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Determination of the stereoisomeric distribution of R-(−)- and S-(+)-methamphetamine in Thai pills in the legal context of "not inconsiderable quantities"

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ABSTRACT

In Germany, the severity of a narcotic offence is determined based on the classification into different categories of quantity. Recently, an amendment to the Narcotics Law regarding the "not inconsiderable quantities" was introduced. The new limits for methamphetamine are derived from the varying potency of the respective enantiomers. Switzerland, however, does not practice this distinction and there is only one limit quantity, without considering the isomeric structure. To examine whether this single value is still contemporary, 26 Thai pill samples from the years 2000, 2001, 2007, 2009 and 2017 were analyzed by HPLC-MS/MS and GC-MS.

Both methods resulted in similar stereoisomeric distributions: the pills mainly consist of the more potent S-(+)-methamphetamine, some even being enantiopure. Others show enantiomeric mixtures of R-(−)-/S-(+)-methamphetamine, but rarely in an equimolar ratio. There even was one sample, where mainly the less potent R-(−)-methamphetamine was detected.

In conclusion, the analyses revealed that the single value for a "not inconsiderable quantity" in Switzerland seems outdated. Most of the sized pills showed a much higher concentration of the more potent S-(+)-methamphetamine. The risks related to taking such a pill are much higher and therefore the limit quantity should be adapted to the potency of the respective enantiomers.

1. Introduction

According to the United Nations Office on Drugs and Crime's World Drug Report 2019, there are 29 million past-year users of amphetamine-type stimulants (ATS) in 2017, being the third largest group of users, directly after cannabis and opioids. Moreover, it showed that the form of ATS used diverges substantially from region to region. Whereas the non-medical use of prescription stimulants and methamphetamine predominate in North America, crystalline methamphetamine prevails in East and South-East Asia and Oceania (Australia) and amphetamine in Western and Central Europe and the Near and Middle East (World Drug Report, 2019).

ATS are structurally and functionally close to endogenous amines and act on the central nervous system increasing the concentrations of the neurotransmitters dopamine, serotonin, and norepinephrine in the brain. This induces enhanced alertness, increased arousal and generates behavioral excitement stimulating motivation, movement, pleasure, and reward centers (Kuczenski et al., 1995; Melega et al., 1995; Kish, 2008). The leading compounds of this class of drugs are amphetamine (α-methylphenethylamine) and methamphetamine (*N,*α-dimethylphenethylamine), with the latter having a higher potency and a longer duration of action due to the additional methyl moiety. This component makes the molecule more lipophilic and therefore facilitates the passage of the blood brain barrier. Both substances possess a chiral center, which results in the drugs being present either as single enantiomers or as a mixture of both, depending on the product, the source and/or the synthesis route (see Fig. 1) (Mendelson et al., 2006; Maas et al., 2018). The latter is subject to the availability of precursors and can vary from region to region. The International Narcotics Control Board's 2018 Annual Report on Precursors suggests that the majority of illicit manufacture of methamphetamine in Asia and Oceania, in Africa and in some regions in Europe still use ephedrine or pseudoephedrine. In North America, however, illicit methamphetamine is nowadays mostly manufactured using phenylacetone (P-2-P) (INCB, 2018a). For this reason,

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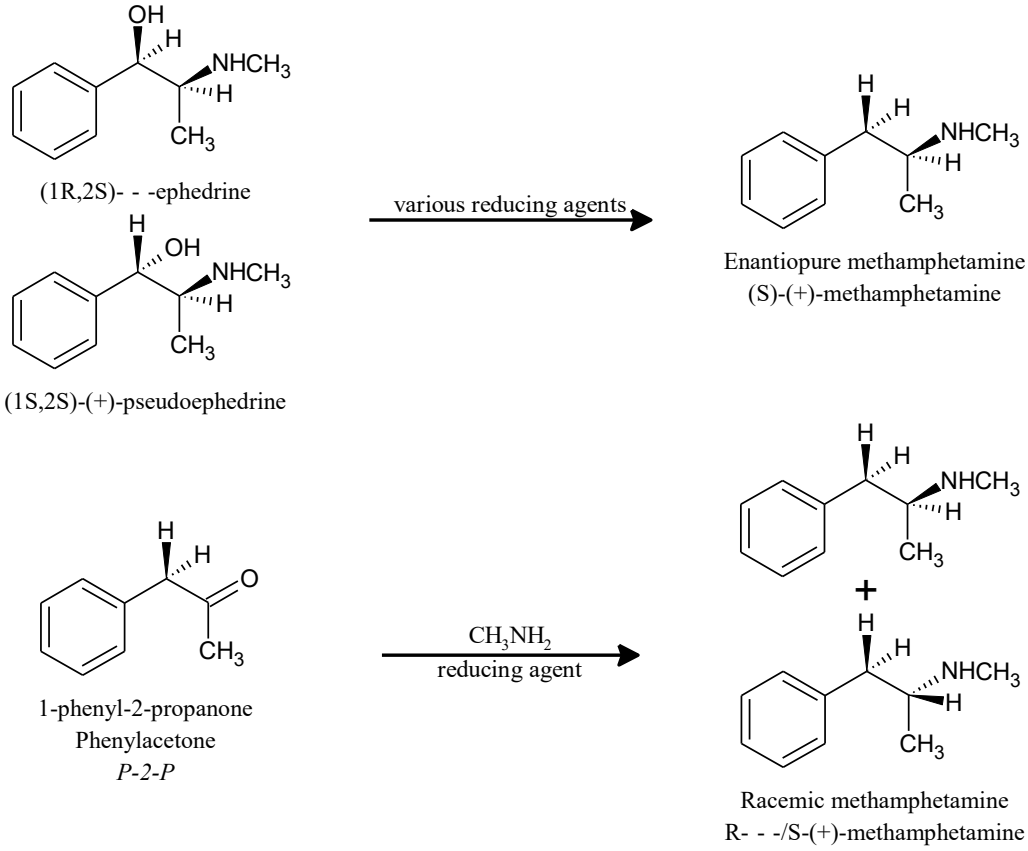

Fig. 1. Precursors and routes of synthesis for S-(+)-methamphetamine and racemic methamphetamine (according to Mendelson et al., 2006).

methamphetamine is most often encountered on the street as an enantiomeric mixture in the United States. In contrast, it can be assumed that the majority of illicit methamphetamine in other parts of the world mainly consists of the more potent S-(+)-enantiomer, which provides greater stimulant effect and is preferred as illegal street drug. In general, the S-(+)-enantiomers are two to four times more potent than their corresponding R-(−)-enantiomers (Alles, 1939).

There are several reasons why it may be important to distinguish between the two enantiomers. First, from a toxicological point of view, it is necessary to be able to discriminate between a legal and an illegal uptake of methamphetamine. This, of course, presupposes that there are drugs, which are readily available, like e.g. several over-the-counter decongestant products in the United States containing the R-(−)-isomer (West et al., 2013). Toxicological analyses can be performed on different samples, e.g. blood/plasma (Hess et al., 2019; Newmeyer et al., 2014; Peters et al., 2003; Rasmussen et al., 2006), urine (Iio et al., 2005; Wang et al., 2015a) or oral fluid (Borg et al., 2018). Second, from the perspective of national and international health authorities, enantiomeric profiling can be used to determine drug use and abuse. Often, these studies use wastewater-based epidemiology approaches because it provides a near-real time profile of substance abuse (Archer et al., 2018; Castrignano et al., 2018; Gao et al., 2018; Xu et al., 2017; Goncalves et al., 2019). However, these do not take into account that enantiomeric ratios may change during metabolism if racemic methamphetamine is consumed (Mendelson et al., 2006). Third, from a chemical point of view, enantiomeric analysis can be employed for profiling of methamphetamine seizures by inferring the synthetic pathways and providing information concerning its precursors. Different analytical methods are currently in use for the separation of the two enantiomers: classical approaches like capillary electrophoresis (Cui et al., 2018; Liau et al., 2003), GC-MS with derivatization (Lee et al., 2007; Tsujikawa et al., 2013) and LC-MS/MS (Wang et al., 2015b) or sophisticated methods like the use of molecularly imprinted resin (Alatawi et al., 2018). Currently, no systematic analysis of the enatiomeric ratios of so-called “Thai pills”, tablets containing methamphetamine and mostly imported from Thailand, or crystal meth is carried out in Switzerland. Furthermore, there is only very little recent data on enantiomeric ratios of confiscated methamphetamine in other European or overseas countries available in literature.

Besides, there is the legal perspective, which of course is closely linked to all other three purposes, but above all to forensic toxicology and chemistry. In Germany, the severity of a narcotic offence and the associated penalty are determined on the basis of the classification into different categories of quantity. There recently has been an amendment to the Annexes of the Narcotics Law regarding the “not inconsiderable quantities”. Based on pharmacological and toxicological findings, the following limit quantities for methamphetamine were set: 10 g for the enantiomeric mixture of R-(−)/S-(+)-methamphetamine, 5 g for the more potent S-(+)-enantiomer and 50 g for the R-(−)-enantiomer. Swiss legislation proceeds in a similar way, but defines a “serious” or a “qualified” offence. However, no distinction is made between enantiopure methamphetamine and an enantiomeric mixture, there is only one limit quantity of 12 g, without any specifications regarding the isomeric structure and therefore the potency. To examine, whether this single value is still contemporary, we have analyzed 26 Thai pill samples from different seizures in the Canton of Bern and surrounding Cantons in Switzerland from the years 2000, 2001, 2007, 2009 and 2017 with two different methods: HPLC-MS/MS and GC-MS with derivatization.

2. Material and methods

2.1. Chemicals and reagents

Cerilliant (Round Rock, TX, USA) provided the enantiopure

Table 1
Determination of the sampling size of Thai pills.

Number of pills (X) per sample	Sampling size
1 pill	Use the 1 pill
2–400 pills	$\sqrt{x}+1$ (round up)
>400 pills	$\sqrt{x}$ (round up)

reference standards R-(−)- & S-(+)-methamphetamine, the racemic reference standard (±)-methamphetamine and its deuterated internal standard (±)-methamphetamine-d_5. The derivatization agent (R)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (R-(−)-MPTCl) and ammonium bicarbonate (NH_4HCO_3) were purchased from Sigma-Aldrich (Buchs, Switzerland). Merck (Darmstadt, Germany) provided acetonitrile (MeCN, HPLC gradient grade, 99.9%)), ammonium hydroxide solution (NH_4OH, 25%), ethanol (EtOH), ethyl acetate (EtOAc) and potassium hydroxide (KOH). Biosolve B.V. (Valkenswaard, Netherlands) supplied methanol (MeOH, absolute, HPLC grade) and ultrapure water type 1 was prepared in-house with a Direct-Q water purification system from Millipore (Zug, Switzerland).

2.2. Thai pills

Thai pills from a total of 11 seizures from the years 2000–2017 were examined. For investigative reasons, some of these seizures have already been split into different samples (e.g. seizure 17–02). Where necessary, these samples were divided again into different subsets because of colour differences of the pills (e.g. sample 07–01.1). Sampling of the different samples was conducted in accordance with internal quality system procedure (see Table 1) (Steiger et al., 2009). The sampled pills were then ground to powder by mortar and pistil. The composition of the Thai pills was determined by HPLC-DAD: On average, one Thai pill weighed 90 mg and contained 21.2% methamphetamine (range from 16.2 to 31.2%).

2.3. Sample preparation

HPLC-MS/MS sample preparation has been adjusted according to internal quality system procedures: 1 mg of powdered sample was dissolved in 2 mL of MeOH, sonicated for 5 min and centrifuged for 5 min at 20 °C and ~2500 g. From this solution, 100 µL were withdrawn, diluted with 900 µL of MeOH and vortexed. For the analysis, 75 µL of the diluted solution were taken and 15 µL of ISTD (10 µg/mL) and 1.41 mL of water were added.

Sample preparation for GC-MS with derivatization to obtain diastereomers was performed according to Liau et al. (2003) and Rasmussen et al. (2006): 10 mg of powdered sample were dissolved in 1 mL of 0.2 N KOH and vortexed for 5 min. Then, 100 µL of this solution were extracted with 1 mL of EtOAc, vortexed for 5 min and centrifuged for 5 min at 20 °C and ~900 g. 900 µL of the organic phase were withdrawn and 25 µL of derivatization agent (50 µL of R-(−)-MTPACl were diluted in 1 mL of MeCN) were added (see Fig. 2). The sample was then heated for 2 h at 80 °C, cooled down to room temperature, and re-heated for 15 min at 75 °C after adding 100 µL of EtOH. Afterwards, the sample was evaporated to dryness under a gentle stream of nitrogen, reconstituted in 900 µL of EtOAc and sonicated for 2 min. For the analysis, 10 µL of the reconstituted solution were then again diluted with 190 µL of EtOAc.

2.4. HPLC-MS/MS instrumentation

Enantiomeric concentrations of methamphetamine were determined according to Phenomenex® Application Note (Phenomenex Chiral Amphetamines, 2363). The LC-MS/MS system consisted of an UltiMate 3000 HPLC system (Dionex, Olten, Switzerland) coupled to a 5500 QTRAP hybrid triple quadrupole/linear ion trap mass spectrometer with a Turbo V ion source (SCIEX, Brugg, Switzerland). Analyst software version 1.6.2 (SCIEX, Brugg, Switzerland) was used for data acquisition and analysis.

Chiral separation by LC was performed with a Lux 3 µm AMP column (150 × 3.0 mm), obtained from Phenomenex® (Torrance, CA, USA). Mobile phase A was 5 mM NH_4HCO_3 in water adjusted to pH 11 with NH_4OH and mobile phase B was MeOH. One microliter aliquots were injected and the samples were separated running a gradient from 60% B to 95% B over 1 min after an isocratic hold for 10 min. The column was re-equilibrated after 2 min, resulting in a total runtime of 13.1 min.

Mass spectrometric data were acquired in positive electrospray ionization and multiple reaction monitoring mode, with an ion spray voltage of 5500 V and an ion source temperature of 490 °C. Measured transitions were R-(−)-/S-(+)-methamphetamine, *m/z* 150.2 → 91.0* and *m/z* 150.2 → 119.1; and R-(−)-/S-(+)-methamphetamine-d5, *m/z* 155.1 → 92.0*. The transitions marked with an asterisk were used for quantification.

2.5. GC-MS instrumentation

The samples were analyzed using an Agilent Technologies (AT, Basel, Switzerland) 5973*Network* GC system combined with an AT 5973*inert* mass selective detector, an AT 7683 Series injector and auto sampler, and MSD ChemStation ver. E.02.02.1431.

GC was performed with an AT HP-5 MS (cross-linked 5%-phenyl-methylpolysiloxane) capillary column (30 m × 0.25 mm i.d., 0.25 µm film thickness) with 1 µL splitless injection. The temperature program for the column oven was as follows: 50 °C for 3 min, a linear ramp to 150 °C at 5 °C/min, then ramped linearly to 275 °C at 25 °C/min and held at 275 °C for 4 min. The total analysis time was 32 min. Helium carrier gas was used at a constant flow rate of 1.0 mL/min.

Mass spectrometric parameters were as follows: ionization energy, 70 eV; ion source temperature, 230 °C; full-scan, 30–450 amu.

3. Results & discussion

A validation of the HPLC-MS/MS method was performed according to internal quality system procedures. Linear regression analysis over seven different calibrator levels demonstrated good linearity between 2.5 and 1250 ng/mL for R-(−)- and S-(+)-methamphetamine with correlation coefficients ≥ 0.9994 (1/x weighting). The limit of detection (LOD) and the lower limit of quantification (LLOQ) were found to be 1.0 ng/mL and 2.5 ng/mL, respectively. Accuracy and imprecision of the method were evaluated at four quality control levels. Average accuracy for R-(−)- and S-(+)-methamphetamine were 91.8% and 94.3%, respectively. Average imprecision were 3.70% relative standard deviation (CV) and 2.57% CV for R-(−)- and S-(+)-methamphetamine,

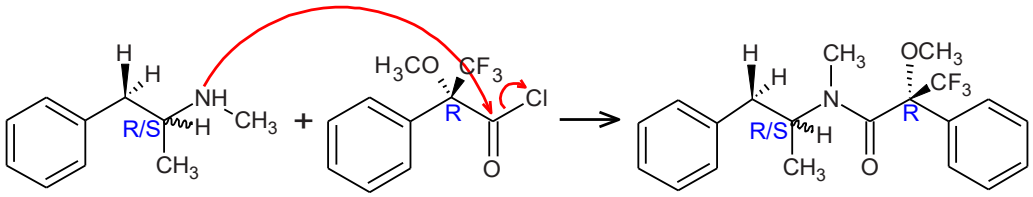

Fig. 2. Reaction of R-(−)-/S-(+)-methamphetamine with chiral derivatization reagent R-(−)-MTPACl to form diastereoisomers.

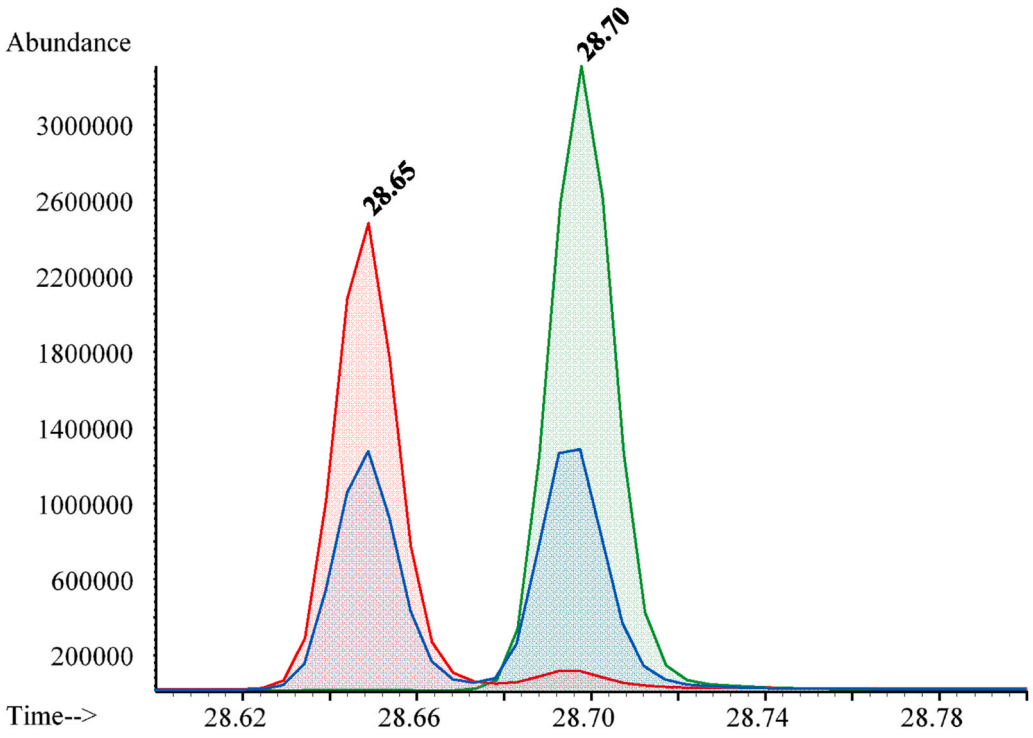

Fig. 3. GC chromatograms (TIC) of three derivatized methamphetamine (Meth) samples. Red: R-(−)-Meth (17–04.1); Green: S-(+)-Meth (01-01); Blue: racemic Meth (17–02.2). T_R 28.65 min: R-(−)-Meth deriv.; T_R 28.70 min: S-(+)-Meth deriv. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

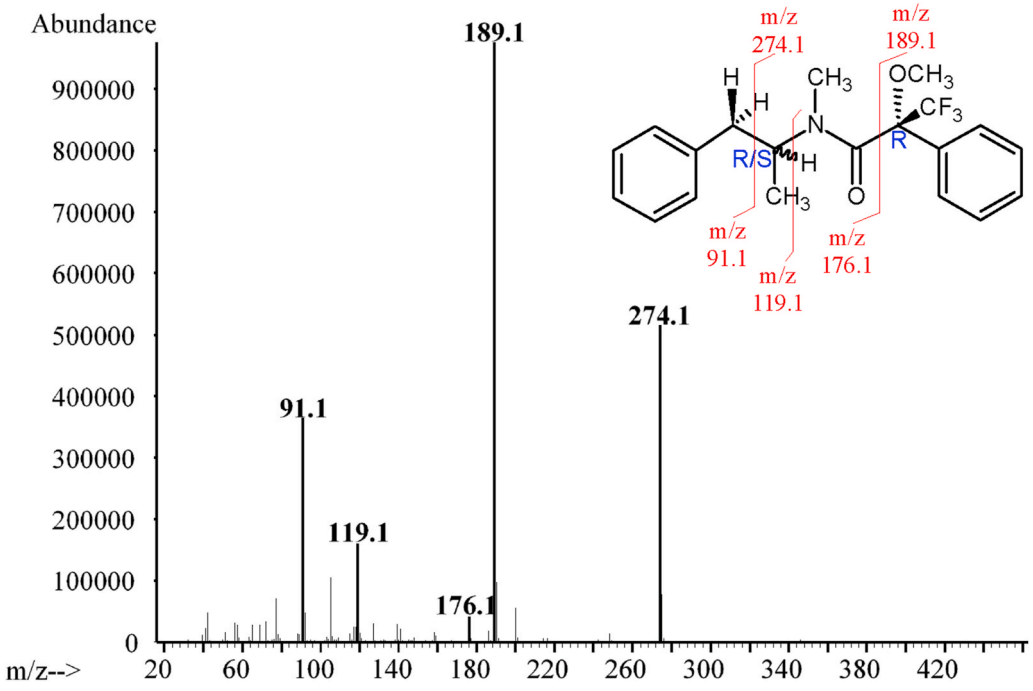

Fig. 4. Electron impact mass spectrum of R-(−)-MTPA-(R/S)-Meth with molecular structure and possible fragment pattern obtained by GC-MS (see Fig. 3).

respectively. The GC-MS method was tested as alternative method and only used for comparison. Since the results were comparable with those obtained with the validated LC-MS/MS method, no further validation was performed for the time being.

Enantiomeric separation was achieved with both methods. The chromatograms show that baseline separation was obtained for the diastereomers with GC-MS, while a slight overlap of the two enantiomers can be seen with chiral LC-MS/MS (see Figs. 3–5). Nevertheless, the concentrations measured with both methods are very similar and comparable (see Tables 2 and 3). They indicate that the Thai pills mainly consist of S-(+)-methamphetamine, some seizures even being enantiopure and only containing the more potent stereoisomer (e.g. sample 01-01). Others show enantiomeric mixtures of R-(−)-/S-(+)-methamphetamine, but rarely in an equimolar ratio. The concentration of the more

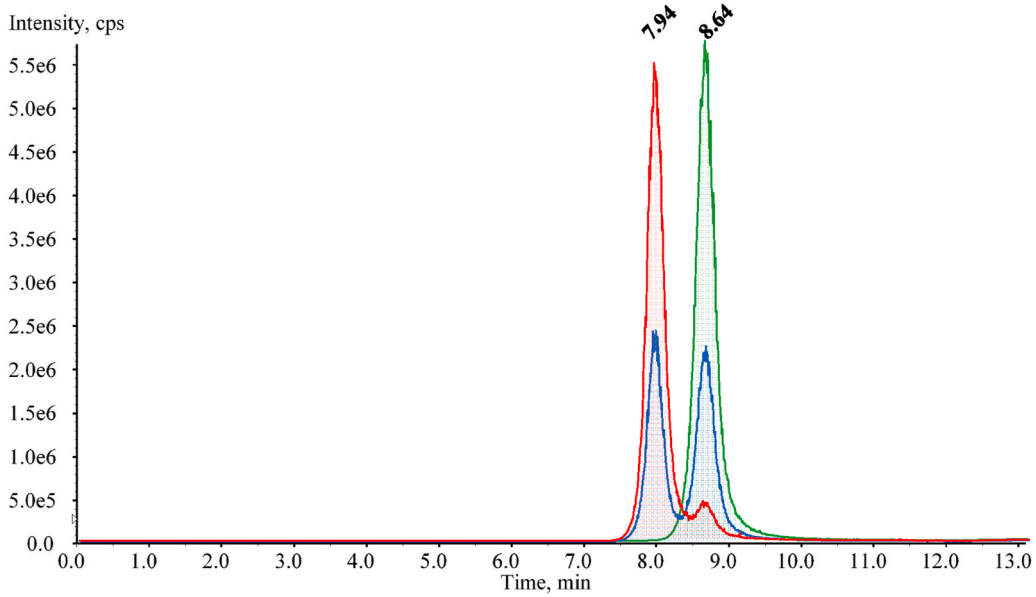

Fig. 5. LC chromatograms (MRM1) of three methamphetamine samples. Red: R-(−)-Meth (17–04.1); Green: S-(+)-Meth (01-01); Blue: racemic Meth (17–02.2). T_R 7.94 min: R-(−)-Meth; T_R 8.64 min: S-(+)-Meth. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

potent S-(+)-methamphetamine most often exceeds that of the R-(−)-enantiomer (e.g. samples 07–01.1_1–4). However, there are also two cases with an equimolar ratio (e.g. samples 17–02.2 & 17–04.6) and even one case, where mainly the less potent R-(−)-methamphetamine was detected, but only a small amount of the S-(+)-enantiomer (sample 17–04.1).

Even within samples originating from one seizure, different ratios for R-(−)- and S-(+)-methamphetamine were detected. Samples 17–02.1 to −02.4, for example, resulted all from the same drug bust. Both, pills containing pure S-(+)-methamphetamine were found, but also those with an enantiomeric mixture. The same applies to samples 17–04.1 to −04.6, where in addition pills containing mainly the less potent R-(−)-enantiomer were encountered. This suggests either that the dealers have multiple suppliers or that the manufacturers are using different routes of synthesis and precursor substances.

Furthermore, it can be noticed that the seizures of the years 2000 and 2001 contain pure S-(+)-methamphetamine, indicating that most likely ephedrine or pseudoephedrine was used as precursors. Later, only a few of such seizures were found, but almost only enantiomeric mixtures, suggesting that mainly P-2-P was utilized as precursor. Similar observations have been made in other studies, e.g. by Lee et al. (2007) in Korea, where enantiomeric impurity started to appear from 1997 and have since then gradually increased, or by Wang et al. (2015b) in China, where this increase was also discovered between the years 2008 and 2014. These changes in enantiomeric purity, depending on the route of synthesis, are a result of the regulation of available precursors. Ephedrine and pseudoephedrine, for example, have been controlled substances for some time. It is no longer possible to determine the exact time at which these two substances were subjected to the narcotic legislation in Switzerland. It certainly took place before 2005, but older versions of the Ordinance on precursor chemicals, which came into force in 1997, are no longer held by the Federal Chancellery [personal communication by Swissmedic]. Internationally, these substances have been under control for even longer. After the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances in 1988, the International Narcotics Control Board (INCB) compiled the so-called "Red List", containing a list of precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under international control, figuring ephedrine, norephedrine, pseudoephedrine, but also P-2-P and some of its precursors (INCB, 2018b). Furthermore, the INCB reported, as mentioned in the introduction, that in some regions of Europe the use of ephedrines is predominant in the illicit manufacture of methamphetamine (INCB, 2018a). This statement, however, cannot be confirmed by the results of Thai pills sized in 2017 and earlier in Switzerland. They show mainly enantiomeric mixtures of R-(−)- and S-(+)-methamphetamine, but in non-equimolar ratios, which suggests that the intermediate equimolar products from synthesis with P-2-P are purified to obtain a more potent substance. This optical resolution can, for example, be conducted using *l*- and *d*-tartaric acid (Grzechnik et al., 2018).

Considering the change of concentration of methamphetamine in the seized Thai pills over the past years, one can see a small decrease in potency, while the weight of the pills stayed constant (at about 90 mg). Whereas the pills in the years before 2010 contained a mean concentration of 23% of S-(+)-methamphetamine, the pills sized in 2017 only contained 16% in average. This concentration is comparable to the one published in the narcotic statistics by the Swiss Society of Forensic Medicine (SGRM, 2017). The enantiomeric fraction (EF), which is calculated as the fraction between the S-(+)-concentration and the total methamphetamine concentration, can be an indicator of purity. The resulting EFs, which with a few exceptions are between 0.8 and 1.0, are comparable with the EFs from another study (Xu et al., 2017).

Further international comparisons remain difficult because very rarely the pills are analyzed directly, but only the concentrations in blood and/or urine after the consumption of methamphetamine. However, this can also help to get a better overview of the situation on the illegal market and to get an answer to the legal question. Wastewater analyses in different regions of the world show that the methamphetamine consumed in Australia, China, South Africa and a big part of Europe is mainly the S-(+)-enantiomer, with some exceptions like the UK or Norway, where consumption of racemic methamphetamine was detected. The EFs in these studies are also comparable to the ones shown in Table 2 (Archer et al., 2018; Castrignano et al., 2018; Gao et al., 2018). However, one needs to be careful when interpreting these data, as it is not possible to distinguish whether the residues originate from abuse or other sources, e.g. direct disposal or administration of prescription drugs (Xu et al., 2017). Furthermore, the differences of metabolisation ratios between enantiopure and racemic

Table 2
Concentrations of R-(−)- and S-(+)-methamphetamine in Thai pill samples analyzed by HPLC-MS/MS.

SAMPLE	R-Meth		S-Meth		Enantiomeric
(YY–N°_subset)	[ng/mL]	[%]	[ng/mL]	[%]	Fraction (EF)
00–01_1	nd	N/A	602	22.2	1.0
00–01_2	nd	N/A	501	22.4	1.0
00–02	nd	N/A	393	19.3	1.0
01–01	nd	N/A	868	31.2	1.0
01–02	nd	N/A	784	25.6	1.0
07–01.1_1	4.20	0.20	628	26.1	1.0
07–01.1_2	62.0	2.4	618	24.9	0.9
07–01.1_3	79.3	3.0	534	21.7	0.9
07–01.1_4	nd	N/A	587	25.0	1.0
07–01.2_1	43.5	2.1	448	21.2	0.9
07–01.2_2	72.5	2.8	542	21.9	0.9
07–02	2.71	0.12	589	23.1	1.0
09–01.1	nd	N/A	492	19.1	1.0
09–01.2	nd	N/A	404	18.1	1.0
17–01	96.9	2.9	471	14.8	0.8
17–02.1	< LLOQ	N/A	601	16.7	1.0
17–02.2	322	11.8	354	10.5	0.5
17–02.3	nd	N/A	650	19.4	1.0
17–02.4	< LLOQ	N/A	519	16.3	1.0
17–03	39.6	1.5	375	15.2	0.9
17–04.1	698	20.3	56.9	1.7	0.1
17–04.2	238	8.4	252	9.1	0.5
17–04.3	61.4	2.2	417	15.7	0.9
17–04.4	102	3.2	437	14.3	0.8
17–04.5	51.0	2.2	354	15.4	0.9
17–04.6	330	8.1	301	8.1	0.5

Table 3
Concentrations of R-(−)- and S-(+)-methamphetamine in % of Thai pill analyzed by GC-MS.

SAMPLE	R-Meth [%]	S-Meth [%]
(YY–N°_subset)		
00–01_1	N/A	22.2
00–01_2	N/A	22.4
00–02	N/A	19.3
01–01	N/A	31.2
01–02	N/A	25.6
07–01.1_1	0.7	25.6
07–01.1_2	2.5	24.8
07–01.1_3	3.7	21.0
07–01.1_4	0.1	24.9
07–01.2_1	2.1	21.2
07–01.2_2	2.6	22.1
07–02	0.3	22.9
09–01.1	N/A	19.1
09–01.2	N/A	18.1
17–01	3.1	14.7
17–02.1	0.2	16.6
17–02.2	10.6	11.8
17–02.3	N/A	19.4
17–02.4	0.2	17.1
17–03	1.5	16.1
17–04.1	20.9	1.1
17–04.2	8.3	9.2
17–04.3	2.0	15.8
17–04.4	2.3	15.3
17–04.5	1.9	15.7
17–04.6	8.6	7.6

methamphetamine need to be taken into account as well.

A similar picture emerges when looking at the results of toxicological studies. Two recent studies conducted in Germany show that only one case in 106 samples contained both enantiomers, suggesting that racemic methamphetamine was consumed. In all other samples only the S-(+)-enantiomer was detected, indicating the consumption of enantiopure methamphetamine (Maas et al., 2018; Hess et al., 2019). A similar result was obtained by a study conducted in China, where only 14 out of 86 forensic case samples showed presence of both enantiomers (Wang et al., 2015a).

4. Conclusion

Enantiomeric separation of methamphetamine in Thai pills from the years 2000, 2001, 2007, 2009 and 2017 seized in Switzerland revealed that the majority of the samples contain a much higher concentration of the more potent S-(+)-methamphetamine. Enantiomeric fractions ranged between 0.8 and 1.0 (85%), indicating a mainly enantiopure product containing the S-(+)-enantiomer, with a few exceptions of 0.5 (12%), implying a racemic mixture, and even one case of 0.1, pointing towards a product containing primarily the less potent R-(−)-methamphetamine. Furthermore, literature research about international wastewater and toxicological studies also show that methamphetamine is mainly consumed in an enantiopure form of the more potent S-(+)-methamphetamine. The risk of taking this substance has become much higher and therefore the single limit quantity of 12 g for a “serious” or “qualified” offence seems to be outdated and should be adapted to the potency of the respective enantiomers.

Limitations

The authors are aware that the sample size in this study is limited. However, this is related to the fact that only cases that had already been closed from a legal perspective could be analyzed. Furthermore, only cases with a minimum number of Thai pills could be included in the study. As a result, for example, there were no cases that met these criteria for the whole year of 2018 and until the completion of this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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