filter and followed by a 0.2 μm filter (polysulphone). A 100 mL aliquot of the filtered sample was extracted using Solid Phase Extraction (SPE) cartridges (150 mg Oasis HLB) via an automated extraction and elution setup (GX-274 ASPEC, Gilson Middleton, USA). The methanol eluates were then further automatically concentrated (Barkey, Optocontrol, Germany) by using heated nitrogen and made up to reach a final extract of 90/10 water and methanol.

2.3. Analysis

Two methodologies were used to identify and quantify chiral drugs in wastewater. Identification and quantification of drugs was undertaken with non-chiral HPLC–LTQ–Orbitrap–MS method. SPE-chiral–LC–MS/MS was used for the verification of enantiomeric fractions of chiral drugs.

2.3.1. Identification and quantification of chiral drugs with HPLC–LTQ–Orbitrap–MS

A hybrid LTQ–Orbitrap mass spectrometer (Thermo Electron, Bremen, Germany) provided with an electro spray ionisation source was interfaced to a Surveyor HPLC system (Thermo Electron). For the chromatographic separation an XBridge C18 column (150 mm × 2.1 mm I.D., particle size 3.5 μm) (Waters, Etten-Leur, The Netherlands) preceded by a 4.0 mm × 2.0 mm I.D. Phenomenex Security Guard column
(Phenomenex, Torrance, USA) maintained at a temperature of 21 °C was used. From the extract 20 μL was injected, and by using a gradient of ultra-pure water (Milli Q, Millipore, Billerica, USA) and methanol both with 0.05% formic acid, the compounds were separated at a constant flow of 0.3 mL/min and directly introduced to the mass spectrometer. With every batch run mass calibration was performed by using a mix of polystyrene 1,3,6 solution at a flow rate of 10 μL/min. The capillary used was a metal needle maintained at a temperature of 300 °C. For the ionisation nitrogen gas was used, the sheath, auxiliary and sweep gas was set to arbitrary units of 30, 10 and 10. A source voltage of 3.6 kV and a capillary voltage of 35 V were used only in the positive mode. The tube lens was set to 50 V. Full scan high accuracy mass spectra acquired in the range of 150–400 m/z with the resolution set at 30,000 were used for quantification with a 5 ppm mass window. For confirmation a list of target compounds was specified and when a preset threshold of 10,000 counts was exceeded the LTQ iontrap triggered to product-ion scan mode and hence confirming the identity. The acquisition and validation parameters for this method can be found in Table 1. More details on the analytical procedure are provided in (Bijlsma et al., 2012; Bijlsma et al., 2013).

2.3.2. Enantiomeric separation of chiral drugs with chiral LC–MS/MS

A Waters ACQUITY UPLC™ system (Waters, Manchester, UK) consisting of a ACQUITY UPLC™ binary solvent manager and a

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**Table 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amphetamine</th>
<th>MDMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor ion [M + H]⁺</td>
<td>m/z 136.11208</td>
<td>194.11755</td>
</tr>
<tr>
<td>Normalised collision energy</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Production 1</td>
<td>m/z 119.1</td>
<td>163.1</td>
</tr>
<tr>
<td>Production 2</td>
<td>m/z 91.1</td>
<td>58</td>
</tr>
<tr>
<td>Abundance</td>
<td>% 0.5</td>
<td>1</td>
</tr>
<tr>
<td>RSD abundance</td>
<td>% 15</td>
<td>21.3</td>
</tr>
<tr>
<td>Internal standard</td>
<td>Amphetamine-d11</td>
<td>MDMA-d5</td>
</tr>
<tr>
<td>Influent LOQ</td>
<td>ng L⁻¹ 40</td>
<td>12</td>
</tr>
<tr>
<td>Linearity</td>
<td>r² 0.9960</td>
<td>0.9999</td>
</tr>
<tr>
<td>Instrumental LOQ</td>
<td>pg 58</td>
<td>14</td>
</tr>
</tbody>
</table>

a de Voogt et al. (2011).
b Bijlsma et al. (2013).
c Linearity range studied: 0.7–288 μg/L.
ACQUITY UPLC™ sample manager was used for the separation of enantiomers. A Chiral-CBH column, 100 × 2 mm, 5 μm (Chromtech, Congleton, UK) and a Chiral-CBH 10 × 2.0 mm guard column (Chromtech) were used for the separation of enantiomers of amphetamine, MDA and MDMA. The separation of chiral drugs was undertaken under isocratic conditions with the usage of mobile phase composed of 90% H₂O, 10% 2-propanol and 1 mM ammonium acetate. 20 μL of the sample was injected into the system. The column was kept at 25 °C and the temperature in the sample manager was kept at 4 °C. The flow rate of mobile phase was 0.075 mL/min, which allowed for the introduction of mobile phase from LC into MS without splitting.

A Xevo TQD (triple quadrupole) mass spectrometer (Waters, Manchester, UK), equipped with an electrospary ionisation source, was used for the quantification of the chiral drugs. The analyses were performed in positive mode with a capillary voltage of 3.13 kV, a source temperature of 150 °C and a desolvation temperature of 150 °C. A cone gas flow of 50 L/h and desolvation gas flow of 650 L/h were used. Nitrogen, used as a nebulising and desolvation gas, was provided by a high purity nitrogen generator (Peak Scientific Instruments Ltd, UK). Argon (99.999%) was used as a collision gas. Masslynx 4.1 (Waters, UK) software was used to collect and analyse the obtained data. Mass spectrometry analyses were performed in the multiple reaction monitoring (MRM) mode, measuring the fragmentation of the protonated pseudo-molecular ions of each chiral drug (Table 2). Validation parameters for this method can be found in Table 3. For more details on analytical procedure please refer to the following publications: (Kasprzyk-Hordern and Baker, 2012a,b).

### 3. Results and discussion

#### 3.1. MDMA in the city of Utrecht

#### 3.1.1. Loads of MDMA in sewage influents

The average weekly normalised load of MDMA in the influent from the city of Utrecht in 2011 was 615 mg/day/1000 inhabitants (Thomas et al., 2012) corresponding to an average daily load to the STP of 184 g/day. This load would roughly correspond to an average consumption of 1.2 kg MDMA per day, taking into account an excretion factor of 6.7 (Abraham et al., 2009). Assuming a dose of 100 mg of pure MDMA per person per day this load would correspond to a prevalence of 5.5% for the people between 15 and 64 years living in Utrecht, which is 4 times higher than the last reported figure of 1.4% in 2009 (European Monitoring Centre for Drugs and Drug Addiction, Statistical Bulletin, 2012). This average prevalence is highly unrealistic as it is twice the figure of 2.4% of the United Kingdom. It is important to note that the same STP in the city of Utrecht was also subject to monitoring for a period of 7 days in 2010 (Bijlsma et al., 2012). The loads of MDMA to the STP (in g/day) observed in both sampling campaigns are shown in Fig. 2. The average weekly load of MDMA of 184 g/day in 2011 is 20 times higher than the average load observed in 2010 (9.3 g/day). These results raised suspicions about the origin of the high MDMA loads observed in 2011. After viewing police reports on the internet it became clear that a possible cause for the abnormally high levels could be connected to a police raid into a private home in Utrecht 2 days before the sampling started in 2011. The location raided appeared to be equipped for producing MDMA tablets, but only starting materials, additives, empty tablet bags and a few tablets were found. The police estimated that the total amount in the empty bags could have been a total of 30 kg comparable with more than half a million of XTC tablets.

### Table 2

Optimised MRM conditions for the analysis of chiral drugs by UPLC/MS/MS (CV – cone voltage [V]; CE – collision energy [eV]).

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CV/CE</th>
<th>MRM1 (quantification)</th>
<th>CV/CE</th>
<th>MRM2 (confirmation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/S(±)-Amphetamine</td>
<td>18/8</td>
<td>136.16 &gt; 119.10</td>
<td>18/16</td>
<td>136.16 &gt; 91.10</td>
</tr>
<tr>
<td>R/S(±)-MDMA</td>
<td>24/13</td>
<td>194.09 &gt; 163.10</td>
<td>24/24</td>
<td>194.09 &gt; 105.10</td>
</tr>
<tr>
<td>R/S(±)-Amphetamine-d11</td>
<td>18/8</td>
<td>147.16 &gt; 130.10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>R/S(±)-MDMA-d5</td>
<td>26/13</td>
<td>199.1 &gt; 165.10</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table 3

Validation parameters for SPE-Chiral LC–MS/MS method.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Instrumental parameters</th>
<th>ERa ± SD **</th>
<th>ERb ± SD **</th>
<th>R²***</th>
<th>IQL (S/N &gt; 3)</th>
<th>IQB (S/N &gt; 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine (S): AMPH-d11</td>
<td>R(−)</td>
<td>0.51 ± 0.02</td>
<td>1.92 ± 0.12</td>
<td>0.9996</td>
<td>0.3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>S(+), IS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDMA (S): MDMA-d5</td>
<td>R(−)</td>
<td>0.48 ± 0.01</td>
<td>1.99 ± 0.16</td>
<td>0.9997</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>S(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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IS — Internal standard.

* ERa — enantiomeric fraction in standard solution spiked with racemic chiral drug (concentrations: IDL-144 μg/L).

** ERb — Enantiomeric resolution.

*** Studied linearity range: IDL-144 μg/L.

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** Fig. 2. ** Daily mass loads of MDMA of wastewater entering the STP in Utrecht calculated from samples collected during a week in years 2010 and 2011, respectively.

where: tR1, tR2 are the retention times of the first- and second-eluted enantiomers and W1, W2 are the widths of these responses at the base line.
In order to verify whether the high mass loads of MDMA in the wastewater observed in 2011 result from consumption or direct disposal of unused MDMA, enantiomeric profiling of wastewater was undertaken.

3.1.2. Enantiomeric profiling of MDMA in wastewater

MDMA has one asymmetric carbon centre and therefore it can exist in the form of two enantiomers, which differ both quantitatively and qualitatively in pharmacological activity: S (+)-enantiomers are more amphetamine-like stimulants and R (−)-enantiomers are more hallucinogenic (Fantegrossi, 2008). MDMA’s enantiomers have different serotonin (5-HT) neurotoxicity: S (+)-MDMA is a more potent neurotoxin than R (−)-MDMA (Moore et al., 1996). There are four principal precursors, which can be used in manufacture of MDMA and related drugs: safrole, isosafrole, piperonal, 3,4-methylenedioxyphenyl-2-propanone (Piperonylmethylketone, PMK). Many illicit syntheses start with PMK and use either the Leuckart route or various reductive aminations (Renton et al., 1993). All of these methods produce racemic MDMA (King, 2009). S (+)-MDMA is however known to undergo preferential metabolism in human (bile and urine) to more active metabolites, which leads to enrichment of MDMA with R (−)-enantiomer and preferential formation of S (+)-MDA. Moore et al. (1996) observed that both primary routes of excretion in human (bile and urine) had greater concentrations of R (−)-MDMA than the S (+) isomer (EF of 0.57, autopsy findings). These fluids also contained twice the concentration of S (+)-MDA than the R (−)-isomer (EF = 0.37, autopsy findings) as reported by Moore et al. (1996). This is very important information, which allows for the verification of whether drug residue present in wastewater results from its actual consumption (EF > 0.5) or direct disposal (EF = 0.5). As MDMA does not currently have medical applications its presence in biological specimens is believed to result from its abuse.

The results of the present study (Fig. 3) indicate that during 2010 sampling campaign, MDMA was found in wastewater in the form enriched with R (−)-MDMA. The mean EF value for raw wastewater collected during one week sampling was found to be 0.68 ± 0.04. This correlates well with published data on metabolism of MDMA in humans (Moore et al., 1996) and results from the UK study (Kasprzyk-Hordern and Baker, 2012b), and suggests that MDMA found in the sewage of Utrecht sampled in 2010 results from MDMA abuse rather than direct disposal of unused drug.

In contrast, in the 2011 sampling campaign, MDMA was found to be racemic (EF = 0.51) during the first 2 days of sampling, with a slow increase of EF to 0.57 throughout the sampling week (cf. Fig. 3). It is important to mention that an increase in EF (showing enrichment with R (−)-MDMA) correlated well with the decrease in daily loads of MDMA, indicating higher contribution from consumed MDMA to the overall mass loads throughout the sampling week. Levels of MDA (human urinary metabolite of MDMA) detected in 2010 were equivalent to those observed in 2011. We identified but could not quantify enantiomers of MDA in wastewater in both 2010 and 2011, which proves that MDMA was disposed of in 2011. Furthermore, MDMA profiling in wastewater samples collected from Eindhoven during the same 2011 sampling campaign revealed that average EF of MDMA in these samples was, similarly to 2010 sampling, 0.69 ± 0.03 (Fig. 3).

3.2. Amphetamine in the city of Eindhoven

3.2.1. Loads of amphetamine in wastewater

The loads of amphetamine in the STP (in g/day) in both sampling campaigns are shown in Fig. 4. The average load of amphetamine in the sewage influent of Eindhoven was 1431 g/day in 2011, which is 14 times higher than the average load observed in 2010 (99 g/day). These results raised suspicions about the origin of high amphetamine loads. The average normalised load of amphetamine in the influent from the city of Eindhoven in 2011 was 3040 mg/day/1000 inhabitants (Thomas et al., 2012). This load would roughly correspond to an average consumption of 4.7 kg of pure amphetamine per day, taking into account an excretion factor of 3.3 (Zuccato et al., 2008). Assuming a daily dose of 0.4 g of pure amphetamine this would be equivalent to a prevalence of 1.5% for the people between 15 and 64 years living in the catchment area of Eindhoven, which is 3 times higher than the last reported figure of 0.4% in 2009 (European Monitoring Centre for Drugs and Drug Addiction, Statistical Bulletin, 2012). The corresponding prevalence calculated for the Sunday of 4% is even more unrealistic.

As in the case of MDMA, in order to verify whether the high mass loads of amphetamine in the wastewater observed in 2011 result from consumption or direct disposal of unused amphetamine, enantiomeric profiling of wastewater was undertaken.

3.2.2. Enantiomeric profiling of amphetamine

Amphetamine, similarly to MDMA, is a chiral compound with one asymmetric carbon. It can exist in the form of two enantiomers, which significantly differ in potency: S (+)-amphetamine has twice as high stimulant activity than R (−)-amphetamine (Anderson et al., 1978). Amphetamine is most commonly synthesised via the Leuckart method.
Amphetamine can also be excreted as a result of metabolism of methamphetamine and certain prescription drugs. For example, \( R(-)- \) amphetamine is excreted as a result of administration of selegiline (marketed as \( R(-)- \) enantiomer). \( S(+) \)-Amphetamine is formed as a result of an administration of clozapine. On the other hand, metabolism of famprofazone leads to the formation of \( S(+)/R(-) \)-amphetamine. Similarly, administration of fenproporex leads to the formation of \( S(+)/R(-) \)-amphetamine. Benzphetamine metabolism results in the formation of \( S(+) \)-amphetamine (Cody, 2002). Furthermore, metabolism of amphetamine is known to be stereoselective: \( S(+) \)-amphetamine metabolises faster than \( R(-) \)-enantiomer (Kasprzyk-Hordern and Baker, 2012b).

Due to different legal and illicit uses of amphetamine available in different enantiomeric forms, distinction between consumption and direct disposal of unused amphetamine poses a significant challenge (Kasprzyk-Hordern and Baker, 2012b). In the present study amphetamine found in wastewater was racemic in both 2010 and 2011 sampling campaigns (Fig. 5) (0.54 ± 0.02 and 0.53 ± 0.02 in Utrecht 2010 and 2011 respectively and 0.52 ± 0.01 and 0.52 ± 0.02 in Eindhoven 2010 and 2011 respectively). These results did not correlate with results from another study undertaken by the authors in England, where amphetamine found in wastewater was enriched with \( R(-) \)-enantiomer (median \( EF = 0.64 \)) indicating abuse of racemic amphetamine (Kasprzyk-Hordern and Baker, 2012b). Indeed, amphetamine is usually abused as racemate.

Furthermore, according to CVZ statistics in The Netherlands, only \( S(+) \)-amphetamine is prescribed (dexamfetamine 11 kg/2010) (The Health Care Insurance Board, 2013). These are relatively low levels when compared to illegal use (usage of amphetamine: 1.5–2 tonnes yearly) (European Commission Directorate General for Justice, 2013; survey-based estimates of usage). Methamphetamine, which metabolises to amphetamine, is not popular in The Netherlands: usage is mainly restricted to small niches in the gay scene and amongst psychonauts due to the limited availability and higher price € 100 per g (Nabben et al., 2010). In 2010 (Bijlsma et al., 2012) and 2011 (Thomas et al., 2012) no methamphetamine at levels above the LOD was detected in wastewater from the cities of Utrecht and Eindhoven during the week long monitoring campaigns. Therefore, amphetamine levels in Dutch wastewaters formed as a result of metabolism of methamphetamine are negligible.

Amphetamine can also be excreted in different enantiomeric forms as a result of metabolism of methamphetamine and certain prescription drugs (e.g. selegiline, prescription in The Netherlands 2.3 kg in 2010 (The Health Care Insurance Board, 2013), which leads to the metabolic formation of \( R(-) \)-amphetamine and \( R(-)- \)-methamphetamine). Again, these quantities are insignificant when compared to actual estimated abuse of amphetamine in The Netherlands. Therefore, the amphetamine case is not clear cut in The Netherlands when compared to the UK. Further work will have to be undertaken to fully understand sources of amphetamine in Dutch wastewaters. There are two obvious reasons, which could be considered in order to explain the presence of racemic amphetamine in wastewater.

- Direct disposal of unused amphetamine (relatively high contribution from the disposal of unused amphetamine to the overall load in wastewater).
- Illicit use of both racemic amphetamine and enantiomerically pure \( S(+) \)-amphetamine.

4. Conclusions

A sampling campaign undertaken in 2010 and 2011 in two Dutch cities: Utrecht and Eindhoven aiming at verification of illicit drug consumption revealed that the levels of MDMA found in 2011 in the city of Utrecht did not correspond with those observed in the previous year 2010. Enantiomeric profiling of wastewater samples collected in Utrecht and Eindhoven in years 2010–11 proved that MDMA is usually present in wastewater due to its consumption ( MDMA enriched with \( R(-) \)-enantiomer). Excessively high mass loads of MDMA during sampling campaign in Utrecht in 2011 were shown to be racemically indicating direct disposal of unused MDMA possibly as a result of a police raid at a nearby illegal production facility. The fact that levels of MDA were similar in 2010 and 2011 in wastewater from Utrecht also supports this conclusion since the only aberrant level was MDA. Due to the removal efficiency of only 5% for MDMA in the STP of Utrecht (Bijlsma et al., 2012) this large quantity was directly disposed to the aquatic environment. Further research needs to be undertaken to investigate the impact in the environment.

Enantiomeric profiling was also undertaken in order to verify the origin of unexpectedly high mass loads of amphetamine in the city of Eindhoven in the 2011 sampling campaign. Unfortunately, due to the different legal and illicit uses of amphetamine available in different enantiomeric forms, a distinction between consumption and direct disposal of unused amphetamine in Dutch wastewater could not be achieved. Further research will be undertaken to provide comprehensive verification of the sources of amphetamine in wastewater in The Netherlands.

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