Review

Drug Testing and Analysis

Received: 12 September 2010 Revised: 18 November 2010 Accepted: 23 May 2011 Published online in Wiley Online Library: 6 September 2011

(www.drugtestinganalysis.com) DOI 10.1002/dta.323

The Drug Information and Monitoring System (DIMS) in the Netherlands: Implementation, results, and international comparison

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The Ministry of Health in the Netherlands has made illicit drug testing for drug users possible since the 1990s, in order to prevent serious health hazards associated with unexpected dangerous substances. This system of illicit drug testing is called the Drug Information and Monitoring System (DIMS). In nearly two decades, more than 100 000 drug samples have been handed in at DIMS testing facilities. This review describes the DIMS methodology and overviews results of the three main psychostimulant drug markets that have been monitored, i.e. ecstasy, amphetamine (speed), and cocaine. Additionally, monitoring results of hallucinogens are also described for the first time. For comparison, alternative international monitoring systems are described briefly alongside some of their results. Finally, drug monitoring is discussed from the perspectives of policy, prevention, and the drug users themselves.

Keywords: drug monitoring; cocaine; Ecstasy; MDMA; amphetamine

Introduction: Dutch drug policy

From a historical point of view, drug policy and legislation on drug use in the Netherlands is substantially different from that in many other countries. The aim of Dutch policy is to reduce both the demand for and the supply of drugs, and to limit the risks of drug use. One of the main features of Dutch policy on drugs is harm reduction, i.e. preventing drug use and limiting risks and harm to users and the people with whom they associate. This policy is based on the recognition of the fact that, in an open society, drugs are quite simply available, and therefore (problematic) drug use is also unavoidable.[1] In the Netherlands, it is an offence to produce, possess, sell, and import or export drugs, although it is not considered an offence to *use* them. Preventive strategies are aimed to reduce the demand for drugs, while professional care limits the harm they cause to users and the people they associate with. To cut off supplies, the authorities are cracking down on organized crime. Because in the Netherlands drugs are primarily regarded as a health issue, the Minister of Health is responsible for the overall coordination of policy on drugs. The central objective of the Dutch drug policy was formulated in the 1970s. As in many Western countries, the drug problem in the Netherlands underwent a fundamental change at the end of the 1980s, and the beginning of the 1990s. In the slipstream of the increasingly popular rave scene, the popularity of synthetic drugs such as Ecstasy grew rapidly. Ecstasy became popular due to its non-addictive properties and euphoric effect.

The Dutch drug policy in 1990s was characterized by great uncertainty about the substances being used, the user groups, and the risks.[2,3] Use of the new synthetic drugs involved effects and risks that were different from those associated with the traditional substances of abuse. Instead of addiction, the most important risks became acute and chronic damage to the user's health. However, the risks that these new substances posed to health varied considerably, depending on their contents, the settings in which they were taken, and individual factors. The characteristics of the new drug users were also very different from those of the traditional drug addicts.[4] Users of synthetic drugs were not marginalized, deviant young people who had adapted lifestyles revolving around drug use. The new psychotropic substances were consumed on an incidental, recreational basis by young people who did not differ from non-users in most respects. In fact, the only similarity with the previous decade was that the drugs being used were also psychoactive substances.

During the 1990s and at present, besides using new synthetic drugs, new generations of recreational drug users also started to embrace more traditionally abused drugs, like cocaine.[5] Because of its psychostimulant properties, not that different from amphetamines, it had an image of an associated successful and prosperous lifestyle. Because cocaine use poses its own unique array of health risks, especially when as casually used by recreational users as synthetic drugs, and is a traditionally adulterated substance with various pharmacological compounds, its widespread use has added an additional concern for the health authorities in the Netherlands.

The Ministry of Health developed information material aimed at discouraging young people from using Ecstasy and other drugs associated with the nightlife settings.[3] Specific measures were propagated to prevent or deal with problems caused by drug use at dance venues, raves, and clubs, such as good ventilation, the presence of first aid teams and availability of free drinking water.[6] The scale in which they were used and the specific risks that the range of new recreational drugs brought about, such as the lack of certainty about their dosage and composition, made the

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government decide to monitor this market adequately.[3,7] Illicit drug market monitoring was deemed necessary for surveillance, in order to detect acutely hazardous substances, dosages, or situations at an early stage of appearance on the drug market.

The Drug Information and Monitoring System (DIMS)

From the viewpoint of harm reduction and prevention, it was essential to gain knowledge about the appearance of new risky substances on the drug market and to take decisive preventive action. To enable the adequate monitoring of the rapid changes on the market for recreational drugs, testing services were set up where users could have the composition and dosage of their XTC tablets and other drugs tested. These testing services, provided within the framework of the national Drug Information and Monitoring System (DIMS), offer valuable insights into the dynamic recreational drug market, particularly for policymakers. Additionally, it enables prevention activities to be expanded towards a group of drug users that would normally not be reached. The testing facilities of the DIMS network are usually embedded in the prevention departments of institutions for the care of addicts. Traditionally, these departments have much experience in prevention activities on the very problematic level of drug addicts; recreational drug users were not seen by these institutions. Since the foundation of DIMS, users are frequently warned about the health risks associated with recreational substances. The authorities act immediately when dangerous drugs are in circulation. Depending on the severity of circumstances, the network of testing facilities is alerted, flyers are distributed at clubs and rave venues and/or warnings are published in the regional or national press.[7]

A nationwide network of test facilities at drug prevention institutions in different places in the Netherlands takes part in DIMS. Drug users hand in Ecstasy tablets or other preparations anonymously for a test. The personnel working at these testing facilities are health and prevention professionals; they communicate about the effects of the particular substances and their associated risks. A few of the participating institutions are merely receiving stations and directly send all the samples they receive to the DIMS Bureau at the Trimbos Institute and do not offer the opportunity for identifying any tablets at their own offices. However, most of the testing facilities are able to identify some of the tablets the moment they are handed in by the drug user. This is referred to as 'office testing'.

Office testing

First, the outward characteristics of tablets are registered, including diameter, thickness, weight, colour, presence of a groove, light or dark speckling (if present), and any logo visible (and its design). Second, a Marquis reagent test is performed to find out whether a tablet contains any Ecstasy-like substances, amphetamine, a hallucinogenic compound, or none of these. The next step is to determine whether information is already available about the specific tablet based on these external characteristics and results of the Marquis test. This is done with the help of an online electronic database which is updated weekly by the DIMS Bureau. The database contains features of all (Ecstasy) tablets that have recently been analyzed in a laboratory. Because of this weekly input of information on tablets and because of the fact that Ecstasy tablets are usually produced in large batches, certain tablets can be determined and recognized through this specially developed and weekly updated database on the DIMS website, the 'recognition list'. The average MDMA (3,4-methylenedioxymetamphetamine) content and the variation of the tablet are then known, and the tablet does not have to be analyzed necessarily in the laboratory. When the consumer decides to have the tablet analyzed in the laboratory anyway, its analysis results can be used for validation of the recognition list. This has shown a 99% reliability of the recognition list. Therefore, this 'office testing' recognition system provides the testing facilities throughout the country with a tool to give the drug consumer an immediate and accurate test result, without having to hand over the actual tablet. On average, 30% of tablets are determined this way.

Tablets that are not recognized by this online determination system and those about which doubt exists together with other drugs samples such as powders, capsules, and liquids are forwarded to the DIMS Bureau at the Trimbos Institute. When possible, additional information, such as the place of purchase, the price that was paid, and the consumer's knowledge and opinion of the product is added. Finally, at the testing facility, a unique individual number is given to the drug consumer by which he or she is able to communicate regarding the particular drug sample's test result one week later. At the DIMS Bureau itself, all samples received are registered, and details are carefully re-examined for possible re-assessment of the determination that was done by the testing facilities. Basically, all samples received by the DIMS Bureau are then coded, packaged, and transported to the laboratory for full chemical analysis (Figure 1).

Laboratory analyses

Qualitative and quantitative analyses of the drugs samples that have been sent to the DIMS Bureau were performed in the laboratory of the Delta Psychiatric Hospital (Deltalab, Poortugaal, the Netherlands), which specializes in analyzing drug samples. A set of robust analytical methods was used to identify known and unknown components, to quantify and classify them. After crushing and homogenizing the sample, three separate analytical techniques were used. First, thin layer chromatography (Toxilab®A) was performed for identification. Therefore, a small part of the sample (approximately 2 mg) was concentrated on a Toxidisc®, placed in the chromatogram and developed according to the Toxilab®A procedure. The analytes were identified by relating their position (RF) and colour to standards through four stages of detection: a colouring stage I (Marquis reagent), a washing stage II, an UV fluorescence stage III, and finally a colouring stage IV with Dragendorff's reagents. The Toxilab® methodology including three reference samples provides a robust identification.[8] An extensive library enables the chromatographer to check on correct location of spots as well as the identification of new substances.

Subsequently, the quantification of the main components (e.g. amphetamine, metamphetamine, 3,4-methylene-dioxyamphetamine (MDA), 3,4-methylene-dioxyethylamphetamine (MDEA), N-methyl-a-(1,3-benzodixol-5-yl)-2-butamine (MBDB), caffeine, cocaine and heroin) was performed with gas chromatography - nitrogen- phosphorous detection (GC-NPD). The samples were pretreated: after being crushed, 25 mg sample was ultrasonified in 0.01 M HCl. An internal standard was added

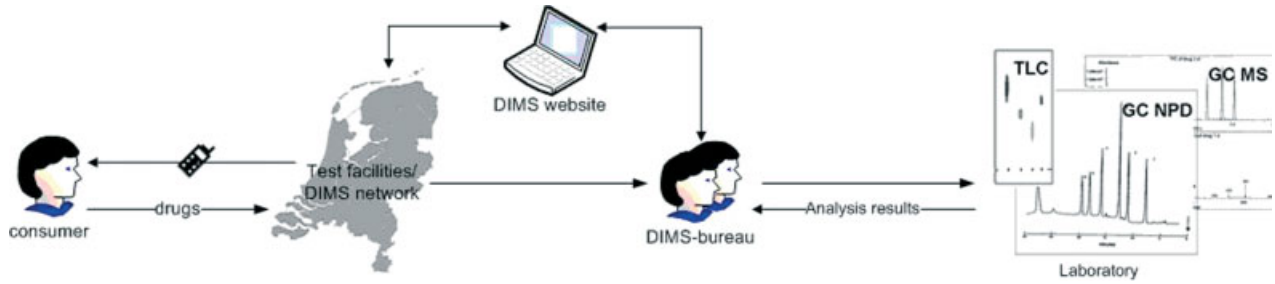

Figure 1. A schematic representation of the DIMS system.

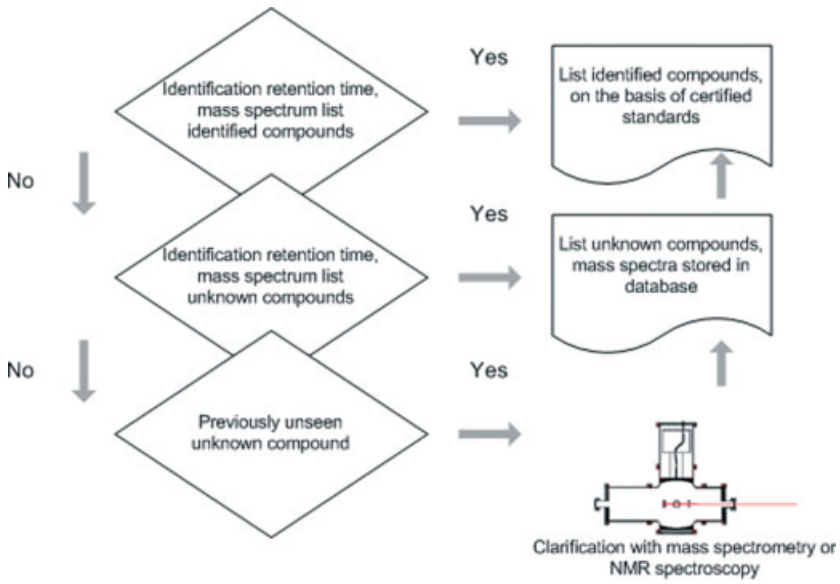

Figure 2. A flowchart representing the procedure of clarification of substances by the laboratory.

(Chirald, Sigma-Aldrich, Zwijndrecht, the Netherlands); thereafter a liquid-liquid extraction was performed with Toxitube® A, a diluted sample of the extract was used for the cold-on-column injection on the GC-column (WCOT-CP-Sil-8-CB, length 25 m, id 0.32 mm df 0.25 µm). The total runtime was 12–28 min on a programmed time–temperature scale (75–280 °C) with nitrogen-phosphor-detector and helium as carrier gas. The two methods were running independently and were used as a mutual confirmation. In case of any discrepancies, or trace amounts requiring quantification, a gas chromatography-mass spectrometry (GC-MS) method was introduced as the tiebreaker. This generally needed to be done in approximately 10% of the samples. GC-MS (Varian Saturn 4D, Varian Medical Systems, Houten, the Netherlands) conditions were similar to GC-NPD and substances were identified full scan (EI) with the NIST-library. GC-MS was also used for quantification of certain uncommon substances (e.g. γ-hydroxybutyrate (GHB), γ-butyrolactone (GBL), *para*-methoxyamphetamine (PMA), *para*-methoxymethamphetamine (PMMA), ephedrine, ketamine and lysergic acid diethylamide (LSD)). In exceptional cases, identification was performed using advanced GC-MS and nuclear magnetic resonance (NMR) spectroscopy structural analysis (e.g. 2,5-dimethoxy-4-bromophenethylamine (2C-B), 2,5-dimethoxy-4-bromoamphetamine (DOB) and 4-methylthioamphetamine (4-MTA)). Combining different routes for clarification and quantification leads to a growing list of identified compounds in illicit drugs found over the years (Figure 2).

Drugs users

An important difference between DIMS and other ways of collecting toxicochemical data on drug samples, such as drug seizures by the police, is the fact that data are collected directly on the user's level and there is contact with the user. With DIMS, this means there is an information exchange between the personnel at the testing facilities and the users. Most important information, such as personal adverse effects, or adverse effects experienced by friends, with the drug sample in question is recorded and saved in the DIMS database. Other important inputs in the database are regional origin, date, source of purchase, price, and reason for testing. Other relevant information may be added by the testing personnel, but anonymity of the drug user is always guaranteed, one of the main conditions of keeping the DIMS system trustworthy for drug users. The information supplied by the users is often crucial in determining which substance is associated with unexpected risks and in which part of the country these risks may possibly occur. From the perspective of the institutions for addiction and mental healthcare that provide the testing facilities, it is important to have one-on-one contact with young, recreational drug users to target their prevention and harm reduction activities.

There have been at least two studies that attempted to describe the users that utilize DIMS as a test facility for their drugs.[9,10] These suggested that users utilizing testing systems are broadly similar to non-testing users. We can therefore consider the target group of the DIMS system as a reasonable reflection of all recreational drug

users. The vast majority of drug users who visit the DIMS testing services are youths or men with an ethnic Dutch background who are engaged in paid employment or study. The group includes both experienced users who take Ecstasy every week and less experienced ones who just take it occasionally. As well as taking Ecstasy, they report considerable experience with alcohol, tobacco, and cannabis, and to a lesser extent also with cocaine and other drugs. Most of them have no experience with heroin or basecoke. The most common lifetime pattern of Ecstasy use involves increasing amounts taken up to a peak of use, followed by a decline to a somewhat lower level. The average dose is two tablets per occasion. If Ecstasy is taken in combination with another substance, it is usually alcohol, and, to a lesser extent, cannabis. Tablets are usually bought from a friend or a known dealer some time before a night out. When buying Ecstasy, knowing the dealer is considered far more important than obtaining tablets with a familiar logo or colour. Visitors to the test facilities were also asked about the main reason why they have their drugs tested. The majority answered health concerns, followed by curiosity about the results, and circulated warnings about dangerous drugs. With regard to the attitude towards prevention and harm reduction, the testing systems were seen as a very reliable source of information and users also appreciated this way of contact with prevention organizations.[9,10]

The DIMS results are not, by definition, an exact representation of the Ecstasy market in the Netherlands. The DIMS monitoring system depends on drug samples handed in by users, and will therefore not be an exact reflection of the use and availability of drugs on the market. However, DIMS is a qualitative monitor that does not focus on the precise number (quantity) of specific tablets or other drugs on the market, but on the contents (quality - chemically and toxicologically) of drug samples. However, a study comparing drug samples as delivered at DIMS with those obtained from police seizures at dance venues and rave parties, showed that the DIMS results in fact provide a fairly accurate picture of the total Dutch Ecstasy market at consumer level.[11]

Monitoring results

Since DIMS was set up in 1992, the Dutch illicit drug market has now been monitored for almost two decades. In particular, DIMS follows movements of Ecstasy, amphetamines, and cocaine and to a lesser extent, of synthetic hallucinogens on the market. Cannabis products, hallucinogenic mushrooms, and doping-related substances such as anabolic steroids are not systematically monitored. For cannabis-related products, DIMS has a different monitoring system.[12] Here we will discuss the DIMS results of the contents of Ecstasy, amphetamine, cocaine, and LSD drug samples over the past 18 years. More specific details for Ecstasy may be found in Spruit,[7] and Vogels *et al*.,[11] and for amphetamine and cocaine in Brunt *et al*.[13,14]

It is well-known that the Netherlands has been an important country for the illegal production of amphetamines and Ecstasy for many years,[15] and it seems reasonable to assume that most Ecstasy and amphetamines on the Dutch consumer market come directly from this illegal production. This contrasts with cocaine, which is exclusively obtained through illegal imports. Large changes in the composition of amphetamines and Ecstasy are therefore often a direct reflection of changes in production processes, such as shortages of precursors or other chemicals. In contrast, changes in the composition of cocaine could be explained by law-enforcement activities affecting export and import.

As for the overall results of the monitor, a combined total of more than 100 000 drug samples have been handed in at DIMS between 1992 and July 2010. The vast majority of these samples were tablets, falling into the categories 'recognized' or 'analyzed by the laboratory' (Figure 3). Figure 4 shows the proportion of tablets, powders, and other drugs (liquids, capsules, papertrips) that have been analyzed in the laboratory between 1993 and 2010. Powders make up the largest part of the rest of the drug samples; these comprise mainly MDMA, speed, or cocaine powders. Liquids, capsules, or miscellaneous forms of drug samples only make up a very small percentage of the total.

Ecstasy

There is a difference between what in pharmacological literature is defined as Ecstasy and what is called Ecstasy by drug users. Pharmacological and chemical scientific literature defines Ecstasy as 3,4-methylenedioxy-N-methylamphetamine (MDMA).[16] When epidemiological or socio-scientific research refers to Ecstasy, preparations are meant that are known to the interviewees by that name. By no means everything that is sold as Ecstasy is MDMA.[11,17] At the beginning of the 1990s, MDMA, MDEA, and MDA were the substances most frequently found in tablets bought as Ecstasy (Figure 5). MDMA, MDEA, and MDA, often referred to as Ecstasy-like substances, are substituted methylenedioxyphenethylamines, a chemical class of derivatives of the phenetylamine group, to which group also amphetamine belongs. MBDB or 'Eden' is another substance that belongs to the group of methylenedioxyphenethylamines (Figure 6).

The use of MDMA in the Netherlands was first reported in 1985.[18] MDMA induces the so-called entactogenic effect.[19] MDMA and MDEA hardly exert any hallucinogenic effects and MDA causes nothing more than light illusory perceptions and distorted images. MDA has a stronger stimulating effect than MDEA and MDMA, but a weaker entactogenic effect.

The most common form of MDMA incorporated in Ecstasy tablets is the hydrochloride salt. It is a white powder that is easily soluble in water. Ecstasy products on the market are seen typically as tablets with a characteristic logo, less commonly as powders, capsules, liquids, or crystals. A typical Ecstasy tablet contains between 80 and 100 mg of MDMA. From the literature, it may be concluded that people take anything from half a tablet to several tablets per evening or weekend.[20,21] If these figures are used as a reference mark, the recreational doses taken by users amount to 0.5–4 mg/kg, distributed over many hours and sometimes several days. In some cases, peak use can be as high as 10 mg/kg. What people take and how much they take depends, however, on factors such as the effects they want to achieve, their degree of experience, and the actual, often unknown, composition of the tablets.

Figure 5 summarizes the composition of tablets sold as Ecstasy as analyzed by DIMS in the laboratory throughout 1993–2010. The picture shows that there have been two periods during which many tablets contained other substances in addition to or instead of MDMA. In and around 1997, many Ecstasy tablets contained amphetamines and in and around 2009 many tablets contained *meta*-chlorophenylpiperazine (*m*CPP) instead of or in addition to MDMA. At the peak of the shortage of MDMA, in October 1997, only 30% of the Ecstasy tablets handed in at DIMS contained MDMA or a MDMA-like substance. The peak of shortage of MDMA in 2009 was in March, with only 40% of all Ecstasy tablets containing

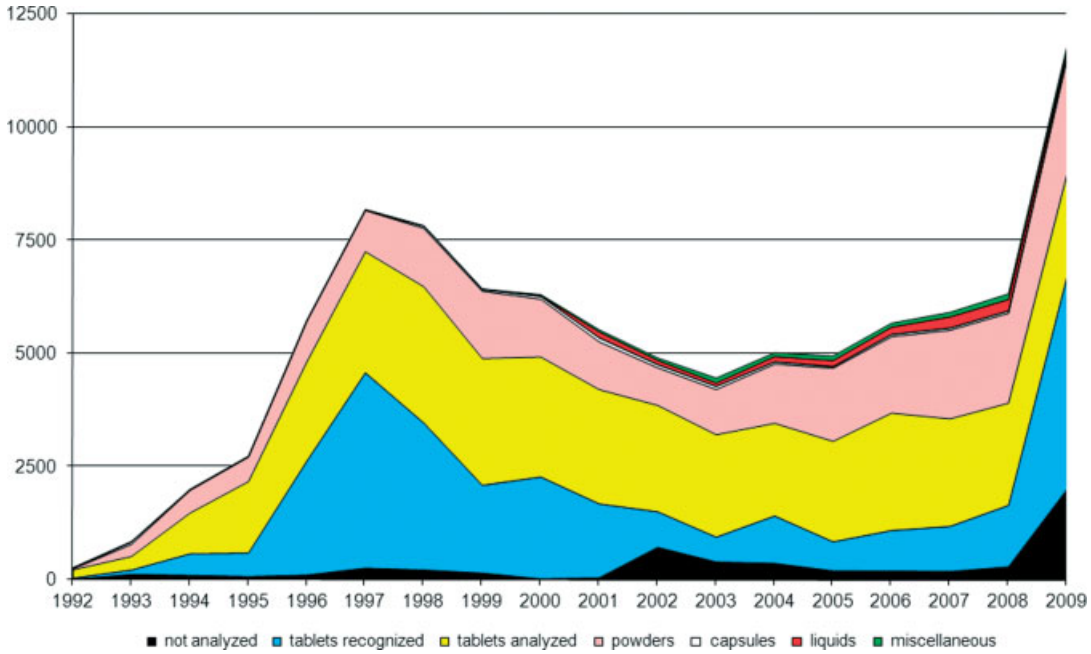

Figure 3. Number of drug samples per year delivered at DIMS between 1992 and 2010. Data reflect pharmaceutical appearance.

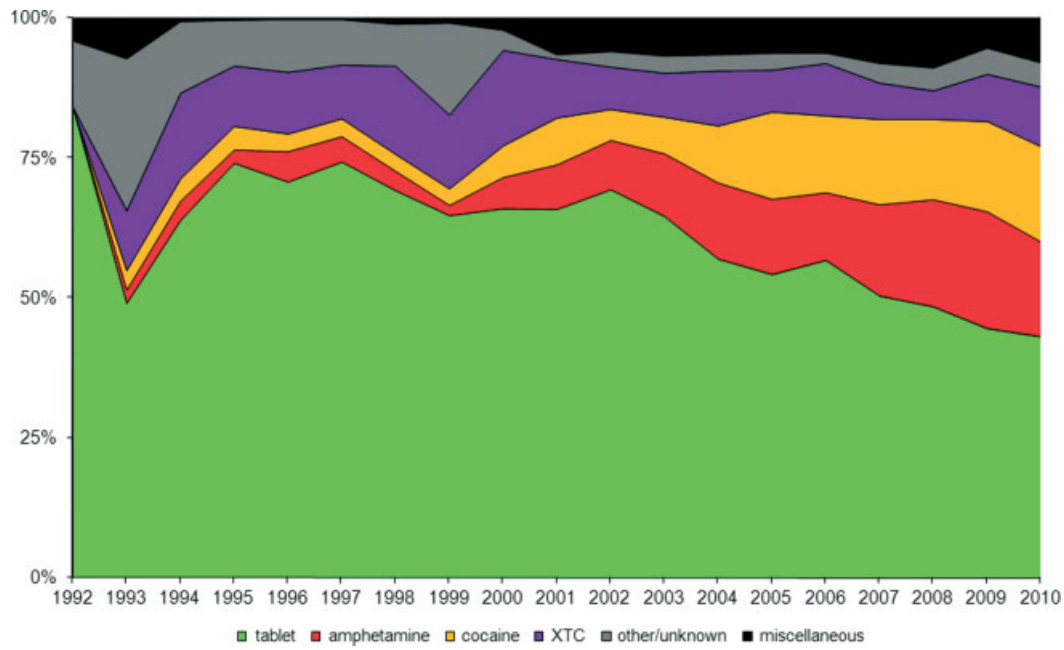

Figure 4. Relative contribution of tablets, amphetamine, cocaine, XTC powders and other drugs delivered at DIMS between 1992 and 2010 that have been analyzed in the laboratory.

MDMA. Between 1996 and 2001, less than 50% of the Ecstasy tablets contained more than 70 mg MDMA; the same applies for 2009, when only 42% of the tablets sold as Ecstasy contained more than 70 mg MDMA per tablet. Before 1997 and between 2000 and 2009, more than 50% of the Ecstasy tablets contained more than 70 mg MDMA per tablet.

MDEA and MDA, which were present in about 30% of the Ecstasy tablets before 1997, have virtually disappeared from the Ecstasy market; MDEA and MDA were never present in substantial amounts, since 1997. Sporadically, nowadays, only small amounts of MDEA and MDA are found, often in combination with MDMA, in tablets. Apart from the marked decline in the number of tablets containing MDMA-like substances, the periods around 1997 and 2009 are characterized by the appearance of other psychoactive substances in tablets sold as Ecstasy, e.g. MBDB, 2C-B, atropine, 4-MTA, PMA around 1997, and mCPP and mephedrone around 2009 (Figure 5). The appearance of PMA was accompanied with a national warning campaign in the Netherlands, since this is a much more hazardous substance as any MDMA-like substance, with a steep dose-response curve.[22] In the late 1990s, PMA appeared in Ecstasy tablets all over the world and caused numerous emergencies and even deaths.[23–27]

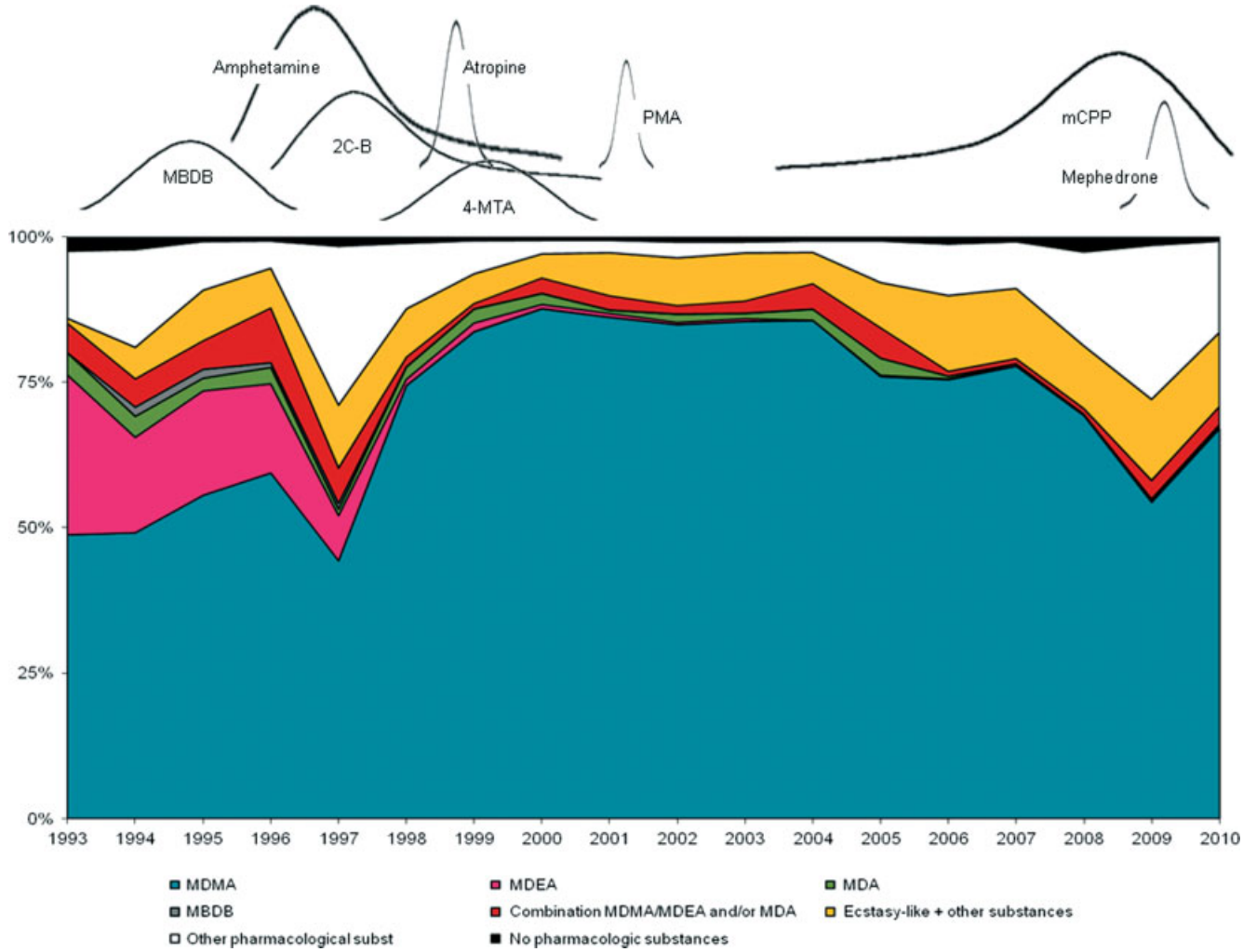

Figure 5. Composition of tablets sold and bought as Ecstasy handed in at DIMS per year, a number of novel substances found are given at the top of the figure, in order of appearance through time.

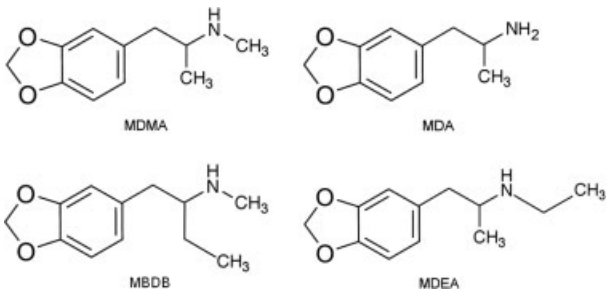

Figure 6. Chemical structures of the methylenedioxyphenethylamines MDMA, MDA, MBDB and MDEA.

Speed

In the 1930s, amphetamine was marketed as a nasal inhaler to shrink mucous membranes under the trade name Benzedrine™. Early users of the Benzedrine inhaler discovered that it had a euphoric stimulant effect, which resulted in it becoming one of the earliest synthetic stimulants widely used for non-medical (recreational) purposes.[28]

Speed and pep are the street names for amphetamine, like XTC and Ecstasy are street names for MDMA. In the Netherlands, amphetamine has been a controlled substance since 1976.[29] The proportion of the people in the Netherlands that have recently used amphetamine, as well as the lifetime prevalence of the general population of twelve years and older, is quite low and relatively stable, in 2005 0.3% and 2.1%, respectively.[30] In the mid-1990s, there was a temporary increase of amphetamine abuse. In that period, speed became especially popular among certain subgroups of partygoers. They often distinguished themselves from others by music preference (hardcore trance) and dress.[31,32] Because amphetamine (speed) is much cheaper than cocaine (coke), it was previously also known as 'coke for the poor'. Methamphetamine is closely related to amphetamine. In Thailand, tablets containing methamphetamine are sold as Yaba.[33] Yaba is much stronger and is much longer acting than amphetamine. In the Netherlands, recreational use of amphetamine is much more common than abuse of methamphetamine; in fact, methamphetamine use is very uncommon.

Unlike MDMA, amphetamine has no entactogenic properties. The recreational user of amphetamine seeks the mental and physical stimulation which it produces. The desired effects usually last up to four hours and as the effects begin to wear off may be

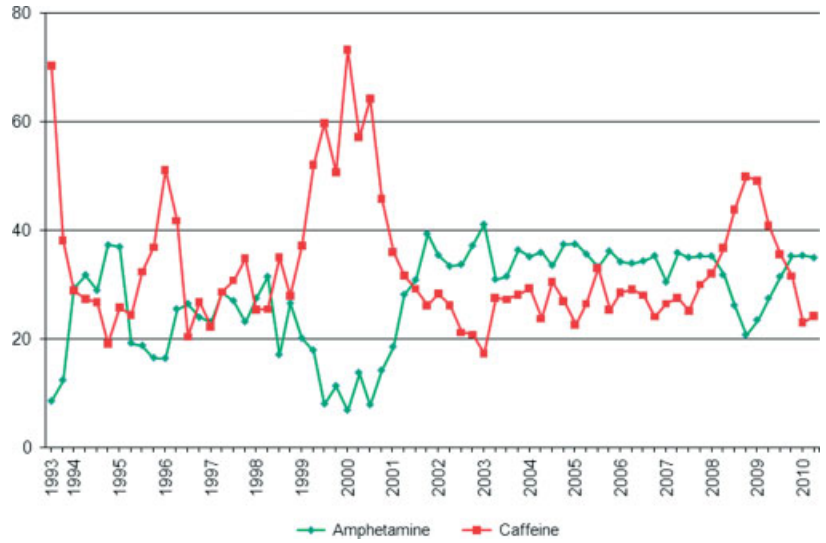

Figure 7. Mean percentage of amphetamine and caffeine in speed powders per year (quartiles indicated by scaling lines on axis). Only powders containing quantifiable amounts of amphetamine (>1%) have been included.

succeeded by a period of restlessness, anxiety, fatigue, disinterest, or tiredness.[28] Some users seek the stimulating properties of amphetamine for other purposes. Those in monotonous occupations may abuse amphetamine in the workplace and students may use the drug to decrease tiredness, enabling studying for long periods of time.[28]

Amphetamine is a member of the phenethylamine family. As an illicit drug, amphetamine is mostly found as a sulfate salt, which is a white powder, easily soluble in water. Although amphetamine appears in tablets with logos similar to Ecstasy, on the street amphetamine is mostly sold in powder form and like cocaine, it is often snorted.[30] When snorted or ingested, a dose may vary from several tens to several hundreds of milligrams depending on the purity and the individual tolerance for the drug.

Between 1992 and July 2010, 8239 powder samples bought as speed were handed in at DIMS. In about 85% of these samples, the amount of amphetamine was high enough for quantification. Between 1997 and 2001, the percentage of samples that did not contain quantifiable amounts of amphetamine was over 20%, reaching a peak of over 40% in 1999. Until 1996, the number of speed samples delivered to DIMS was hardly high enough to describe the speed market. Since 1996, the number of samples increased to over 10 samples per month from 1996 until 1999, and since 2000, on average more than 20 samples per month were handed in. In 2008 and 2009, more than 60 samples per month were received at DIMS.

The analyzed speed powders that were handed in between 1995 and 2010, with detectable amounts of amphetamine, contained on average 30% pure amphetamine (30.2 $\pm$ 0.2%; mean $\pm$ SEM). Between July 1998 and April 2001, the mean amount of amphetamine decreased to less than 20%. In January 2000 the mean amount of amphetamine decreased to less than 5% (Figure 7). This phenomenon reoccurred in 2008/2009, with an absolute low in December 2008, with a mean percentage of amphetamine of 18%. Simultaneously with the decrease in amphetamine concentration, the amount of caffeine in speed powders increased (Figure 7). The purity of speed, expressed as the mean percentage of amphetamine, seems to follow an inverse relationship with the percentage of caffeine over time, with the mean percentage of amphetamine in a powder being high, the percentage of caffeine being low and *vice versa*. The amount of samples handed in did not drop in both instances of amphetamine shortage, and neither did the percentage of samples not containing quantifiable amounts of amphetamine.

The most common route of synthesis for amphetamine is by the Leuckart method.[28] This method uses benzylmethylketone (BMK, 1-phenyl-propanone) as a precursor. Around 1999, and in 2008 and 2009, there were shortages of this amphetamine precursor on the illegal drug production circuit. Therefore, it became extremely difficult to produce amphetamine. The available speed powders hardly contained amphetamine and were cut much more with caffeine. Caffeine is often added to amphetamine at the production source, whereas other cutting agents, such as glucose and other sugars, are usually added elsewhere.[15] Unlike MDMA, a shortage of amphetamine on the illegal drug market does not seem to cause the appearance of 'new' psychoactive compounds in speed powders. However, the transient shortage of amphetamine in 2008/2009 caused the appearance (and disappearance) of two psychoactive substances: 4-fluoroamphetamine and 4-methylamphetamine (not to be confused with methamphetamine), substances that had not been seen in speed powders before (Figure 8).

Cocaine

Cocaine is a natural product extracted from the leaves of *Erythroxylon coca*. Cocaine has a psychomotor stimulant effect similar to that of amphetamine. Cocaine base and the hydrochloride salt are white powders.[34] In recreational use, cocaine is typically snorted whereby it is absorbed through the nasal mucosa.

Since 1993, DIMS received cocaine powders; in the early 1990s, on average between 5 and 10 samples per month, but in subsequent years numbers quickly increased. Since 2004, more than 50 samples per month were handed in. Of the powders that were sold as cocaine, an average of 10% did not contain quantifiable amounts of cocaine. The remaining powders contained 56 $\pm$ 0.3% (mean $\pm$ SEM) pure cocaine. From 1993 to 1999, the average purity was higher than in the past decade

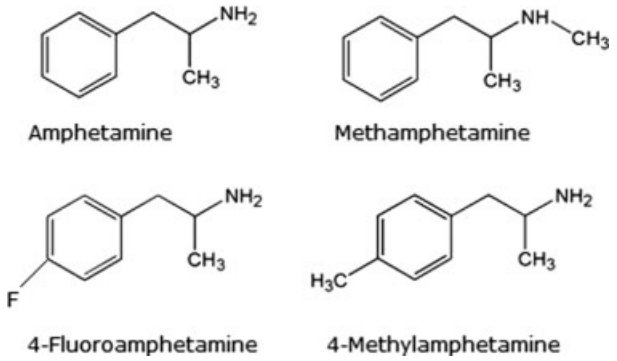

Figure 8. Chemical structures of amphetamine, methamphetamine, 4-fluoroamphetamine and 4-methylamphetamine.

(2000–2010), 66.3 ± 0.7% (mean ± SEM) versus 54.9 ± 0.8% (mean ± SEM), respectively.

Often adulterants are added to increase weight, and sometimes other, mainly less costly substances are added to make up for lost potency.[35] Alternatively, adulterants are added to camouflage the decrease in potency of the cut-up cocaine, usually other local anesthetics, which produce the same numbness to the gums as cocaine, thereby creating the false impression to the consumer of high purity. The cocaine powders that were handed in at DIMS were cut with a variety of substances: inert compounds (mannitol, maltose, inositol, flour, starch), synthetic local anesthetics (lidocaine, benzocaine, procaine, tetracaine) and other pharmacologically active substances (caffeine, phenacetine, levamisole, hydroxyzine, diltiazem).[13]

Approximately 10% of all cocaine samples contained a synthetic local anesthetic. The average amount of pure cocaine in these samples (44.6 ± 0.9%; mean ± SEM) was significantly lower than in the samples not containing synthetic local anesthetics (57.0 ± 0.3%; mean ± SEM). Similarly, cocaine cut with other pharmacologically active substances also contained less pure cocaine (38.8 ± 0.4%; mean ± SEM) than cocaine powders that did not contain these substances (62.1 ± 0.3%; mean ± SEM) (Figure 9). Apparently, all of these adulterants were added for compensatory purposes as already mentioned. Table 1 summarizes the major pharmacologically active substances found in DIMS cocaine powders during the last five years (2005–2009). Atropine was found in 2005, and again in 2007. The presence of atropine in cocaine was accompanied by several hospitalizations and even fatalities in both occasions, in the Netherlands and across the border (Italy, France, Germany, Belgium).[36,37] In situations such as these, it is a vital part of the surveillance function of DIMS to immediately orchestrate a national mass media warning to warn the (potential) users and furthermore, to alert the international network of early warning systems throughout the EU.

Table 1. Psychoactive compounds most commonly found in DIMS cocaine powders (2005–2009)

	Present in % of samples	Mean ± S.E.M.
Phenacetin	38	25.5 ± 1.3 (n=956)
Levamisole	21	7.4 ± 0.3 (n=338)(1)
Caffeine	15	9.0 ± 2.6 (n=502)
Lidocaine	8	n.q.
Procaine	7	n.q.
Diltiazem	6	n.q.
Hydroxyzine	3	n.q.
Benzocaine	0.4	n.q.
Diphenhydramine	0.1	n.q.
Tetracaine	0	n.q.
Atropine	0	2.0 ± 3.0 (n=5)

N.q., not quantified; n, number of samples quantified; (1) Data from 2010.

LSD and other hallucinogens

Of all hallucinogens, lysergic acid diethylamide (LSD or 'acid') is the most prevalent handed in at DIMS. LSD samples are usually papertrips, taken from greater formats of colourfully decorated paper. The LSD is impregnated into the paper at a certain concentration, which does not have to be equally spread among individual papertrips taken from one original sheet of paper. The other form in which LSD is handed in at DIMS is as microdot. This is a minute tablet, usually weighing less than 10 mg, without logo or much other specific characteristics. Most microdots are coloured uniformly black.

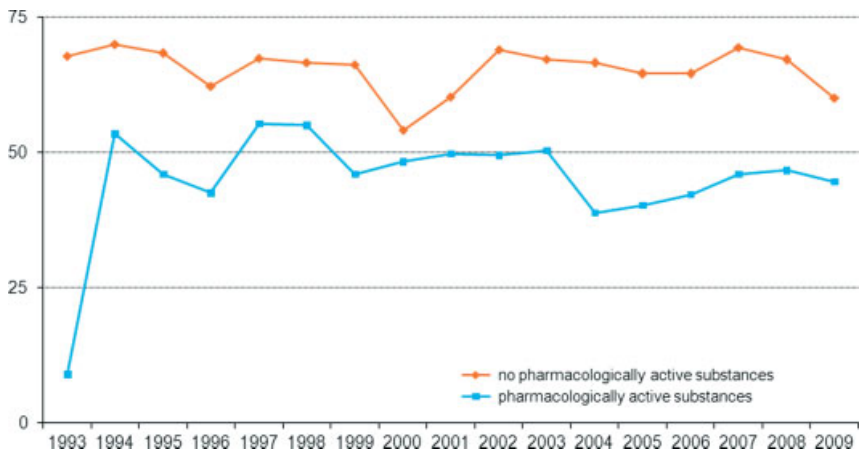

Figure 9. Mean percentage of cocaine (purity) in cocaine powders containing pharmacologically active adulterants and not containing pharmacologically active adulterants. Only powders containing quantifiable amounts of cocaine have been included.

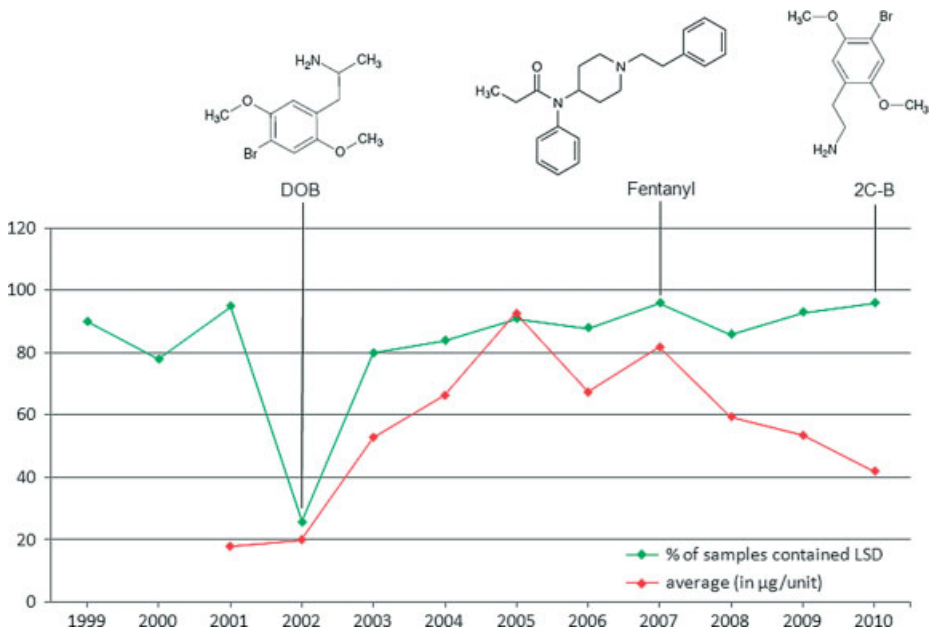

Figure 10. Percentage of samples containing LSD of all samples that were sold as LSD and the average concentration of LSD per unit (papertrip or microdot), three substances found in samples sold as LSD are given at the top of the figure, in order of appearance trough time.

In the Netherlands, LSD is used by small subpopulations of users and in other settings as the mainstream clubs or events where Ecstasy or cocaine are used. One subpopulation is often referred to as the 'psychonauts'; the experimental drug users that are interested in exploring new psychological avenues in the brain as well as going out and listening to dance music.[38] This dance music is often another style (e.g. psytrance, a psychedelic type of dance music) than the more mainstream dance music played at big clubs or events.[5] Because LSD is used in the busy and noisy setting of a dance party, the dosages used nowadays tend to be considerably lower (20–125 µg) than the dosages that were reported in the 1960s and 1970s (300–2000 µg[39]). This reduces the risk of a negative mental experience or 'bad trip', while undergoing LSD's specific effects.

At DIMS, first numbers of LSD samples were seen around 1999. In that year, only six samples were handed in that were sold as LSD. This increased to 10 samples in 2000 and 12 in 2001. From 2002 and onwards the number of LSD samples at DIMS became more and more substantial, with a peak of 99 samples in 2003 and 66 samples for the first six months of 2010. Based on these numbers, something can be said about the LSD market, at least on an annual basis. Around 80% of the samples that were sold as LSD contained the hallucinogenic substance (Figure 10). An exception was 2002, when only 26% of all LSD samples contained the hallucinogen; in the rest of the samples the concentration was either not quantifiable or traces of other compounds were found, such as methamphetamine or DOB. In 2007, some papertrips were handed in containing fentanyl, a very potent synthetic opioid, which led to a special warning campaign, directed at the small target group of LSD users. The average concentration of LSD ranged from 20 µg to 96 µg/unit (unit meaning either papertrip or a microdot) (Figure 10). However, the variation in LSD concentration was substantial: from 1–500 µg/unit. This widespread concentration between units probably represents two extremes of the market: the low dosages, probably being used at nightlife settings, such as dance parties and raves, whereas the higher dosages might come from the more experienced users who take LSD in a more secluded, private setting.[40]

There were only a few other hallucinogens handed in at DIMS with 2C-B being the most prevalent one after LSD. Initially 2C-B was sold as small tablets, with concentrations between 1–15 mg 2C-B per tablet. During the second half of the 2000s, 2C-B was frequently found in tablets sold as Ecstasy and these tablets highly resembled Ecstasy tablets, with similar logos, shapes, and colours. Recently, 2C-B was also encountered in LSD papertrips (Figure 10). Concentrations 2C-B rarely exceeded 5 mg per sample (tablet or papertrip). Other hallucinogens that have been found by DIMS were on sporadic basis and comprised 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2 and 2C-T-7), N,N-dimethyltryptamine (DMT), 5-methoxy-diisopropyltryptamine (5-MeO-DiPT) and dextromethorfan (DXM), among others.

Other drug markets and monitors

Illicit drug testing in order to gain insight into certain drug markets for health or even law enforcement purposes is nothing new. Usually, information concerning the contents of illicit street drugs comes from the various national forensic institutes that are situated in most countries. These forensic institutes often receive parties of drugs that have been seized by the police, either at customs, clandestine production facilities, or from consumers at local events. This is no different from the situation in the Netherlands, were the National Forensic Institute provides important information about the drug market in addition to the DIMS system. The presence of two independent systems offering quantitative and qualitative information about the state of the illicit drug market creates an ideal situation to compare and validate results. It also adds to a more complete picture of the illicit drug market and allows for the specification of which batches of drugs were distributed domestically and which were probably meant for export. Regardless of the advantages, most countries do not have

an additional direct costumer-derived information source of the illicit drug market, besides the seized samples.

However, besides the Netherlands, there are other nations assembling illicit drug market data from additional sources than the forensic institutes, like the French National Identification System for Drugs and Other Substances (SINTES), a combination of police and customs seizures and samples obtained directly from the consumers by social field workers.[41] TICTAC, in the United Kingdom, utilizes amnesty bins from large clubs and venues in some major British cities to describe the chemo-analytical contents of the drugs in these bins.[42,43] There is the 'on-the-spot' dancefloor high performance liquid chromatography (HPLC) analysis by the Check-It team from Vienna, Austria, and in Switzerland there is the Safer Party© initiative, collecting samples from the users directly through fieldwork contacts.[44,45] Their analysis procedure is based on an automated HPLC for the separation process.[45] These HPLC systems are equipped with DAD/UV-Vis Spectrometers (DAD=Diode Array Detector) and autosamplers and analysis results can be obtained within 20 min, making it useful for testing on the dancefloor.

In the United States, there is the DanceSafe initiative; it tests drugs and makes the test results public to the potential consumer audience.[46,47] It more or less seems to work according to the way the DIMS recognition list works, with the exception that the drug consumer has to do the colouring test him-/herself and combine the result of this test with the tablet characteristics given on the website. Finally, the National Drug and Alcohol Research Centre in Australia provides a very elaborate system of monitoring illicit drug markets, and besides using the laboratory analysis information provided by the Australian Crime Commission, it uses a wide network of drug users for information on 'perceived drug purity' for instance, collectively referred to as the Illicit Drug Reporting System (IDRS) and the Ecstasy and Related Drugs Reporting System (EDRS).[48,49] Whereas these initiatives have all contributed to the knowledge of the composition of the illicit drug markets throughout the world, by far, most international chemo-analytical data were reported by the different national forensic institutes.[50–54]

Because of the large differences in types of drug sample monitoring methodologies between the various countries around the world, it is virtually impossible to make a one-on-one comparison between countries on market variables, such as purity, price, or content. Large organizations, such as the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the United Nations Office on Drugs and Crime (UNODC), provide some insight into the variety of the different global illicit drug markets,[55,56] but the quantity of samples and extent of national coverage still differs considerably between countries. Nonetheless, Figure 11 aims to provide some insight into international comparison between the three main illicit drug markets previously discussed in this review, i.e. Ecstasy, cocaine, and amphetamine. Important to bear in mind is that not all countries provided information on every substance; for instance, amphetamine is barely monitored outside of Western Europe, but methamphetamine is. Also, the analytical methods of the different international laboratories might differ considerably, which of course impacts on the results as well. Therefore, the results are more indicative of global trends than they are exact comparisons.

Comparing the different monitoring results to those of DIMS in recent years, it is evident that every country shows its own unique drug market composition and dynamic (Figure 11). Roughly, and not surprisingly, the different Western European Ecstasy markets show more resemblance to each other as to Eastern Europe or Western Australia, for instance. The different Western European 'speed' markets also show a resemblance, but the amphetamine purity in all of them is considerably lower than it is in the Netherlands. In contrast to the Ecstasy markets, the different cocaine markets show a less clear pattern of resemblance between Western European countries. The markets in the USA and Western Australia are in fact very comparable with many European markets (Figure 11). This makes sense, since the source of cocaine (Latin America) is the same in all considered countries.

Additionally, new psychoactive additives are also reported by many countries, providing an alternative source of comparison between drug markets (Table 2). To keep matters simple, only the cocaine and Ecstasy markets are compared, since these two markets are most known for emerging new substances/adulterations anyway. The United States are compared to two major Western European countries, France and Germany, to provide some degree of cross-Atlantic comparison. As is shown, the Ecstasy markets show a lot of similarities between these countries divided by the Atlantic. However, the United States seems to have its own specific compounds appearing in Ecstasy tablets, such as dextromethorphan (DXM) or phentermine for instance. On the other hand, phenethylamines like MBDB or 3,4-methylenedioxy–N-(2-hydroxyethyl)amphetamine (MDHOET) were not seen in the US Ecstasy market. As for cocaine adulterants, there is once again a more uniform spread among all three countries, confirming cocaine as the import product it is to all these countries.[55] Interestingly, from a global diversion point of view, however, are the different time-points that the adulterants arose in the different countries. As with the purity data, it is important to bear in mind that the drug testing systems between these countries probably differ in a number of aspects.

Discussion

Illicit drug market monitoring is recognized as a surveillance tool for the benefit of public health,[63,64] somewhat analogous to agencies concerned with inspecting product quality of foods or medicine, that are well-spread throughout all countries in the world. Similar to warnings about food poisonings, drug monitors try to keep track of acutely hazardous substances found in illicit drugs and issue warnings to take a rapid course of action. The monitoring results of DIMS have provided valuable qualitative information on changes in the content of drug samples in the Netherlands throughout the years. The DIMS results were used for national and international risk assessments and major warning and prevention activities. In this capacity, it functions almost directly at the level of the potential drug consumers and this ensures quick delivery of the prevention message. Secondly, it attempts to accurately follow drug market processes in time. This is in contrast to the forensic institutes which do not generally aim at public health related matters, nor strive to monitor processes through time.

During nearly two decades of monitoring street drugs, DIMS has shown that the different psychostimulant markets are very dynamic and new psychoactive substances and additives are emerging frequently. Interestingly, the rise of new substances often co-occurs with the shortage of a specific illicit drug of abuse. This applied to amphetamine, 4-MTA and PMA, found in Ecstasy tablets, during the 1990s or mephedrone and mCPP during the last couple of years. Mephedrone, actually, is rather a special case as recent literature has made clear.[65–69] It was

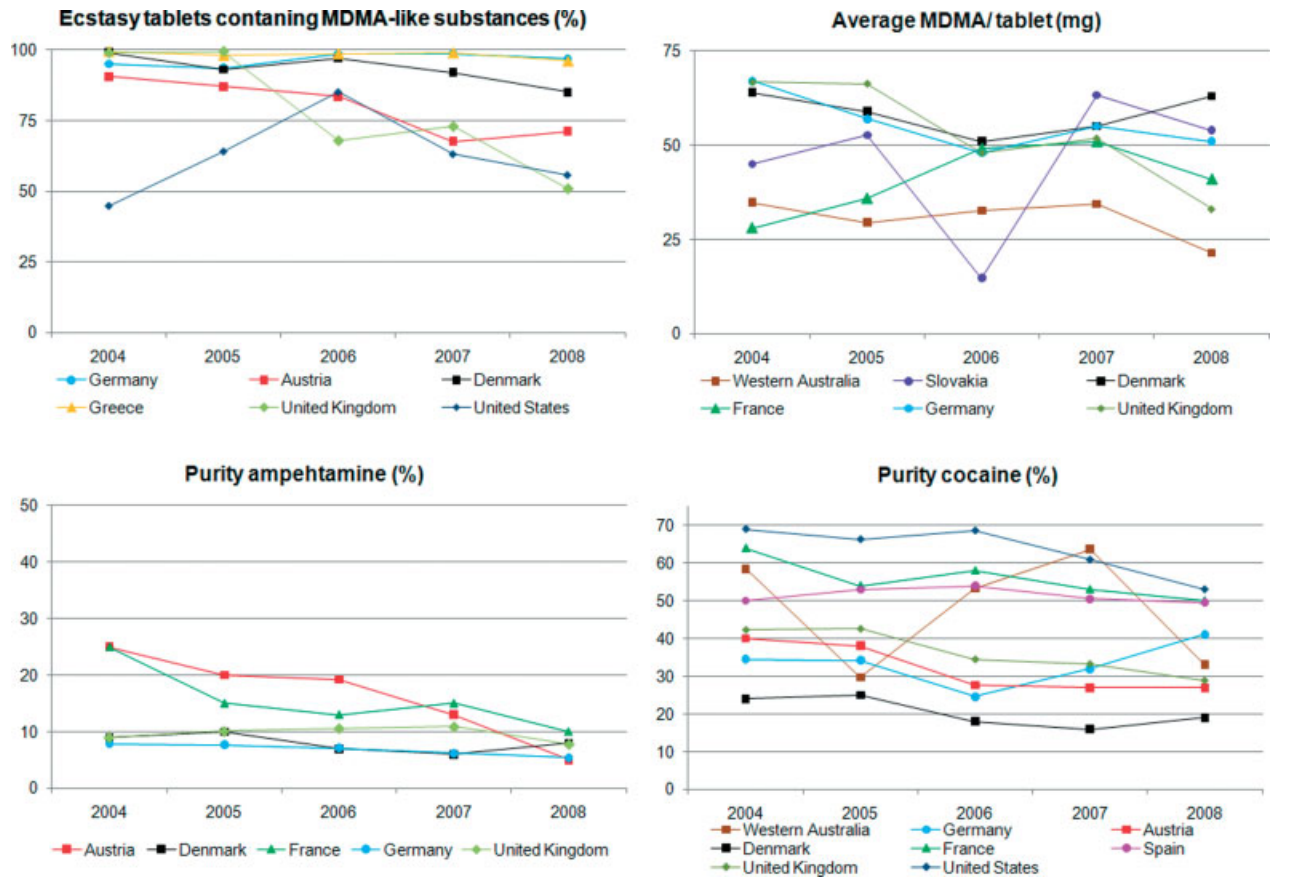

Figure 11. Percentage of analyzed tablets containing MDMA-like substances in six countries between 2004 and 2008.[47,57] Average content of MDMA in mg/tablet in five countries between 2004 and 2008.[58,59] Average amphetamine purity in five countries between 2004 and 2008.[58] Average cocaine purity in eight countries between 2004 and 2008.[58–60] *In Western Australia average MDMA content was expressed as percentage/tablet.

sold through various websites, as plant fertilizer, especially in the UK.[70] Although in the Netherlands it was found as a replacement for MDMA in Ecstasy tablets, mephedrone seems to be a part of a far more greater whole: 'legal highs', referring to drugs sold through the Internet that mostly do not have a legally controlled status. This phenomenon seems to be persistent, because, after the ban of mephedrone in a number of countries, a new generation of post-mephedrone products was already signalled.[67] These products can be produced in laboratories anywhere around the world and their sale via the Internet will make legislation more complex, thereby changing the face of drug trade radically. Besides these new psychoactive substances, also novel adulterants, such as levamisole, could provide new challenges for healthcare and policymaking.[71–74]

In the UK, massive use of mephedrone among youth caused such a stir that it was banned earlier in 2010.[75] It is banned in many other EU member states at the moment and a risk assessment procedure has already been conducted by the EMCDDA,[76] which may possibly lead to a ban in the remainder of the EU member states. Following the continuing rise of new psychoactive substances on the drug markets, described in this review, such collective European efforts to ban substances seem to have increased in frequency over time. Other substances that underwent the same fate and were banned include benzylpiperazine (BZP), 4-MTA, PMA, and MBDB, among others.[56,77] But it is the monitoring systems that are at the core of these Pan-European policy initiatives.

Whereas the special drug policy of the Netherlands makes a system like DIMS possible, other countries have made great efforts of their own to create intelligible insights into their drug markets. Some of these efforts resulted in similar systems like DIMS, whereas others derive drug market information in a different way.[41–43,46,48,78–80] As suggested in this review, analytical testing procedures for drug samples probably differ between many countries, reflecting on the results. Several factors could be of importance: ways of extraction, measuring to the base or salt form, purity definitions, quantification method used, etc. Nevertheless, on various drugs of abuse, very similar results over time were reported by different countries.[55,56] This provides interesting avenues of investigation, such as import, export, routes of dispersion, or sources of adulteration, for example.

Recently, perhaps one of the most striking new chemo-analytical methods of measuring drug market information that has been reported by several research groups is the detection of drugs of abuse, their metabolites, and their adulterants in public wastewater by HPLC-tandem mass spectrometry.[81–86] In this way, drug markets can be monitored without the involvement of anyone participating in the illicit drug circuit; for example, users or producers. But this method rather measures consumption itself and is better developed for large, non-specified, bulk analyses from certain areas. User-specific or sample-specific data are impossible to gain by this method. This method might be useful in assessing the scale of temporal and spatial illicit drug use in the future.

Table 2. New psychoactive substances detected on the Ecstasy and cocaine markets in 2004–2009 in Germany, United States and France

	2004	2005	2006	2007	2008	2009
Germany						
Ecstasy market	2C-I, MBDB	Ephedrine, MBDB	BZP	mCPP	mCPP, BZP	Mephedrone, PMA
Cocaine market	Lidocaine, phenacetin, caffeine, procaine	Phenacetin, lidocaine, caffeine, diltiazem, procaine, levamisole, hydoxyzine, bezocaine	Phenacetin, lidocaine, diltiazem, caffeine, procaine, hydoxyzine, levamisole, benzocaine, amphetamine	Phenacetin, lidocaine, diltiazem, caffeine, procaine, hydoxyzine, levamisole	phenacetin, lidocaine, levamisole	–
United States						
Ecstasy market	Ephedrine, DXM, BZP, TFMPP, creatine	Ephedrine, DXM, fentanyl, mCPP, 5-MeO-MiPT	Ephedrine, DXM, ketamine, mCPP, phentermine, MDDMA, procaine	mCPP, modafinil, ketamine, nicotinamide, procaine, BZP	mCPP, BZP, ketamine, phentermine, 2C-I, 5-MeO-DMT, TFMPP, procaine	mCPP, 2C-B, BZP, ketamine, DXM, FPP, mephedrone, 5-MeO-DMT, TFMPP, diphenhydramine, procaine
Cocaine market	Diltiazem, hydroxyzine, methylephedrine	Procaine, caffeine,	Diltiazem, procaine, caffeine	Diltiazem, procaine, caffeine, hydroxyzine, benzocaine, creatine	Diltiazem, procaine, caffeine, levamisole, nicotinamide	Caffeine, levamisole, lidocaine
France						
Ecstasy market	MBDB, 5-Meo-Dipt	mCPP, MDHOET	4-MTA, ketamine, mCPP, TFMPP, BZP	BZP, ketamine, TFMPP, 2C-B, mCPP	mCPP, BZP	4-fluoroamphetamine, mephedrone
Cocaine market	Phenacetin, lidocaine, procaine, atropine*	Phenacetin, lidocaine, procaine, atropine*	Phenacetin, lidocaine, procaine, caffeine	Levamisole, phenacetin, diltiazem, caffeine, hydroxyzine, lidocaine, procaine	Levamisole, phenacetin, diltiazem, caffeine, hydroxyzine, lidocaine, procaine	–

MBDB, N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine; TFMPP, 1-(3-trifluoromethylphenyl)-piperazine; BZP, benzylpiperazine; MDDMA, 3,4-methylenedioxydimethylamphetamine; DXM, dextrometorphan; MDHOET, 3,4-methylenedioxy–N-(2-hydroxyethyl)amphetamine; 4-MTA, 4-methylthioamphetamine; 2C-I, 2,5-dimethoxy-4-iodophenethylamine.
* Detected in drugs obtained from intoxicated hospitalized patients Sources USA.[47,61] Sources France & Germany.[57,62]

Finally, there is the question of the benefit of a monitoring system for the drug users themselves. Despite the fact that many recreational drug users are relatively well-informed about the risks, they are often willing to accept them nonetheless.[87–89] So how could a system like DIMS possibly aid in prevention or harm reduction? There are at least two arguments to be made in favour of a drug analysis and testing system in this context. First, it has been suggested that individual, directed, harm-reduction advice serves the needs of existing users better than simply promoting abstention.[87] In this sense, the one-on-one contacts the users have with the personnel at the DIMS testing offices, combined with factual information concerning their drug purchase and other drugs circulating the streets largely meets the information needs of drug users. Additionally, young drug users often dismiss government messages as tendentious and untrustworthy and are better persuaded by personal contact with well-informed peers or professionals.[87,88,90–92] It has to be noted, however, that the reach of a drug testing system such as DIMS is limited to a fraction of all (potential) drug users.

Conclusion

Monitoring the market of illicit drugs creates a platform on which to base policymaking and public health preventive activities, as well as for research purposes. This review of DIMS and other drug testing systems has made clear that the market for psychoactive substances of abuse is continuously moving, underlining the necessity to continue the systematic monitoring of this market. Future challenges for DIMS could lie in developing ways to monitor the Internet market and doping drug market, as these seem to be developing rapidly and good insights into these markets are lacking.

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