Expert report provided to support the expert panel in scoring the policy options

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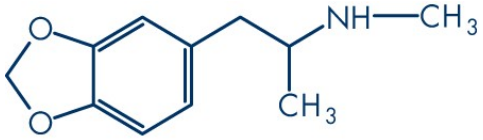
1 Introduction

Notes in advance

1. In this report ‘Ecstasy’ is used as the container word for all tablets, powders and pills containing the psychoactive compound MDMA. Except in some specified cases MDMA is regarded as a synonym of ecstasy.
2. In literature ‘pills’ is a widely used term. Pills should be considered here as identical to tablets, capsules or other pharmaceutical forms.
3. A considerable part of ecstasy users are polydrug users (using multiple substances within a specific time period).



Synonyms	MDMA, 3,4-MDMA; 3,4-methylenedioxymethamphetamine, *N*,α-dimethyl-3,4-methylenedioxyphenethylamine, (+/–)-*N*,α-dimethyl-3,4-(methylene-dioxy)phenethylamine, methylenedioxy-methylamfetamine, ecstasy (E, X, XTC); Midomafetamine Molly (short for 'molecule'; slang term for crystalline or powder MDMA); Mandy, Adam, Clarity, Essence, Hug Drug, Love Drug, beans’, ‘Es’, ‘bickies’ ‘bangers’. The UK term "mandy" and the US term "molly" colloquially refer to MDMA in a crystalline powder form.
Drug class	Empathogen-entactogen, stimulant
Chemical class	Ring-substituted phenethylamine
IUPAC name	(RS)-1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine
CAS Number	42542-10-9; 64057-70-1 (as the HCl-salt)
Formula	$C_{11}H_{15}NO_2$
Molar mass	193.25 g·mol^{-1}
Chirality	Racemic mixture
Appearance	White or off-white powder or as crystals soluble in water. Commonly sold as tablets with a characteristic logo, less commonly as white powder or capsules.
Price	In 2016, the mean retail price of ecstasy tablets reported ranged between € 4 (the Netherlands) and € 17 (Italy)
Solubility	MDMA base is a colourless oil insoluble in water. MDMA-HCl well soluble in water
Boiling point	105 °C at 0.4 mmHg (experimental)
Routes of administration	Common: by mouth; uncommon: snorting, inhalation (vaporization), injection, rectal (EMCDDA, 2015)
Metabolism	Liver, CYP450 extensively involved, including CYP2D6
Metabolites	MDA (main metabolite), HMMA, HMA, DHA, MDP2P, MDOH
Onset of action	30-45 minutes (by mouth) and effects last 3-6 hours
Excretion	Kidney
Elimination half-life	(R)-MDMA: 5.8 ± 2.2 hours; (S)-MDMA: 3.6 ± 0.9 hours

Ecstasy (MDMA, 3,4-Methylenedioxymethamphetamine) is primarily used as a recreational drug for its specific sensory, psychedelic and stimulatory effects. Ecstasy is especially popular at clubs, festivals, house parties and within the rave culture (electronic dance-music scene). In addition, its inhibition-reducing effects which facilitate sociability, empathy and ‘to get together’ (ecstasy is therefore called a ‘love drug’) are highly appreciated by young adults, particularly young males. Ecstasy is used less frequently than other stimulants, typically several times a year. Nowadays, ecstasy is no longer a niche or subcultural drug, but is used ‘recreational’ by a broad range of mainly young people in nightlife settings, including bars, (electronic) dance events and house parties.

2 History

MDMA was first synthesized and patented in 1912 by Merck in an attempt to develop a drug which could stop abnormal bleeding. The precursor at that time was safrole a natural product found in sassafras oil (safrole oil) in the nutmeg.

Since 1970, MDMA is used recreationally in the US (Benzenhofer & Passie, 2010; Sreenivasan, 1972) as a substitute for its analogue methylenedioxyamphetamine (MDA), a popular drug at that time, but banned in 1970 (Pentney, 2001). In 1965, Shulgin synthesized MDMA from piperonal and tried it himself in 1976 (Benzenhofer & Passie, 2010). MDMA was described as inducing "an easily controlled altered state of consciousness with emotional and sensual overtones" comparable "to marijuana, to psilocybin devoid of the hallucinatory component, or to low levels of MDA" (Shulgin & Nichols, 1978). In particular, Shulgin was impressed with the drug's disinhibiting effects which could have a potential for therapeutic purposes. Indeed, in the late 1970s, MDMA was used by psychiatrists, because patients were emotionally less inhibited and more willing to communicate and participate in psychotherapy. According to David Nutt, MDMA was widely used in couples counselling in the US, and was called "empathy". Later it was renamed as "ecstasy" to promote the sales of MDMA.

A small recreational ecstasy-market emerged by the late 1970s. Starting in 1983 (Beck & Rosenbaum, 1994), MDMA was mass-produced in a Texas lab (Eisner, 1994) and imported from California and marketed at bars and discos as a "fun drug" and "good to dance to" (Beck & Rosenbaum, 1994). By the mid-1980s, ecstasy use had spread to colleges around the US (Beck & Rosenbaum, 1994).

As part of the “War on Drugs,” the Drug Enforcement Administration (DEA) successfully petitioned on 27 July 1984 to have MDA classified as a Schedule 1 illicit drug (DEA, 1984; Eisner, 1994), but was surprised when a well-organized group of psychiatrists and health care professionals quickly protested against the proposed scheduling (Pentney, 2001). On 31 May 1985, the DEA announced an emergency Schedule I classification of MDMA. The increased distribution in Texas, escalating street use, and new evidence of brain damage by MDA were mentioned as reasons to declare MDMA as "an imminent hazard to public safety" which formed the legal basis of an emergency measure to classify MDMA as a schedule I drug for a period of one year while the final scheduling process is under way (Beck & Rosenbaum, 1994; NYT, 1985). The ban of MDMA took effect on 1 July 1985. Arguments that MDMA retained an accepted medical usage so that it should be classified as a Schedule III drug were overruled by the DEA, because the therapeutic efficacy of MDMA was not published in medical journals and no double blind studies had yet been performed (Pentney, 2001).

The DEA also lobbied for international scheduling and in 1985 the WHO's Expert Committee on Drug Dependence recommended that MDMA be classified as a Schedule I drug at the 1971 United Nations Convention on Psychotropic Substances. The arguments used were: pharmacological similarity to previously scheduled drugs (e.g. MDA)[1] reports of illicit trafficking in Canada, drug seizures in the US, and lack of well-defined therapeutic use. The Commission on Narcotic Drugs added MDMA to Schedule I at the convention on 11 February 1986 (UNODC, 1986). In The Netherlands, XTC was placed on list 1 (hard drugs) of the Opium Act on November 1988, because the government was afraid of large-scale trade and production. In the late 1980s, the drug spread alongside rave culture to the UK and European cities (Beck & Rosenbaum, 1994), whereas in the US illicit MDMA emerged among young adults in universities and high schools and became, along with cocaine, heroin, and cannabis, one of the four most widely used illicit drugs in the US. For current prevalence rates: paragraph 13.1.

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[1] Surprisingly, MDMA and MDA have quite a different pharmacological profile. The simple N-methylation of MDA reduces the duration of action two-fold (from 8-12 hrs. to 4-6 hrs.) and the overall effects are less powerful Nichols, D. E. (1986). Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. Journal of Psychoactive Drugs, 18, 305-313.. Secondly, and most importantly, MDMA is not a psychedelic drug and - though illusions such as colour or objects distortion are common - psychotic symptoms such as hallucinations and delusions are rarely described ibid.. Finally, there is no cross-tolerance between MDA and MDMA Shulgin, A. & Shulgin A. PIHKAL: A chemical love story. Transform Press, Berkeley, USA.: 1990. . These findings would indicate a distinct mechanism of action for MDMA that is unrelated to MDA, the hallucinogens, or the amphetamines.

3 Methods

A systematic search of Embase MEDLINE and Google Scholar was conducted from the earliest possible date to April 2019. Key words used were MDMA OR ecstasy OR 3,4-methylenedioxymethamphetamine OR N-Methyl-3,4-methylenedioxyamphetamine[MeSH Terms] OR ecstasy drug OR molly. For the risk assessment, only studies to fatal and non-fatal incidents with sufficient sample size (N>5,000) and known prevalence of ecstasy use were included. In addition, once a study had been rated as eligible from a full text review, its references were manually screened for other relevant studies. Exclusion criteria: case reports, case series, emergency department reports and (other) papers not reporting exposure data, like last year use prevalence.

4 Pharmacology

Numerous reviews are available about the pharmacology and the psychological effects of MDMA in humans, e.g. (Dunlap et al., 2018; Gudelsky & Yamamoto, 2008; Michael White, 2014; Mohamed et al., 2011; Morgan, 2000; Schulz, 2011).
MDMA interacts with transporter proteins that regulate the release and re-uptake of neurotransmitters in the central nervous system. MDMA acts as a substrate releaser with high affinity for the serotonin (5-HT) transporter (SERT; responsible for the reuptake of extracellular 5-HT) and somewhat lower affinity for the noradrenaline (NA) and the dopamine (DA) transporters. As such, MDMA is a potent releaser of 5-HT, NA and, to a lesser extent DA (Liechti et al., 2000; Nichols et al., 1982; Rothman & Baumann, 2002; Schmidt & Kehne, 1990; Yamamoto & Spanos, 1988) (cf. Table 1). In other words: MDMA is more a 5-HT drug than a DA-drug which may explain its relatively low dependence potential compared with other drugs. Note that, in contrast to MDMA, amphetamine predominantly acts on the dopaminergic system.

Table 1. Binding affinity for (±) MDMA and stereo-isomers. K_i in nM ± SEM (Murnane et al., 2012).

Receptor	^{3}H-ligand	Ligand Activity	(±)-MDMA	*R*-(−)-MDMA	*S*-(+)-MDMA
5-HT_1	^{3}H-5-HT	Agonist	6,850 ± 1,300	4,200 ± 500	>10,000
5-HT_2	^{3}H-Ketanserin	Antagonist	8,300 ± 1,100	3,310 ± 140	>10,000
DA_2	^{3}H-NMSP	Antagonist	>10,000	>10,000	>10,000

MDMA's induces empathogenic feelings via 5-HT release in the brain, and is in this respect much more potent and effective than cocaine and amphetamine. The 'energising' effects, which become more prominent at higher doses, are probably related to brain NA and DA release and are shared by other psychostimulants. MDMA binds to a variety of receptors, releases NA and DA via the respective transporters (NAT and DAT) and induces reuptake of extracellular 5-HT (cf. Tables 1-4).

Table 2. Effects of MDMA on monoamine release using synaptosomes prepared from rat brains. Values for half maximal effective concentration (EC_{50}) in nM are reported ± st. dev. (Rothman et al., 2001). NA = noradrenaline; DA = dopamine; 5-HT = serotonin.

Compound	NA release	DA release	5-HT release
S-(+)-Amphetamine	7.07 ± 0.95	24.8 ± 3.5	1,765 ± 94
(±)-MDMA	77.4 ± 3.4	376 ± 16	56.6 ± 2.1

Table 3. Effects of MDMA on receptor mediated behavioural effects. Values for half maximal inhibitory concentration (IC_{50}) in µM (Simmler et al., 2018).

	Class	NAT	DAT	SERT	DAT/SERT
MDMA	Empathogen	0.45	17	1.4	0.08
Amphetamine	Stimulant	0.09	1.3	52	40
PMA	Empathogen	0.8	71	2.4	0.03
Cocaine	Stimulant	0.45	0.8	2.4	3.1
Mephedrone	Empathogen-stimulant	0.25	3.3	4.6	1.4

NAT: noradrenaline (NA) transporter; DAT: dopamine transporter; SERT: serotonin transporter.

Table 4. Effects of MDMA on monoamine reuptake using synaptosomes prepared from rat brains. Values for the inhibition constant (K_i) in nM are reported ± standard deviations (Rothman et al., 2001).

Compound	NA uptake	DA uptake	5-HT uptake
S-(+)-Amphetamine	38.9 ± 1.8	34 ± 6	3,830 ± 170
(±)-MDMA	462 ± 18	1,572 ± 59	238 ± 13

MDMA has also been found to increase the blood oxytocin level which would be responsible for the subjective prosocial feelings induced by MDMA. However, the elevation of oxytocin by MDMA did not correlate with the induced prosocial feelings, putting some doubt on the relevance of this hormone for the prosocial effects of MDMA (Kuypers et al., 2017; Parrott, 2016).

5 Pharmacokinetics

The primary routes for metabolism of MDMA are N-demethylation and loss of the methylene bridge connecting the catechol, both of which are mediated by various cytochrome P450s. The common metabolites of MDMA include: MDA, 3,4-dihydroxymethamphetamine (HHMA), 3,4-dihydroxyamphetamine (HHA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), and 4-hydroxy-3-methoxy-amphetamine (HMA). The major metabolite of MDMA in humans is HMMA, which is mainly excreted as the glucuronic acid conjugate (Dunlap et al., 2018).

Table 5. Pharmacokinetic data of MDMA.

Item	Values
Metabolism	Via the liver, CYP_{450} is extensively involved, including CYP2D6
Metabolites	MDA (main metabolite), HMMA, HMA, DHA, MDP2P, MDOH
Onset of action	30-45 minutes (oral consumption) and effects last 3-6 hours
Excretion	Via the kidney
Elimination half-life	(R)-MDMA: 5.8 ± 2.2 hours; (S)-MDMA: 3.6 ± 0.9 hours
Absorption	Following a dose of 75 mg, the maximum plasma concentration of around 0.13 mg/L is reached within two hours
Urine	Following ingestion, most of the dose of MDMA is excreted in the urine unchanged

Following the administration of 100 mg (±)-MDMA in humans, the half-life is approximately 8–9 h, plasma C_{max} is 222.5 μg/L and t_{max} is 2.3 h (de la Torre et al., 2000b). However, MDMA exhibits non-linear pharmacokinetics, implicating that increasing doses of MDMA prolong its half-life, potentially exacerbating the risk for adverse effects and neurotoxicity (de la Torre et al., 2000a). Other pharmacokinetic and some pharmacodynamics parameters are depicted in Table 5.

6 Applications of MDMA

6.1 Medical use

MDMA is not currently used as a pharmaceutical drug, but research efforts are deployed to investigate its therapeutic potential. However and unfortunately, the legal, financial, and political hurdles that accompany Schedule I classified drugs have significantly hindered scientific research into the therapeutic effects of MDMA (Nutt et al., 2013).

After MDMA was criminalized in 1985, most medical use stopped, although some therapists continued to prescribe the drug despite its illegal status. In 2017 the FDA granted MDMA-assisted therapy for PTSD a 'breakthrough therapy designation' (Chodosh, 2017). As of 2018, MDMA has no approved medical uses, but limited exceptions are sometimes made for research to promising treatments and for MDMA to become a prescription drug. For instance, MDMA-assisted psychotherapy has shown great promise for treating posttraumatic stress disorder (PTSD) (Mithoefer et al., 2016; Mithoefer et al., 2011; Mithoefer et al., 2013; Oehen et al., 2013; Ot'alora et al., 2018)(Bedi, 2018; Sessa, 2017; Yazar-Klosinski, 2017). In the United States, a phase III clinical trial to explore whether MDMA-assisted therapy is beneficial in treating severe treatment-resistant PTSD has started in 2018 (Feduccia, 2018a) following the successful completion of an international phase II study. Data submitted to the FDA showed significant and durable rates of remission of PTSD (Feduccia, 2018b). These studies have shown the importance of careful optimization of therapeutic set and setting, resulting in a minimal amount of adverse events as well as maximized benefits, while administering a drug no more than two or three times. Controlled human studies with MDMA show improved self-knowledge, sleep regulation, increased ability to accurately assess others' mental states, better emotion regulation, and cognitive insights (Kamilar-Britt & Bedi, 2015). Phase II trials in seven European countries are expected to start in 2019, the Netherlands likely being the first site, and phase III trials are expected in the following years. A recently completed clinical trial has shown promise of MDMA-assisted treatment for social anxiety in autistic adults (Danforth et al., 2018). Other studies investigating the potential of MDMA-assisted therapy include: cognitive-behavioural conjoint therapy in couples in which one member has PTSD; MDMA-assisted psychotherapy for anxiety in subjects diagnosed with a life-threatening illness; and MDMA-assisted treatment for individuals with alcohol use disorder (Sessa, 2018). Importantly, all clinical research is investigating MDMA's potential as an adjunct or facilitator of psychotherapy, as opposed to a stand-alone pharmaceutical drug. In addition to the aforementioned indications, Yasar-Klosinski & Mithoefer (2017) pointed out that, given the specific effects of MDMA-assisted psychotherapy on attachment and positive affect, this modality may also be useful in treating disorders that involve attachment insecurities, such as depression, obsessive-compulsive disorder, suicidality, and eating disorders (Yazar-Klosinski & Mithoefer, 2017).

6.2 Recreational use

In the late 1980s, 'ecstasy' was associated with the rave culture, but during the 1990s ecstasy became more widely available in many dance clubs and other venues (for prevalence figures see paragraph 13.1). The appreciated effects of ecstasy are: euphoria, a pleasant energetic, enhancement of sociability, extrovert and happy feeling, increased alertness and empathy, the feeling of being closer to the other, changed perceptions of colours and sounds, and at higher dose only mild hallucinations. Only 20% of recreational users have reported experiencing visual hallucinations (Peroutka et al., 1988). Ecstasy dampens the response to negative emotional stimuli, although it impairs the recognition of different emotions (anger, sadness, fear) (Bershad et al., 2016). Within the party scene and else, ecstasy is usually available as a pill (tablet) or in the form of a white powder.

7 Controlled studies (safety pharmacology)

See IMPD file about controlled clinical studies of ecstasy dated July 10, 2018 (MAPS, 2018).

8 Acute toxicity

8.1 Overview of adverse effects

The absolute toxicity of MDMA is low, considering its high lethal dose in rodents (LD_{50} = 49 mg/kg, i.e. 3.5 gram pure MDMA (20-40 pills) is lethal for a human with a body weight of 70 kg) (Davis et al., 1987). As such, it is less toxic than its close congener, MDA.

Acute, but relatively innocent side effects of MDMA are lack of appetite, hot flashes, coldness and sensitivity to cold, dry mouth, thirst, and loss of concentration. Clinically more relevant adverse effects of MDMA use, some of them being typical for sympathomimetic/noradrenergic drugs, include nausea, headache, vomiting, tachycardia, hypertension, increased perspiration, sweating, restlessness, mydriasis, bruxism (grinding and clenching of the teeth leading to tooth wear), insomnia, erectile dysfunction, jaw-clenching, confusion, anxiety and tremor (Carvalho et al., 2012; Greene et al., 2008; Keane, 2014; Meyer, 2013). MDMA can also provoke panic attacks, delirium and short-term psychosis, which quickly disappear. The transient effects sometimes reported from 2 to 5 days after ecstasy use (so called “Tuesday dip”), include lowering of mood, heavy legs, fatigue, depressed feelings, lack of energy, anxiety, impulsiveness, impaired memory, loss of appetite, insomnia, tiredness or lethargy and jaw-clenching (Meyer, 2013; NIH, 2018).

Ecstasy pills containing MDMA alone (at widely varying doses) were reported to have been associated with adverse effects 8% of the time and desired effects 74% of the time. Adverse effects reported from tablets containing MDMA included nausea (most common), headache, hallucinations, dizziness, ‘allergic reactions’ and, more rarely, palpitations, hyperthermic seizures, agitation and abdominal cramps (Brunt et al., 2012).

Severe acute toxic effects of MDMA include hyperthermia, rhabdomyolysis which can lead to multiple organ failure (renal, hepatic), muscle rigidity, metabolic acidosis, cerebral oedema, delirium, coma, heart attacks, epileptic cramps, disseminated intravascular coagulation, and death (NIH, 2018).

The most frequently seen acute serious toxic effects of MDMA are hyperthermia (> 40 °C) and dehydration (Greene et al., 2008; Keane, 2014). For hyperthermia see paragraph 8.2. The consumption of excessive amounts of water without replenishing electrolytes by MDMA users in an effort to stay hydrated is dangerous and has led to cases of life-threatening or fatal hyponatremia-related MDMA related deaths (MRDs) (excessively low sodium concentration in the blood; known as ‘water intoxication’) which can cause cerebral oedema (Greene et al., 2008; Keane, 2014). Evidence suggests women may be particularly prone to hyponatremia (van Dijken et al., 2013).

MDMA induces NA-mediated cardio-stimulation. In addition to increased systolic blood pressure, MDMA can induce cardiac arrhythmias, myocarditis and myocardial infarction, though the cardiovascular risk is considerably lower than with cocaine or amphetamine use (Qasim et al., 2001).

After controlling for co-use of alcohol, the sub-acute adverse effects of MDMA in regular recreational users are relatively modest and transient (Huxster et al., 2006), indicating that previous reports of marked subacute effects of MDMA use may have been confounded by chronic polydrug use before use (Gouzoulis-Mayfrank & Daumann, 2006).

8.2 Hyperthermia

In addition to fatalities, hospital presentations of severe and life-threatening hyperthermia in ecstasy users has been frequently reported and documented (Campbell & Rosner, 2008; Chadwick et al., 1991; Ghatol & Kazory, 2012; Gore, 1999; Hall & Henry, 2006; Maxwell et al., 1993; Patel et al., 2005). Grunau et al. have systematically compiled 53 reports described since 1950, including case reports, describing 71 cases (25 were fatal) of MDMA-related hyperpyrexia (Grunau et al., 2010). In the case reports examined, MDMA-related hyperpyrexia was associated with a wide variety of symptoms, including rhabdomyolysis, hyperkalaemia, shock, acidosis, hyponatremia, hypoglycaemia, acute kidney injury, hepatotoxicity, cerebral oedema, cardiac and cerebral ischemia, cardiac arrhythmias, persistent neurologic deficits and death (Grunau et al., 2010).

Since serotonin is a critical neuromodulator involved in the thermoregulation, with 5-HT_{2A} receptors being a key mechanism responsible for hyperthermia (Herin et al., 2005), the derangements of thermoregulation by MDMA is probably mediated via central serotonergic receptors.

The MDMA-induced elevations in body temperature in humans involve enhanced metabolic heat generation and cutaneous vasoconstriction, resulting in impaired heat dissipation. The hyperthermic

effects of MDMA vary across species, are dose-dependent (Parrott, 2012), and are strongly facilitated at higher ambient temperatures. For instance, rodent studies have shown relatively weak brain hyperthermic effects of MDMA under standard conditions (quiet rest, 22-23 °C), but dramatic MDMA-induced brain hyperthermia in warm environments (29 °C) (Brown & Kiyatkin, 2004; Kiyatkin et al., 2014). Importantly, peripheral vasoconstriction appeared to be a critical mechanism underlying MDMA-induced brain hyperthermia as it prevented proper heat dissipation to the external environment (Kiyatkin et al., 2014). This may also be expected in MDMA users, because MDMA constricts blood vessels via sympathetic stimulation, thereby reducing peripheral blood flow and heat dissipation by convection via the skin (Mills et al., 2004). In humans, MDMA produces under controlled laboratory settings dose-dependently in healthy subjects only mild elevations in core body temperature (range: 0.2-0.8 °C), and no hyperpyrexia (>40 °C) (Liechti, 2014). Note, that in a small laboratory study of 10 healthy subjects, the effect of MDMA (2 mg/kg, p.o.) on body temperature did not depend on the ambient temperature (18 °C or 30 °C) (Freedman et al., 2005).
Hyperthermia and dehydration related to MDMA use is occasionally seen, in particular at dance events, where the indoor environment is relatively warm and poorly ventilated, implying an increased risk of adverse effects under such unfavourable circumstances. In addition, (1) sustained dancing and physical exertion may lead to excessive heat-induced perspiration, electrolyte loss and dehydration, (2) MDMA induced peripheral vasoconstriction prevents heat dissipation (Mills et al., 2004), and (3) concurrent use of multiple stimulant drugs increases the risk of over-heating and sympathetic overdrive (Dar & McBrien, 1996; Schmidt et al., 1991). To prevent dehydration, users of MDMA should be discouraged from drinking alcohol, coffee or soft drinks due to their high sugar content and/or diuretic properties. Information campaigns should also advice to drink (plain) water slowly (not in excess), and to supplement with minerals, including salty snacks, or isotonic sports drinks to prevent hyponatraemia (see below). As such, factors like excessive MDMA consumption, drug interactions or an interaction with environmental factors (e.g. high ambient temperatures and vigorous exercise) may underlie the severe hyperthermic effects of MDMA observed in clinical cases (Parrott et al., 2006).
As a result of a central action of MDMA, tremor of muscles increases which leads to uncontrolled muscle cramps. Dantrolene is given to inhibit such cramping by reducing the heat generation in skeletal muscle (Grunau et al., 2010). During this cramping a lot of energy is generated which leads to hyperthermia (>40^0C) and the patients dies of epileptic insults. In part of hyperthermia cases the liver, and occasionally also the kidney, is severely damaged (Andreu et al., 1998). Various mechanisms may contribute to MDMA-induced liver toxicity, including the increased efflux of neurotransmitters, the metabolism of MDMA, the oxidation of biogenic amines, and hyperthermia.
Body temperatures > 41 °C are rare but can be fatal (Grunau et al., 2010; Henry et al., 1992), whereas moderate forms of MDMA-induced hyperthermia (>38 °C) are observed more often. Increased body temperature (>37.1 °C) was found in 19% of patients (Williams et al., 1998), and hyperthermia (>38 °C) was found in 4% of patients (Liechti et al., 2005) who presented in emergency departments with MDMA-related medical problems. On the other hand, MDMA at the doses administered to humans in laboratory settings produced only marginal effects on body temperature (Dumont & Verkes, 2006).
Conclusion: Hospital presentations of severe hyperthermia in ecstasy users has been frequently reported, though MDMA at the doses administered to humans in laboratory settings produced only marginal effects on body temperature. In seems that factors like excessive MDMA consumption, drug interactions or an interaction with environmental factors (e.g. high ambient temperatures and vigorous exercise) may underlie the severe hyperthermic effects of MDMA observed in clinical cases.

8.3 Hyponatraemia

MDMA shows a dipsogenic (thirst) effect so that users drink more than non-MDMA users (van Dijken et al., 2013). In the past, it has been advised to drink large amounts of water and/or non-alcoholic "energy tonics" to prevent MDMA-induced hyperpyrexia (hyperthermia) and dehydration. However, as a result of excessive water intake, in response to the dipsogenic effect, and in an attempt to prevent dehydration, the MDMA (ecstasy) user is at high risk of water intoxication (with secondary low blood sodium levels - hyponatraemia). In some people, MDMA may cause excessive secretion of antidiuretic hormone, which makes the kidneys retain water, so aggravating the consequences of excessive water

intake (Devlin & Henry, 2008). It is unclear whether the predominant mechanism in those presenting with hyponatraemia following ingestion of MDMA is (a) elevated plasma vasopressin levels (Schifano et al., 1998), or (b) excessive water intake following profuse sweating (Kessel, 1994; Maxwell et al., 1993). In addition, sodium is also lost by vomiting. However, inappropriate secretion of antidiuretic hormone (SIADH), continued secretion or action of the antidiuretic hormone arginine vasopressin (AVP, ADH), is diagnosed in MDMA users with hyponatraemia (Ajaelo et al., 1998; Hartung et al., 2002; Salathe et al., 2018). The syndrome SIADH implies inappropriate, despite normal or increased plasma volume inappropriate secretion of antidiuretic hormone. MDMA use can thus cause hyponatremia in humans. Some fatal cases have been described, but MDMA related hyponatremia is rare (compared to hyperthermia).
A systematic review from 2009 (Rogers et al., 2009) identified 10 case reports of fatalities due to hyponatraemia between 1997 and 2006. All fatal cases were in young women (16 to 21 yrs.) known to be at increased risk (Rosenson et al., 2007; van Dijken et al., 2013). Twenty-four case series or case reports involving non-fatal hyponatraemia were also identified. The propensity for women to be disproportionately affected is probably due to the lower ratio of body water to body mass in women.
Conclusion: Like hyperthermia, MDMA use is also causally related to the rarer adverse effect hyponatraemia (an imbalance in the body's sodium levels) and there are case reports of this outcome among MDMA users, including users who have died as a consequence.

8.4 Acute psychosis

The use of stimulants is associated with acute psychosis though it rarely occurs. For sedative drugs (GHB, alcohol, benzodiazepines), acute psychosis and delirium are sometimes seen as a withdrawal complication. Several case reports have been published about MDMA-related psychosis, usually paranoid type, in users without any psychiatric or medical history (Patel et al., 2011; Potash et al., 2009; Semiz et al., 2005; Vaiva et al., 2001; Van Kampen & Katz, 2001; Virani et al., 2018; Williams et al., 1993), These psychotic episodes are usually transient, but may be persistent (>six months) (Patel et al., 2011; Potash et al., 2009; Vaiva et al., 2001). The European Drug Emergencies Network (Euro-DEN) study collected drug related data on cases with psychosis presented to Emergency Departments (EDs) from October 2013 through September 2014. Psychosis was present in 348 (6.3%) of 5,529 cases. Cannabis (26%) and amphetamine were (25%) most commonly reported, whereas MDMA was less common with 20 cases (6%) (Vallersnes et al., 2016). Users with prior psychiatric histories may have a higher susceptibility for MDMA related psychiatric disorders, and MDMA use contributes to the overall burden of psychosis.
One case report described a man who became aggressive and experienced a "psychotic episode" after consuming ecstasy (Milas, 2000a). One small study followed up 32 patients six months after they were admitted for inpatient treatment after "ecstasy-related hallucinatory-delusive manifestations" and diagnosed as having an "ecstasy-induced psychotic disorder" according to DSM-IV criteria (Landabaso et al., 2002). At the baseline assessment, severe psychotic symptoms were observed, but these subsided following treatment.
Conclusion: There is limited data on the possibility that chronic use of high doses of MDMA might induce psychotic symptoms.

8.5 Use of MDMA in combination with other illicit drugs

Almost as a rule, ecstasy users are polydrug users (See User Characteristics, paragraph 13.2). In the USA, ecstasy use was not significantly associated with initiating injecting drug use (hazard ratio: 0.88, 95% CI: 0.57-1.35), after adjusting for substance use and socio-demographic confounders (Lake et al., 2018); rather it is associated with a reduced likelihood of injecting drug use (adjusted OR=0.57, 95% CI: 0.46-0.69) (Gaddis et al., 2018).
Conclusion: MDMA users are likely to be users of other substances i.e. ecstasy users are typically polydrug users.

9 Chronic toxicity

9.1 Memory

It has been claimed that impairment of cognitive functions persists for at least 6 months after abstinence from regular use of ecstasy at high dose , whereas anxiety and hostility remit after a year of abstinence (Curran, 2000; Morgan, 2000). However, the effect of low MDMA dosages was not clear, and most studies on cognitive impairment did not control for concomitant use of other drugs known to also impair these functions.

Self-reports have shown memory problems related to ecstasy use in mainly 'moderate' and 'heavy' users (Parrott, 2002) whereas 'novice' or short-term users (in terms of lifetime usage) generally remain unimpaired regarding MDMA related memory impairment or other psychobiological problems (Parrott, 2006b). See also the paragraph about neurotoxicity below.

Two early meta-analysis performed in 2007 showed a clear impairment in cognitive function, including memory. Recreational ecstasy users showed significantly impaired short-term (STM) and long-term memory (LTM) when compared with non-ecstasy users, either drug-naïve or ecstasy-naïve ones (Laws & Kokkalis, 2007b). However, the MDMA induced impairments in STM and LTM, verbal and visual memory showed moderate-to-large effect sizes with (Cohen's d) of -0.63, -0.87, -1.00, -0.27, respectively (Laws & Kokkalis, 2007a). The visual memory of ecstasy users was hardly affected and if affected it was due to concurrent cannabis use. There was no relationship between lifetime consumption of ecstasy tablets and any memory measures (Laws & Kokkalis, 2007b). Using relatively stringent inclusion/exclusion criteria, Kalechstien et al (2007) revealed that ecstasy users displayed a range of neurocognitive deficits when compared to controls matched in terms of age, education and intellectual functioning (Kalechstein et al., 2007). Associations between ecstasy exposure and psychomotor speed, attention, verbal learning and memory, nonverbal learning and memory and executive function showed small to medium effect sizes with d-values ranging from 0.40 to 0.73 (Kalechstein et al., 2007).

Similarly, the meta-analysis of (Nulsen et al., 2010) showed that the heaviest ecstasy users (light and moderate users were excluded from analysis) showed impaired working memory which was related to total lifetime ecstasy consumption ($N=27$, $\beta=-0.38$, $t(25)=2.05$, $p=0.05$), but not in short-term memory ($N=36$, $\beta=-0.08$, $t(34)=0.05$, $p=0.62$). Studies performed with polydrug controls showed similar results. Executive functions, consisting of a set of general-purpose control processes, required for regulating thought and action, are components of the working memory. Roberts et al. (Roberts et al., 2016) showed that ecstasy was associated with an overall executive dysfunction compared to drug-using controls [standardized mean difference (SMD) = −0.18; 95% CI: −0.26 to −0.11, Z = 5.05], with significant ($p < 0.001$) performance deficits in access (SMD = −0.33; 95% CI: −0.46 to −0.19, Z = 4.72), switching (SMD = −0.19; 95% CI: −0.36 to −0.02, Z = 2.16) and updating (SMD = −0.26; 95% CI −0.37 to −0.15, Z = 4.49). A recent study compared largely pure (primary) ecstasy users vs. polydrug ecstasy users (Wunderli et al., 2017). Effect sizes were highest for declarative memory ($d_{primary}$: 0.90; d_{poly}: 1.21), followed by working memory ($d_{primary}$: 0.52; d_{poly}: 0.96), executive functions ($d_{primary}$: 0.46; d_{poly}: 0.86), and attention ($d_{primary}$: 0.23; d_{poly}: 0.70), indicating that primary ecstasy users showed strong and relatively discrete declarative memory impairments, whereas ecstasy polydrug users displayed broad and unspecific cognitive impairments. It should be noted, that this study was restricted to heavy MDMA users (0.91 pills per week or 180 mg per two weeks, i.e. biweekly use), which represents only 15% of all MDMA users and these findings can thus not be generalized to all XTC users (see also (Szigeti et al., 2018). In contrast to these studies, a meta-analysis by Murphy et al. (2012) about the effects of ecstasy on visuospatial memory performance showed no evidence of a linear relationship between estimated ecstasy consumption and effect sizes.

9.2 Neurotoxicity

9.2.1 Introduction

Neurotoxicity is a much debated issue when it comes to recreational ecstasy use. For example, the group of Parrott claims that increased exposure to ecstasy is associated with increased cognitive deficits (Parrott, 2006a; Parrott et al., 2000), which is supported by the fact that 'heavier' users often perform worse than 'light' users on some neuropsychological tests. Though the possibility of ecstasy induced neurotoxicity is supported by preclinical studies of MDMA-induced neurotoxicity and

behavioural deficits, such preclinical studies have been criticised because of the disproportionately high doses of MDMA that were used and because certain rodents differ from humans in pharmacokinetics (Green et al., 2012). Possible mechanisms of MDMA-induced neurotoxicity involve glutamate-induced excitotoxicity, increased oxidative stress, hyperthermia, mitochondrial damage, and increased inflammation (Dunlap et al., 2018). However, the observed associations between ecstasy use and cognitive deficits may also result from confounding or represent reversed causation.

9.2.2 Confounding and other methodological issues

These issues raised much debate and scientific disagreement and controversy about the possible neurotoxicity of ecstasy. Some continue to argue there is solid evidence to classify ecstasy as a neurotoxic drug (Parrott, 2014), while others state that this is still open to debate and suggest that neurotoxicity exists but is reversible (Cowan, 2007; Doblin et al., 2014). Still others claim that the observed associations are due to (residual) confounding or representing pre-existing cognitive deficits that increase the probability to start using ecstasy (reverse causation) (Amoroso, 2018). Moreover, the criteria to define light and heavy ecstasy users differ per study which may easily lead to false or biased findings. Finally, note that the cognitive deficits in ecstasy polydrug users may be due to the use of cannabis and other psychoactive substances rather than ecstasy.
A recurring methodological problem in controlled drug studies is how to define the control condition. Whilst age, gender and IQ can be matched relatively easily, deciding upon the appropriate drug use history for a comparison group is more problematic.

A systematic literature review performed by Amoroso (2018) compared the criteria used across studies with respect to light and heavy ecstasy users and found in the 19 studies reviewed nine unique points of dichotomization for ecstasy use, varying from 10 to 80 pills or using quite other points for dichotomization e.g. lifetime doses. In many cases, heavy users in one study would have been considered light users in another study and vice versa, and the majority of studies (N=11) did not explain how or justify why a particular criterion was chosen. This issue is even more problematic when studies with such heterogeneous criteria are combined in meta-analyses. Such methodological issues, making dose-response relationships inconclusive, bring into question the validity of research suggesting that ecstasy is the cause of cognitive deficits (Amoroso, 2018).
The human neuroimaging studies are also littered with methodological problems, including inadequate sampling of subjects and controls, and lack of baseline data which lead to interpretative difficulties concerning causality between ecstasy use and potential toxicity, because it leaves open the possibility that differences between ecstasy users and controls were pre-existent. In a later study Amoroso (2019) showed that some studies have included users who abused ecstasy, whereas it is known that ecstasy does not always contain MDMA. Secondly, the consumption of adulterated pills, which may contain a wide range of other psychoactive compounds (see par. 13.4), introduces biases in establishing the actuals risks associated with ecstasy use. Moreover, most meta-analyses show that the deficits found in ecstasy users are small and most meta-analyses reported clinically irrelevant differences between ecstasy users and controls (Murphy et al., 2012; Nulsen et al., 2010; Roberts et al., 2016; Rogers et al., 2009) while effect sizes in studies showing cognitive deficits have decreased steadily over time (Taylor et al., 2011). Especially the studies performed in the United States reported more dramatic cognitive deficits in ecstasy users than European studies. Furthermore, the ecstasy literature suffers from publication bias (Fanelli et al., 2017; Murphy et al., 2009; Roberts et al., 2016; Rogers et al., 2009; Sumnall & Cole, 2005), because of selective reporting of findings that support the a priori hypotheses. This suggests that there may be unpublished research with negative finding, i.e. without significant associations between impaired cognition and ecstasy use (Amoroso, 2018). Finally, ecstasy research is predominately retrospective, so that the results may be affected by a variety of pre-existing (confounding) factors.
Recreational ecstasy use is common among adolescents and young adults and many of them are ‘experimenters’ who take ecstasy incidentally and will not become heavy or regular users. However, serotonin brain imaging studies are predominantly focused on heavy ecstasy users. This became evident form a systematic literature search of 10 imaging studies on serotonin transporter levels in recreational ecstasy users (Szigeti et al., 2018). It appeared that participants consumed on average 720% more pills over a year than the participants of the Global Drug Survey consume on average

(GDS, 2016). This indicates that the serotonin brain imaging literature has focused on unusually heavy ecstasy users, implicating that these studies are likely to overestimate the extent of serotonergic alterations experienced by the majority of ecstasy users (Szigeti et al., 2018). This corroborates with the findings of the only prognostic study available (8.1 months follow-up) performed by de Win et al. in ecstasy-naive volunteers. They found no indications for structural neuronal damage i.e. no extensive axonal loss was found after low dose ecstasy use (mean cumulative dose of 1.87±1.3 pills; maximum cumulative dose of 10 pills; median cumulative dose of 3–6 pills) (de Win et al., 2007). On the other hand, this observation does not exclude the possibility that incidental use of ecstasy can be harmful. For example, in a larger sample of the same study population, low-dose ecstasy use was associated with small but significant decreases in verbal memory relative to non-users (Schilt et al., 2007).
Several neuroimaging studies in ecstasy users have shown that neuronal adaptations may occur neurophysiologically before they manifest functionally. For instance, ecstasy users displayed increased blood flow to areas of the PFC during a verbal fluency task, but no impaired performance (Roberts & Montgomery, 2015), suggesting that ecstasy users just have to work harder to achieve similar performance to controls. Similar conclusions have been drawn from EEG studies whereby ecstasy users showed a similar performance in comparison with controls, but they had apparently to recruit additional resources (Burgess et al., 2011; Roberts et al., 2013a; Roberts et al., 2013b; Roberts et al., 2013c). Similarly, neuroimaging studies have shown neurophysiological correlates of executive performance before the manifestation of behavioural effects. For instance, fMRI studies have shown alterations in neuronal activation consistent with ecstasy-related damage, but no impaired performance (Daumann et al., 2005; Jager et al., 2008; Roberts & Garavan, 2010). However, it cannot be excluded that subtle impairments are not found in certain behavioural studies due to neural adaptation/compensation or lack of statistical power.

9.2.3 Neurotoxicity studies

A review about the effects of ecstasy on neurotransmitter systems showed that MDMA induced in particular in heavy users a significant loss of 5-HT transporter (SERT) binding, suggesting 5-HT neurotoxicity, but significant recovery of SERT binding over time in abstinent users (Vegting et al., 2016). A recent systematic review about neuroimaging studies in moderate ecstasy users (an average of <50 lifetime episodes of ecstasy use or an average lifetime consumption of <100 ecstasy pills) showed no convincing evidence that moderate ecstasy use is associated with structural or functional brain alterations in neuroimaging measures (Mueller et al., 2016). In 2016, Roberts et al. performing a meta-analysis of molecular imaging of SERT in ecstasy/polydrug users (7 studies comprising 157 ecstasy users and 148 controls), showed significant SERT reductions in 11 out of the 14 regions in ecstasy users (Roberts et al., 2016). This was recently confirmed by a meta-analysis to chronic alterations in the brains of ecstasy users which showed that ecstasy decreased SERT density in eight of 13 investigated regions. The alterations were positively associated with abstinence, but not with lifetime use, suggesting that the alterations were to some extent reversible (Muller et al., 2019).
Reneman et al. explored the differences between moderate and heavy use and long-term effects of ecstasy on 5-HT neurons and found that moderate use did not significantly reduce SERT and that the neurotoxic damage in several but not all brain regions of ex-ecstasy users is reversible (Reneman et al., 2001). Moderate users were defined as taking 50 pills of ecstasy or less prior to the study.
As part of the Netherlands XTC Toxicity study (NeXT study), a prospective cohort of ecstasy-naive subjects with a high risk for future first ecstasy use was studied. Of 188 healthy ecstasy-naive volunteers (mean age, 22 years) 58 subjects started using ecstasy. At baseline, there were no statistically significant differences in any of the neuropsychological test scores between persistent ecstasy-naive subjects and future ecstasy users. However, at follow-up, change scores on immediate and delayed verbal recall and verbal recognition were significantly lower in the group of incidental ecstasy users compared with persistent ecstasy-naive subjects, though there were no significant differences on other test scores (Schilt et al., 2007). It should be noted that the sample size was rather small and the effect sizes rather big. Moreover, after control for multiple testing the observed cognitive effects would not have remained statistically significant. Therefore, it cannot be excluded that no verbal memory deficits were present in these ecstasy users. Moreover, it can also not be excluded that the observed differences were reversible. In the same cohort, de Win et al. compared, again in a prognostic design, persistent ecstasy-naive subjects and future ecstasy users. They found no

indications for structural neuronal damage with the imaging techniques they used i.e. proton magnetic resonance spectroscopy (^{1}H-MRS), diffusion tensor imaging (DTI) and perfusion-weighted imaging (PWI). Their results did not support the concern that incidental ecstasy use leads to extensive axonal damage. However, sustained decreases in relative regional cerebral blood volume and apparent diffusion values may indicate that even low MDMA doses can induce prolonged vasoconstriction in some brain areas, although it is not known whether this effect is reversible (de Win et al., 2007). In the discussion, the authors note that additional correction for the use of multiple techniques as indicators for ecstasy-induced brain damage showed that most of the significant findings were no longer significant. The authors concluded that there were no indications for structural neuronal damage after a low dose of ecstasy use and that their data do not support the concern that incidental ecstasy use leads to serious axonal loss, but that even a low dose of ecstasy can induce sustained vasoconstriction in some brain areas, although we do not know whether these findings are permanent.
Another NeXT study assessed the impairment at long term of neurocognitive brain functions (working memory, attention, and associative memory) in 25 subjects before and after their first episode of ecstasy use (mean cumulative dose of 2.0 +/- 1.4 ecstasy pills, on average 11.1 +/- 12.9 weeks since last ecstasy use), compared to 24 persistent ecstasy-naive controls using fMRI (Jager et al., 2007). The follow-up period was 15.9 months (SD 4.6). The results showed that low dose of ecstasy (1-6 pills in total) did not impair working memory, selective attention, or associative memory. A subsequent study by the same group in sample of 71 subjects (including 33 heavy ecstasy users; mean 322 pills lifetime) (Jager et al., 2008) showed that associative memory performance was affected by amphetamine much more than by ecstasy.

9.2.4 Conclusion

Brain imaging studies have shown convincing evidence of ecstasy-related neurotoxicity in humans, especially among heavier users. However, it is unclear whether the abnormalities observed in markers of neurotoxicity precede or are consequences of ecstasy use. The only prognostic studies available i.e. those from the Netherlands XTC Toxicity study (NeXT study) (de Win et al., 2007; Schilt et al., 2007) suggested that ecstasy use may result in small to moderate deficits in memory, whereas all other included studies had a cross-sectional design and showed conflicting results. In addition, placebo controlled studies have consistently shown that administration of a single dose of MDMA causes transient impairment of verbal and spatial memory during intoxication but not during abstinence. Without evidence of the temporal relationship between exposure and outcome, it is difficult to draw any causal inferences. However, there is evidence for some small decline in a variety of domains, including verbal memory, even at low cumulative dose, but the effects size of such deficits appears to be relatively small and their clinical relevance is unclear, especially because some of these problems may remit after abstinence. Still, long-term effects of use cannot be ruled out. In other words: there is presently little evidence of longer-term harms to the brain in terms of either its structure or function.

9.3 Hallucinogen Persisting Perception Disorder (HPPD)

Hallucinogen Persisting Perception Disorder (HPPD) is a disorder characterized by visual phenomena that appear following the use of hallucinogen drugs. The syndrome may arise after one single use of such drugs and occur while sober (days or weeks after consumption) and may be long-lasting (years).
Though MDMA is considered as a hallucinogenic substance, but it does - in contrast with LSD - not induce visual hallucinations. Usually, ecstasy does not cause hallucinations (Green et al., 2003), although these may sometimes occur as an adverse effect (Davidson & Parrott, 1998). However, the Trimbos estimated that ecstasy use is responsible for only 4% of HPPD complaints in The Netherlands, an estimation based on a website survey performed in 2010 in the USA among users of hallucinogens (Baggott et al., 2011) who reported that 4.2% was treated for hallucinogen use related HPPD. Obviously, such data collection via websites suffers from reporting bias (over-reporting) and refers to a wide variety of hallucinogenic substances, including LSD. A review of the Trimbos Institute (Litjens et al., 2014) described 27 ecstasy users with signs of HPPD. However, all 27 subjects were polydrug users with eight subjects (30%) also having used other hallucinogens, like LSD and/or psilocybin mushrooms. The total number of ecstasy users with signs of HPPD or total number of HPPD patients in The Netherlands was not presented.
Conclusion: There is no substantial evidence for causality between MDMA-use and HPPD.

9.4 Prenatal effects

Prenatal ecstasy exposure is related to poorer motor development in the first two years of life of the child (Singer et al., 2015; Singer et al., 2016). Using the single cell gel (Comet) assay, MDMA (1.25, 2.5 and 5 mg/kg i.p.) induced extensive genotoxic damage in blood cells, brain cells and (only at the highest doses used) in liver cells (Alvarenga et al., 2010). However, it is important to stress that the Comet assay does not necessarily predict mutagenic potential. MDMA from the mother can be found in the unborn rat pup amniotic fluid and brain (Campbell et al., 2006). MDMA exposure has resulted in measurable effects on rats exposed in the prenatal/perinatal/postnatal period (Piper, 2007; Vorhees et al., 2007), but there are notable limitations of the extent to which these findings may be extended to humans. Studies of population based samples of women and prospective studies assessing ecstasy use and later outcomes have not yet been performed.

Conclusion: Animal studies provided conflicting evidence on MDMA's ability to affect the developing rat foetus in utero. Similarly, studies to prenatal effects in babies born to women who use MDMA have been inconclusive because of the small number of participants in these studies.

10 Non-fatal incidents related to recreational ecstasy use

10.1 Introduction

Although acute MDMA toxicity is rare, it can result in serious incidents with medical complications (Gowing et al., 2002). Serious incidents are defined here as (non-fatal) adverse health incidents where the user sought medical aid requiring medical stabilisation at the IC. For several reasons, it is difficult to collect reliable data about the number of serious incidents, including fatal cases, and to pinpoint MDMA as the causal agent in these cases.

Firstly, there is globally a lack of structured, comparable and systematic reporting systems about drug-related incidents and deaths. Systematic studies into serious ecstasy related incidents - except for MRDs (MDMA Related Deaths) in the UK - are therefore also scarce, and most information about ecstasy intoxications is derived from case reports, case series, retrospective audits, and observational studies. In the UK, Australia and US, ecstasy related adverse health incidents are not systematically collected. Various emergency departments (EDs) in these countries and elsewhere have reported ecstasy related hospital admissions, but as the prevalence of use (e.g. last year use) in such samples was not reported, they are of no value for a risk assessment. Secondly, though hyperthermia is the most commonly reported adverse effect of ecstasy use both in non-fatal and fatal cases (Rogers et al., 2009), the reports fail in general to document properly the circumstances and dose that led to the hyperthermia. Finally, ecstasy related adverse health incidents are probably underreported. For example, Turris and Lund (Turris & Lund, 2017) found twelve overdose fatalities specifically related to music festival attendance in the academic literature (1996-2014), including MDMA fatalities compared to 96 similar deaths in media reports. Another factor resulting in underreporting may be insufficient administrative means and feelings of shame of the user since roughly a quarter of last year ecstasy users participating to the Global Drug Survey (GDS) felt using ecstasy was simply never acceptable (Szigeti et al., 2018).

The International Classification of Disease version 10 (ICD-10) was designed to properly code ED attendances. Unfortunately, the registration of ecstasy related incidents is poor because they are not well captured by the ICD-10 coding system as ecstasy lacks a formal ICD-10 code, and in many countries ICD-10 codes are only given when patients are hospitalised beyond the ED. Furthermore, fatal ecstasy cases are not routinely subjected to autopsy and full toxicological screening. Consequently, post-mortem toxicology data is not always available, nor consistently used for coding and monitoring of drug-related deaths.

A majority of ecstasy users is polydrug using, i.e. they consume either concomitantly or simultaneously multiple substances. The simultaneous use of ecstasy and other psychoactive substances, including alcohol, may increase the hazard of an ecstasy related incident or fatal outcome. For a review about drug interactions, see: (Mohamed et al., 2011). Indeed, when autopsies and toxicological analysis are conducted in MRDs, MDMA is rarely (up to 28% of cases) the only drug found in the victim's blood (Ghodse et al., 2001; Ghodse et al., 2003; Schifano et al., 2003).

In addition of being a polydrug user, substances are occasionally ingested deliberately along with ecstasy to increase or dampen the ecstasy effects. Examples of such co-ingested substances are: (a) stimulants, including cocaine to remain alert and boost energy during rave parties (Boeri et al., 2008; Rigg & Sharp, 2018), (b) cannabis to prolong their high and socialising once the ecstasy effects begin to wane (Rigg, 2017) and (c) benzodiazepines to counteract the stimulant effects of ecstasy and/or alleviate the unwanted symptoms of ecstasy's so-called stimulant drug comedown stage (Kurtz et al., 2017; Rigg & Sharp, 2018) (d) ecstasy + GHB by the sensualists, (e) ecstasy + amphetamines by hard-core users and (f) ecstasy + LSD by the 'psychonauts' (Nabben, 2010). In addition, alcohol is commonly consumed with ecstasy to achieve a better high (Rigg, 2017). For example, two thirds (65%) of the regular Australian ecstasy users reported drinking alcohol when taking ecstasy; 69% of them reported to consume usually more than five standard drinks (Breen et al., 2006). Due to the diuretic effect of alcohol, the user becomes more dehydrated and puts them at higher risk of overheating.

Serious adverse health effects, including fatalities following ecstasy use appear also to be associated with a variety of factors (presumably some in combination), like (a) use under improper conditions (crowding, insufficient drinking, poor ventilation, heavy physical exertion while rigorously dancing for hours until early in the morning), (b) poly-substance use and (c) consumption of 'false',

adulterated or high-strength pills. In addition, both contaminated pills and 'false' pills (pills sold as ecstasy, but containing no or little MDMA) may increase the risk of (fatal) incidents. Notably, ecstasy pills have occasionally been adulterated with p-methoxy-amphetamine (PMA) and p-methoxy-methamphetamine (PMMA) which are substantially more dangerous than MDMA, because of the unforeseen delayed effect (Steele et al., 1992). It remains as yet unclear whether the recent increase in strength of ecstasy have increased the rate of ecstasy related incidences. Based on self-reported effects of ecstasy pills from 5,786 drug users and known content of the strength of the pills used, the strength of the pills was shown in 2011 to be dose-dependently related to reported adverse effects, like headache, hallucinations and agitation at doses above 120 mg per pill (Brunt et al., 2012). On the other hand, the Dutch Trimbos Institute recently reported no increase in serious incidents in the period 2015-2018 when high dose MDMA pills (> 65% of pills were dosed 150 mg or more) appeared on the Dutch market (Lameijer et al., 2018). It cannot be excluded that users have meanwhile become more prudent and start every event by using first a half ecstasy pill.

10.2 Casuistic data

This section describes casuistic observations which have been reported world-wide since 2000. These reports are not suitable for a risk assessment, because the exposure i.e. prevalence of use in the samples have not been described.

10.2.1 Clinical trials world-wide

Serious Adverse Reactions (SARs) related to administration of MDMA at doses ranging from 12.5 mg to 150 mg in MAPS-sponsored clinical trials (MAPS, 2018) have been rare and none have been life threatening. One possibly drug-related expected SAR has occurred to date in this clinical development program. This event was an increase in frequency of ventricular extrasystoles experienced during open-label treatment with 125 mg MDMA, which resolved with full recovery to baseline after the study drug's effects ceased. The subject was hospitalized for observation and recovered fully after the event, with no cardiac damage. Excluding people with cerebrovascular or cardiovascular disease will reduce the likelihood of risks arising from the cardiovascular effects of MDMA.

10.2.2 European Union

Some 65% of hospital emergency presentations in the EU in 2015 involved the use of illicit drugs, like heroin, cocaine, cannabis and ecstasy (EMCDDA, 2017). The Euro-DEN network has collected systematic data on drug-related presentations to EDs across 16 sentinel centres in 10 European countries. From October 2013 to December 2014, 549 intoxications (8% of total; two fatal cases) were related to ecstasy use, mainly (70%) occurring in young males. Sixteen patients (3%) developed hyperthermia and/or significant complications such as rhabdomyolysis. Around three-quarters of cases were discharged direct from the ED, mostly within 12 hours and critical care was required in 5% of cases. On average two different drugs had been used in these intoxications, in about half of the cases (47%) only ecstasy and 29% of cases involved the use of one additional substance, usually alcohol (EMCDDA, 2016c). Unfortunately, the EURO-DEN study only partly specified the location where MDMA was used; at least 99 of 467 incidents could be linked to ecstasy use in bars/nightclubs (Dines et al., 2015).

10.2.3 UK

The total number of ecstasy related hospital admissions (ecstasy alone or in combination with other drugs) in the UK is not known. ED presentations related to ecstasy are usually associated with poly-substance use (80% with alcohol, 24% cocaine and 21% ketamine) (Dargan, 2008). This was already found in an early study from 1998 which demonstrated that poly-substance use (most commonly amphetamines and cocaine) involved half of 48 presentations at the London accident and emergency department in the UK (Williams et al., 1998). The London centre of the National Poisons Information Service (NPIS) reported between December 1993 and March 1996 seventeen cases of hyponatraemia following ecstasy use (analytical confirmation of MDMA in ten patients) of whom two patients died. In six cases (1 fatal), only ecstasy was consumed; in the other four cases ecstasy was consumed in combination with alcohol (Hartung et al., 2002).
Data from EDs in Newcastle show that the number of ecstasy related admissions between 2000 and

2007 varies between 22 and 35 per year. Data from the ED of St Thomas' Hospital, London (2005 to 2008) show that ecstasy was the third most common drug behind cocaine and GHB. Ecstasy was involved in a total of 382 ED presentations (Dargan, 2008). Of these ecstasy presentations, only 14% referred to ecstasy as the sole drug, whereas 85% involved co-ingestants. Alcohol, GHB and ketamine were the most common co-ingestants (Dargan, 2008). Based on these ED data, the total number is likely to be some several thousand per year. For comparison: over 57,000 hospital admissions were recorded in 2006/07 with a primary diagnosis of alcohol intoxication and 846 with a primary diagnosis of cannabis intoxication (NDTMS, 2008).

10.2.4 USA

The Drug Abuse Warning Network (DAWN) was a national surveillance system in the US (discontinued in 2011) that monitored ED visits involving drug use. Between 2005 and 2011 the number of ecstasy incidents more than doubled, probably due to an increase in the prevalence of use, (from 4,460 mentions to 10,176 mentions) (SAMHSA, 2013).

In a case series of twelve patients concerning ecstasy related toxicity from a single rave event in San Francisco, two patients died. In only three cases serum was sampled which contained toxic MDMA concentrations (no other substances) (Armenian et al., 2013). In Los Angeles, 18 patients reported to ED for ecstasy-related complaints within 12 hours of a rave party. ecstasy was apparently used (no blood analysis) by three subjects, whereas the other 15 had used ecstasy either in combination with alcohol or other drugs (CDC, 2010). During a 3-day electronic dance festival in New York with a total cumulative attendance of 58,000, 84 patients were enrolled over 2.5 days. Of the 38 subjects who initially presented with abnormal vital signs, incl. four with hyperthermia, 34 (90%) had used ecstasy or other drugs (Friedman et al., 2017).

A retrospective review of 545 documented cases (54% females) involving ecstasy intoxication reported over five years (2000-2005) to the California Poison Control System (CPCS) showed 188 cases (35%) with a documented serum sodium, of which 73 (39%) with hyponatremia ($Na^+ < 130$ mM). Of the 73 subjects with hyponatremia, there were 55 (75%) females (Rosenson et al., 2007).

10.2.5 Australia

A study of ecstasy related presentations in two hospital emergency departments in Melbourne (Australia) (2008 to 2010) reported a decrease of ecstasy related incidents from 26% of all ED visits (N=1,347 visits) in 2008 to 14% (N=188 visits) in 2009. According to the authors, this decrease is likely to reflect the reported decrease in ecstasy consumption at the population-level (Horyniak et al., 2014) in that period. Presentations were commonly related to GHB (N=480; 36%), amphetamines (N=255; 19%) and ecstasy (N=236; 18%). However, 75% of ecstasy cases involved concomitant alcohol use. In 2010, a 3-year review of ecstasy and other recreational drug presentations at two Sydney electronic dance events showed that the ecstasy related cases made up just 12% of the 5,148 illicit-drug-related presentations, which is presumably an underestimate considering that the drug type was unspecified in 43% of presentations (Indig et al., 2010).

10.2.6 Other countries

Grunau et al. have systematically retrieved from literature between 1950 and 2008 53 reports describing 71 cases (26 were fatal; 45 survived) of ecstasy-related hyperpyrexia (Grunau et al., 2010).

A French study reported two cases of two young men who presented with life-threatening complications after the recreational consumption of ecstasy. One case presented with an ischemic stroke MDMA and MDA plasma concentrations measured 5 days after the consumption were 10.2 mg/L and 2.3 mg/L, respectively. The plasma levels of MDMA and MDA in the second case, who presented with hyperthermia and multiple organ failure, were measured three days after the consumption and amounted 133 mg/L and 126 mg/L, respectively (Di Trapatani et al., 2018). In Israel, in 2001 three patients who had consumed ecstasy were in a comatose state associated with seizures and transferred to the ICU. Urine analyses were all positive for MDMA and negative for barbiturates, benzodiazepines, cocaine and tricyclic antidepressants (Ben-Abraham et al., 2003). A Spanish study reported 135 ecstasy users who attended at the ED for anxiety, agitation or cognitive disturbances, reduced consciousness or motor disturbances. Specimen of 54 out of 135 cases were screened for ecstasy resulting in 47 confirmed cases of ecstasy use. A high proportion of users had also used

alcohol (35.4%) or illicit drugs (50%) (Sanjurjo et al., 2004).
Analysis of blood samples from 106 intoxicated patients, collected during an indoor electronic dance event in Belgium, detected amongst others ecstasy in 34% of cases, but in only six of these cases, MDMA was the sole substance found. Of interest was the high-risk polydrug use, especially among ecstasy users in whom very high MDMA concentrations (> 0.8 mg/L) were found (Calle et al., 2018). Four victims attending an electronic dance event collapsed, were sent to the Emergency Department in Hong Kong and showed life-threatening clinical symptoms of serotonin toxicity i.e. hyperthermia. One patient died 30 minutes after arrival to the ED. In all four cases both MDMA and midazolam was found in their urine (Chu et al., 2018). In Bern, Switzerland, 503 ED presentations related to intoxications of recreationally used substances were seen in the period May 2012 to April 2016. Cumulative over four years, only 34 (7%) intoxications were related (as reported) to ecstasy use (cannabis: 129; cocaine: 148) (Liakoni et al., 2017). Another Swiss study of 52 self-reported ecstasy ED presentations between January 2001 and December 2003 showed that most patients had used ecstasy in combination with other substances, including alcohol (52%) or other illicit drugs (71%) (Liechti et al., 2005).

10.3 Studies suitable for the risk assessment of non-fatal ecstasy related incidents

Many incidents related to ecstasy use have been described in literature (see previous paragraph), but the majority of these studies did not report the prevalence of use, e.g. the last year use so that these data are not suitable for an assessment of a risk for serious incidents. The same holds for MRDs (see below).
Due to the poor quality of the available evidence, it is difficult to quantify the risk of non-fatal incidents in a meaningful way. Only two reports (1) the Global Drug Survey (GDS) and (2) the Dutch Monitor Drug-related Incidents (MDI) provide data which allow a proper risk assessment of non-fatal ecstasy related incidents.

10.4 Reports of ecstasy related non-fatal incidents

Many incidents related to ecstasy use have been described in literature, but the majority of these studies did not report the prevalence of use, e.g. the last year use so that these data are not suitable for an assessment of a risk in individuals for serious incidents. The same holds for MRDs (see section 11).
The Global Drug Survey (GDS), collecting information from users via a web-based questionnaire, reported that in 2013 0.3% of last year ecstasy users were seeking emergency medical treatment ‘world-wide’ which increased to 0.8% in 2016 (GDS, 2016). In this period, the use of ecstasy increased 3-fold (GDS, 2016), but this does not explain the increase of ecstasy related incidents. Interestingly, women were 2-3 times more likely to seek emergency treatment in 2016 than men (GDS, 2016).
The Dutch ‘Monitor Drug-related Incidents’ (MDI), conducted by the Trimbos Institute, reported 5,905 drug use related incidents in 2017. The data are based on self-report of drug use without toxicological confirmation (Lameijer et al., 2018). MDI collects data from The monitor includes SHE’s directly reporting to the MDI and data of hospitals collected by ‘Letsel Informatie Systeem’ (LIS, Injury Information System), conducted by ‘VeiligheidNL’ (Panneman & Blatter, 2016), ambulance stations, forensic doctors and First Aid posts in the Netherlands, but does not fully cover The Netherlands (coverage estimated here: 50% to 70%). MDI uses the following categorisations: ‘light intoxications’ when adverse effects of ecstasy are mild and the patient is well responsive; ‘moderate intoxications’ when the patient is insufficiently responsive and ‘severe intoxications’ when the patients is non- responsive (using the Glasgow Coma Scale) due to (sub) comatose state or aggressive behaviour, possibly in combination with disturbed vital signs (temperature, pulse, blood pressure).

Main findings in 2017 (Lameijer et al., 2018) were that ecstasy was involved in 1,747 out of 5,905 (29.6%) drug-related incidents of which in 1,201 cases (69%) if used alone and in 31% if used in combination with (an)other drug(s). Ecstasy had been used in combination with other drugs in 546 (31%) of all ecstasy-related incidents in 2017 (mostly alcohol and GHB were involved in these combined intoxications: 43% and 36%, respectively). Of the incidents related to ecstasy use in combination with other drug(s), 57% was moderate or severe, whereas of incidents related to ecstasy

use alone, 29% was moderate or severe. This finding indicates that the use of ecstasy in combination with other drug(s) leads in general to a higher harm level than the use of ecstasy alone. For instance, the proportion of moderate to severe intoxications was higher if ecstasy had been consumed in combination with alcohol (35% vs. 21%) (Lameijer et al., 2018).
About half of 2,517 drug-related incidents reported by First Aid posts, mainly present at large parties and festivals, was ecstasy-related (N=1,351) of which 73% resulted from the use of ecstasy alone. Of the 1,351 intoxications at festivals 79% was relatively innocent, 19% moderate and 3% serious. Moderate or severe ecstasy intoxications at First Aid posts decreased from 28% in 2015 to 21% in 2017 (despite that around 65% of pills on the Dutch market were meanwhile dosed 150 mg or more).

10.5 Risk assessment of non-fatal incidents in the Netherlands

Based on the data extracted from the MDI, the Dutch Trimbos Institute recently estimated that yearly at least one out of 250 ecstasy users (0.4%) seeks medical assistance due to any adverse health effect following ecstasy use (Wijers et al., 2016).
Estimating that MDI covers 50% to 70% of all ecstasy incidents in the Netherlands, the number of incidents nation-wide in 2017 would be (100/50) x 1,747 = 3,500 incidents occurring in 370,000 last year users in the Netherlands (van Laar et al., 2019). This represents an incidence rate of one out of 106 (0.9%) for any ecstasy-related incident (overall risk).
However, some amendments can be made to obtain a more realistic estimate of (serious) non-fatal incidents occurring in ecstasy users (cf. Table 6). Ecstasy is a 'party drug' as it is typically used by 'outgoing' young adults (< 35-40 yrs. old) primary at parties and festivals (93%), and seldomly at home (Goosens et al., 2013). For instance, last year prevalence of 'outgoing' young adults was 61%, and 78% in those visiting parties and festivals more than once per month (Goosens et al., 2013). The frequency of ecstasy use is right-skewed.
The Global Drug Survey 2015 (Szigeti et al., 2018) reported an average worldwide frequency of 8.0 times per year and an average dose of 1.5 pills per session. In a later interview, Szigeti reported that the average person in a sample of 11,168 GDS respondents who had used ecstasy at least once in the previous year, took 12.2 ecstasy pills per year (Johnson, 2018). Very recently, GDS reported a frequency of five times per year (GDS, 2019). These estimates are close to the results of the Dutch Party Panel internet survey from 2016 among 637 'party goers' where an average dose of 1.5 pills per session and a use frequency of 8.8 times per year was found (Peters, 2018a). According to the latest Antenne survey from 2017 among Dutch clubbers/'party goers' , the average number of sessions is even higher, i.e. 9.3 sessions yearly. About half of them (45%) used ecstasy 4 times a year; 35% 10 times a year and 20% more than 10 times a year (Nabben et al., 2018). The proportion of occasional users i.e., those who used ecstasy only 1-2 days per year, was 21%. The median and mean number of days (sessions) ecstasy was used was 8.5 and 5.0, respectively (Nabben et al., 2018). Previous 'Antenne' surveys have been performed among students (Nabben et al., 2017), and visitors of pubs (Benschop et al., 2015) and coffee shops (Nabben et al., 2016) in the Netherlands who had used ecstasy in the last year. The aggregated results showed that about one-third (35-38%) of them were occasional users (1-2 days per year). Across the three groups, the use was on average 1.2 pills of ecstasy per session on 4.0 days per year (median values). The mean number of days ecstasy was used per year was 4.9 (visitors of pubs), 7.5 (students) and 5.4 (visitors of coffee shops).

Correction factors used to assess the health risk of MDMA (cf. Table 6)

Item	Multiplier
Coverage	50%
Pills per session	1.2
Sessions per year	4.0
Pills per year per user	4.8

In summary, a conservative estimate of ecstasy use is 4 days (4 sessions) per year, where 1.2 pill is consumed per session or 4.8 pills per year per user. In other words: in the Netherlands with 370,000 last year ecstasy users 1.78 million pills are consumed yearly (370,000 x 4.8). As such, the incidence rate of overall ecstasy-related incidents per pill is one out of 500 (1.78 million / 3,500 incidents) or 0.2%. As depicted in Table 6, 172 serious ecstasy-related incidents were reported in 2015 giving an

incidence rate for serious incidents per pill of one out of 10,000 (1.78 million / 172 serious incidents) or 0.01%. This yearly estimated risk of a serious ecstasy-related incident for an ecstasy user is 0.05% (172 serious ecstasy-related incidents occurred yearly in 370,000 ecstasy users). Similarly, the estimated risk for moderate to severe incidents is one out of 2,700 (1.78 million / 662 moderate/severe incidents) or 0.04%.

Table 6. Risk estimation based on 3,500 ecstasy-related incidents (1,747 incidents at a coverage of 50%) and 370,000 last year users of ecstasy and eleven million consumers of alcohol in the Netherlands. For coverage of 25%: the ecstasy related risk should be doubled.

Adjusting factor	% Risk	Risk	Nominator	RR*
Ecstasy-related incidents				
At full coverage in the Netherlands [1]	0.9%	1:100	Per user	100
All incidents per pill (per session) [2]	0.2%	1:500	Per pill	20
Moderate to serious incidents per pill	0.04%	1:2,700	Per pill	3.7
Serious incidents per pill [3]	0.01%	1: 10,000	Per pill	1
Serious incidents per user	0.05%	1:2,150	Per user	
Alcohol-related incidents [4]				
Serious incidents [5]	0.05%	1:2,000	Per user	5
Serious traffic accidents [6]	0.03%	1:3,000	Per user	3.3
Assistance of SEH required; variable severity [7]	0.15%	1:650	Per user	15

[*] RR: relative risk (fold higher risk); [1] based on estimated coverage of 70%; [2] based on four sessions yearly (1.2 pill is used per session); [3] 21% of incidents is serious, when the patient requires medical stabilisation at the IC; [4] based on a total of eleven million drinkers in the Netherlands; [5] in 2017, 6,000 alcohol-related intoxications required SEH treatment (van Laar et al., 2006); [6] nearly four thousand serious alcohol-related traffic related injuries required hospitalization; [7] 17,800 alcohol use related accidents where some SEH-assistance was necessary (van Laar et al., 2006).

10.6 Discussion

10.6.1 Relative risk

It is not possible to compare the risk for a non-fatal incident of ecstasy with that of alcohol, because the risk of drinking depends on a variety of factors, like the number of drinks consumed, personal traits of the drinkers and environmental factors. Perhaps even more important are: (1) the much higher potency of one ecstasy pill compared with one alcoholic drink, and (2) the apparent absence of a dose-incident relationship of both alcohol and ecstasy. As an alternative, the relative risk of a non-fatal incident of being an average ecstasy user can be assessed and compared with other means of activities giving pleasure. For example, serious accidents in bikers may serve as a suitable comparator for the risk of ecstasy. In 2017, 13.5 million Dutch inhabitants owned a bicycle and they were collectively involved as the victim in 13,419 of 21,300 (63%) serious road accidents (Hendriks, 2018). The risk for a serious road accident among cyclists was therefore 0.1% (13,419 /13.5 million), yearly, or one out of 1,000. This risk is 2.5-fold higher than the risk for a moderate to serious incident of 0.04% per ecstasy pill (172 serious ecstasy-related incidents per 1.78 million pills consumed) and two times higher than the average risk of being a user of ecstasy (0.05%; 172 serious ecstasy-related incidents occurred in 370,000 users). With respect to fatal incidents, ecstasy use cannot be properly compared with alcohol, because alcohol-related fatalities usually result, in contrast to those of ecstasy, from long-term heavy alcohol use.

10.6.2 Non-fatal incidents

The overall risk for any ecstasy-related incident of 0.9% (cf. Table 2) compares well with the rate reported in the GDS survey (0.8% of last year ecstasy users was seeking emergency medical treatment) (GDS, 2016). Table 6 also shows that the risk for a serious and moderate to severe ecstasy-related incident per pill of 0.01% (one per 10,000 pills) and 0.04%, respectively, which is considerably higher than e.g. the adverse health risks related to cannabis use.

The risk of an ecstasy-related incident may be increased by consumption of the drug under unfavourable or risky conditions (crowding, insufficient drinking, poor ventilation, excessive physical

exertion) which may decrease the safe-dose level. Another additional risk is the consumption of high-strength pills, because it may lead to adverse health incidents due to overdosing. It remains as yet unclear whether high-dose ecstasy pills/tablets have increased the rate of ecstasy-related incidents. Based on self-reported effects of ecstasy pills from 5,786 drug users and known content of the strength of the pills used, the strength of the pills was shown in 2011 to be dose-dependently related to reported adverse health effects, like headache, hallucinations and agitation at doses above 120 mg per pill (Brunt et al., 2012). Note that this observation does not directly translate in a dose-dependency of ecstasy-related serious incidents or fatalities. Indeed, the Dutch Trimbos Institute recently reported no increase in serious incidents over the period 2015-2017 when high-strength MDMA pills (> 65% of pills were dosed 150 mg or more) appeared on the Dutch market (Lameijer et al., 2018). It cannot be excluded that users have meanwhile become more prudent and start for example every event by using half an ecstasy pill first before re-dosing, which has been shown to be a successful harm reduction strategy (Fernandez-Calderon et al., 2019).

About half (56%) of ecstasy-related incidents in 2017 was due to the combined use of ecstasy with other substances (mostly alcohol and GHB; in 36% - 43% of mixed use cases) (Lameijer et al., 2018). This reflects a high prevalence of polysubstance use among ecstasy users (Office, 2014; Scholey et al., 2004; Wu et al., 2009). Of higher importance is the observation that of the incidents related to ecstasy use in combination with (an)other drug(s), 57% was moderate or severe, whereas considerably less (29%) of incidents related to ecstasy use alone was moderate or severe. This indicates that the use of ecstasy in combination with other drug(s) leads in general to a higher harm level than the use of ecstasy alone.

Very recently, GDS reported that 0.6% of MDMA-using respondents sought medical treatment in the last 12 months following MDMA use (1.3% of respondents from the UK). Of those drug users who sought emergency medical treatment, 42.9% of MDMA users was hospitalised (for alcohol: 59.3%; for cannabis: 53.1% and for heroin: 60.7%) indicating the relative lower potential of MDMA for serious harm (GDS, 2019). Based on the rate of 0.6% for serious MDMA-related incidents (“seeking medical treatment”) reported by the GDS survey, gives a rate of 0.125% (0.6% / 4.8) when the use frequency of 4.8 pills per year is taken into account. This rate of 0.125% corresponds well with the risk for moderate to serious incidents per pill (0.12%) as presently assessed (cf. Table 6).

10.7 Conclusion

For conclusion see paragraph 11.7.

11 Fatal incidents related to recreational ecstasy use

11.1 Introduction

Numerous cases of MRDs have been reported world-wide and may include traumatic accidents due to impaired judgement or perception of risk (e.g. drowning, fall from height, road traffic accidents), psychiatric problems caused by the drug (e.g. suicide using mechanical means) or even homicide. The primary cause of death in MRDs following recreational use was a severe medical complication, such as rhabdomyolysis (the destruction of striated muscle cells), disseminated intravascular coagulation (which results in widespread bleeding and tissue necrosis), renal failure and liver damage. However, details of the clinical symptoms are not systematically reported.

A pre-requisite to assess the risk of MRD is that the fatalities are registered nation-wide, in addition to exposure rates, e.g. last year prevalence of use. In the UK fatal incidents are systematically recorded in death registers by the UK coroner (Schifano et al., 2003), including which substance was involved in the cause of death. As the last year prevalence of use i.e., exposure to ecstasy in the UK is also known, the risk of MRDs in the UK can be assessed. This contrasts with other countries where MRDs are not systematically registered and toxicological data on the drugs detected post-mortem are not (always) cited on the death certificate.

Other difficulties in collecting accurate information about the numbers of MRDs are the ingestion of ecstasy or the use of ecstasy in combination with other substances, and the time lag between death and toxicological analysis. An integration of data, mainly from ED reports in literature since 1996 about MRDs world-wide (cf. the figures presented in Table 7 and 8; figures partly overlap) indicate that about a quarter of MRDs resulted from the consumption of solely ecstasy (no other drugs detected). In the other cases MDMA may have contributed to the cause of death.

Table 7. Number of reported MRDs, where MDMA was used in combination with other substances. Some of the studies may show an overlap in cases.

Country	Period	N (per year)	References
Australia	1992-1997	2 (0.4)	Byard et al., 1998
Australia	2000-2005	48 (9.6)	Kaye et al., 2009; Roxburgh et al., 2011
Australia	2001-2005	10 (2.5)	Pilgrim et al., 2009
Australia	2002-2008	17 (2.8)	Pilgrim et al., 2011
Belgium	1976-2004	9 (0.3)	De Letter et al., 2006
Croatia	1997-2007	5 (0.5)	Susnjara et al., 2011
England/Wales	1997-2000	50 (16.7)	Schifano et al., 2003b
England/Wales	1997-2007	501 (50.1)	Schifano et al., 2010
England/Wales	2017	21 (21.0)	ONS, 2018a
France	2007-2013	4 (0.7)	Le Roux et al., 2015
France	2010-2013	23 (7.7)	Mallaret and Micallef, 2015
Netherlands	1999-2004	20 (4.0)	Verschraagen et al., 2007
Netherlands	2006-2015	26 (2.4)	Vreeker et al., 2017
Netherlands	2009-2015	7 (1.2)	Niesink, 2016
Spain	1993-1995	5 (0.4)	Lora-Tamayo et al., 1997
Spain	2003	2 (2.0)	Garcia-Repetto et al., 2003
Taiwan	2001-2009	9 (1.1)	Lin et al., 2009
UK	1990-1991	1 (1.0)	Henry et al., 1992
UK	1993-1996	1 (0.3)	Hartung et al., 2002
UK	1992-2008	22 (1.4)	Milroy, 2011
UK	1994-1996	2 (1.0)	Milroy et al., 1996a
UK	2005	4 (4.0)	Elliott, 2005
USA	1991-2006	4 (0.3)	Li et al., 2011
USA	1997-2000	7 (2.3)	Gill et al., 2002

Table 8. Number of MRDs where the use of MDMA alone was reported as the primary cause of death (25.8% of all reported MRDs). Some of the studies may show an overlap in cases.

Country	Period	N (per year)	References
Australia	2000-2005	12 (2.4)	Kaye et al., 2009; Roxburgh et al., 2011
Australia	2001-2005	1 (0.3)	Pilgrim et al., 2009
Belgium	1976-2004	4 (0.1)	De Letter et al., 2006
England/Wales	1997-2000	6 (2.0)	Schifano et al., 2003b
England/Wales	1997-2007	104 (10.4)	Schifano et al., 2010
England/Wales	2017	35 (35.0)	ONS, 2018a
France	2010-2013	9 (3.0)	Mallaret and Micallef, 2015
Greece	2002	1 (1.0)	Raikos et al., 2002
Netherlands	1999-2004	30 (6.0)	Verschraagen et al., 2007
Netherlands	2006-2015	21 (2.3)	Vreeker et al., 2017
Netherlands	2009-2015	6 (1.0)	Niesink, 2016
Spain	1993-1995	1 (0.5)	Lora-Tamayo et al., 1997
Spain	2003	1 (1.0)	Garcia-Repetto et al., 2003
Taiwan	2001-2009	16 (2.0)	Lin et al., 2009
UK	1990-1991	6 (6.0)	Henry et al., 1992
UK	1993-1996	1 (0.3)	Hartung et al., 2002
UK	1992-2008	13 (0.8)	Milroy, 2011
UK	1994-1996	3 (1.5)	Milroy et al., 1996a
UK	2003	2 (2.0)	Greene et al., 2003
UK	2005	1 (1,0)	Elliott, 2005
USA	1997-2000	6 (2.0)	Gill et al., 2002

The time lag between death and toxicological analysis is of importance considering the high volume of distribution of MDMA, which makes MDMA liable to post-mortem redistribution resulting in high concentrations in cardiac blood and blood-rich organs such as lungs and liver which notably occurs at longer post-mortem intervals during putrefaction (De Letter et al., 2010). These factors i.e. polydrug use and redistribution may explain that the level of ecstasy assessed in specimen does not correlate well with the severity of symptoms nor the clinical course. For instance, one fatal case had a serum MDMA level of 1.26 mg/L, while another patient, whose serum level was 7.0 mg/L, received supportive treatments only and survived (Hegadoren et al., 1999). In another case, a patient suffered from severe rhabdomyolysis, acute renal failure and disseminated intravascular coagulation, whereas blood levels of MDMA were only 0.2 mg/L (Barrett & Taylor, 1993).

11.2 Casuistic reports on ecstasy related fatal cases

11.2.1 European Union

Systematic data on acute toxicity of MDMA in Europe is not available, but the number of reported MRDs is low (EMCDDA, 2016c) as compared with the almost 8,000 (78%) annually reported opioid-related deaths (EMCDDA, 2018a).

11.2.2 USA

In the US, numerous MRDs have been reported in case series and case reports, which do not allow to the calculation of annual estimates. The Office of Chief Medical Examiner of New York City investigated all 22 deaths that tested positive between January 1997 and June 2000 for MDMA. Of these fatal cases, six were due to MDMA alone, seven to a combination of MDMA and opiate and/or cocaine, and nine to a trauma (Gill et al., 2002). In Maryland, US, 149 drug related death were reported between 1991 and 2006 of which only four cases (2.7%) were due to a combination of MDMA and narcotics (Li et al., 2011). In 2009, the estimated number of MRDs in the US averaged some 50 per year (Rogers et al., 2009).

11.2.3 Australia

The Adelaide and the South Australian State Coroner's Department identified two MRDs which occurred from February 1992 to January 1997. Both were due to an intoxication by MDMA in combination with PMA (Byard et al., 1998). The National Coroners Information System (NCIS) in Australia, which only captures deaths which are referred to coronial services, identified 112 MRDs over a four year period (three times more accidental deaths attributed to opioids are seen in Australia every year) (Kinner et al., 2005a). In 51 (46%) of these cases, MDMA was the 'primary' contributing factor. Analysis of amphetamine-class drug related fatal cases (N=169) reported to the coroner from 2001 to 2005 in Australia showed MDMA was detected in eleven cases. In one case, MDMA was the only substance detected. This patient died of cardiac arrhythmia (Pilgrim et al., 2009). In the other ten cases other substances had been used, as well. Using the National Coroners Information System (NCIS) in Australia, Kaye et al. (2009) reviewed the fatal cases where MDMA was the cause of death from July 2000 to July 2005. Over this period they found 82 MRDs; 82% was directly caused by some drug of which 23% only by MDMA and 59% by a combination of MDMA and other drugs (Kaye et al., 2009; Roxburgh et al., 2011). A subsequent and similar study (Victorian State Coroner) reported 106 MRDs between 2002 and 2008 (Pilgrim et al., 2011).

11.2.4 The Netherlands

The National Forensic Institute (NFI) in the Netherlands reported 50 MRDs over the years 1999-2004 of which MDMA was the primary cause of death in 30 cases (Verschraagen et al., 2007). Over the years 2006-2015, the NFI reported 68 MRDs of which in 21 cases (31%) MDMA was the primary cause of death, in 26 cases death was caused by MDMA in combination with other substances, like amphetamine, cocaine, GHB, alcohol, benzodiazepines (Vreeker et al., 2017a), and in 21 cases the cause of death was secondary or could not be well established. The MDI reported 13 MRDs over the period 2009-2015 of which six (46%) were due to MDMA alone and seven due to MDMA in combination with amphetamine, cocaine, cannabis or GHB). In 2017, no MRDs were reported by the MDI (Lameijer et al., 2018). Some of the studies cited above may show an overlap in cases. Moreover, data are not systematically registered so that they are not suitable for the estimation of risk for a fata incident.

11.2.5 Other countries

After integration of three ED studies (Liechti et al., 2005; Sanjurjo et al., 2004; Williams et al., 1998) the death rate of the incidents was 0% to 2%, suggesting that most acute adverse effects resolve either spontaneously or with treatment, even among those serious enough to present at hospital. In Croatia, 190 drugs related deaths in the period 1997-2007 were registered. MDMA was found in blood in 5 out of 133 cases (3.3%) where illicit substances were found (Marasovic Susnjara et al., 2011). In Greece, in 2002 one case due to MDMA intoxication and three cases of MDMA related drownings were reported (Raikos et al., 2002). In the period 2010-2013, the French surveillance system 'DRAMES' detected in blood various substances in 32 MRDs of which in 9 cases (28%) only MDMA (Mallaret & Micallef, 2015). One hundred and five cases of phenethylamine poisonings between January, 2007 and December, 2013 were extracted from the Poison Centers database in western France. MDMA was with 40 cases (38%) the most commonly reported poisoning. Four out of nine severe cases, for which toxicological-analytical data were available, were related to MDMA use in combination with a variety of other substances (Le Roux et al., 2015). A systematic Spanish study of all cases of deaths brought to the attention of the Madrid department of the Instituto Nacional de Toxicologia from 1993 to 1995 detected 6 MRDs of which one fatal case was due to intoxication by MDMA alone (16%) (Lora-Tamayo et al., 1997). Three further MRDs were reported in Spain in 2003. One case was due to intoxication by MDMA alone and the two others by a combination of MDMA and benzodiazepines (Garcia-Repetto et al., 2003). In Belgium, 34 fatalities related to a variety of amphetamines between January 1976 and December 2004 were retrieved from medico-legal files. Thirteen cases were MDMA-related. In nine other MRDs, a large variety of substances were detected, as well (De Letter et al., 2006). Details of two out of four fatal cases of MDMA abuse were reported in Slovenia. The first case was the accidental intoxication with MDMA on a rave party, the second case was a suicide using MDMA in combination with insulin (Karlovsek et al., 2005).

In a Canadian case series of 59 MRDs (MDMA confirmed in blood) 13 cases (27%) were attributable to the toxicity of MDMA alone, in 22 cases due to MDMA and other substances, and 24 MRDs due to trauma, like driving accidents (Milroy, 2011). In 2015, stimulant-related deaths in Turkey included 166 cases with MDMA of which 62 (37%) were attributed to use of MDMA alone (EMCDDA, 2017). In a case series of 59 fatalities occurring in the period of 2001 to 2009 in Taiwan where MDMA was determined as the cause of death, ketamine was also found in 28 of these cases. In total 25 fatal cases were MRDs (no ketamine) of which sixteen cases were solely due to MDMA (Lin et al., 2009).

11.2.6 Traffic related fatalities

On the road studies have noted impairments in lane deviation and speed maintenance ability after administration of MDMA (75 mg. p.o.) (Ramaekers et al., 2006). From the Swedish national forensic toxicology database 13,963 single-drug fatal intoxications by drugs (accidental, suicidal or undetermined intent; blood values available) attributed by pathologists were extracted, but none of the cases involved MDMA (Jones et al., 2016). A similar study from Norway about fatal intoxications (194 autopsy cases and 4,811 DUID cases) following a combination of psychoactive drugs during 2012 neither reported the involvement of MDMA (Edvardsen et al., 2017).
The National Coroners Information System (NCIS) in Australia identified over four years (2001-2004) 112 MRDs of which 31 (28%) were related to road traffic accidents (Kinner et al., 2005b). However, in only six of all cases (5%) MDMA as the only drug found (three related to drug toxicity). By comparison, in 2004 alone, there were a total of 374 accidental deaths attributed to opioids in Australia. According to the authors, fatalities directly caused by MDMA appear to be very rare in Australia by comparison with the extent of use, and MDMA is usually only one of a range of drugs detected at autopsy and a substantial proportion of MRDs involve a motor vehicle accident.
Of note: the following three additional risk factors involved in MDMA-related traffic fatalities: the driver (1) drives often in the dark very early in the morning after a night of partying (2) consequently suffers from sleep loss, and (3) is relatively young (MDMA is mainly used by young adults).

11.3 Reports suitable for the risk assessment of MRDs

The number of MRDs seems relatively small in comparison to its widespread use and compared to other Class A substances, like cocaine and heroin. Though systematic data on acute toxicity of MDMA in Europe is not available, the number of reported MRDs is low (EMCDDA, 2016c) as compared with the almost 8,000 (78% of all drug-related mortalities) annually reported opioid-related deaths (EMCDDA, 2018a).

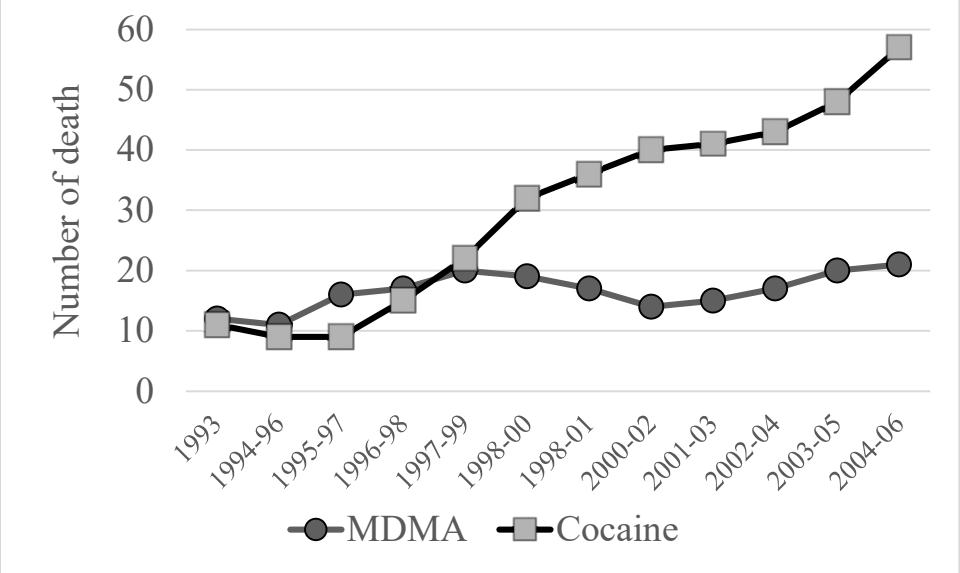


Figure 1. General Mortality Register drug-related deaths 1993–2006 (sole drug mentioned): three-year rolling averages for MDMA and cocaine. Reproduced from (Rogers et al., 2009).

11.3.1 UK

Only in the UK, fatal incidents are systematically recorded in death registers by the UK coroner (Schifano et al., 2003), though unfortunately, toxicological data on the drugs detected post-mortem are not always cited on the death certificate. As the last year prevalence of use in the UK is also known, the risk of MRDs in the UK can be estimated.

Similar data from the General Mortality Register (GMR) (cf. Fig. 1) show that MRDs have increased up to 2001, but to have stabilised thereafter (Rogers et al., 2009). Though MRDs have increased over the last decades, it is important to point out that its use has increased over the last decade, as well (SAMHSA, 2015).

The GMR data further reflect an annual mean number of 17 MRDs in which solely MDMA was involved (cf. Fig. 1) and 33 MRDs per year where co-use of MDMA with other drugs was mentioned (not shown). For heroin, morphine and methadone collectively the annual number was 597 (86% of all drug-related mortalities) (ACMD, 2009). Likewise, the data from the National Programme on Substance Abuse Deaths (np-SAD) cumulatively recorded 495 MRDs (annual mean number of 50 MRDs) between 1997-2006. In 97 out of these 495 MRDs (20%) solely MDMA was involved (annual mean number of 10 MRDs) in the cause of death. However, this does not exclude that MDMA was not relevant in other MRDs. Alcohol was involved in 44% of these 495 cases (Rogers et al., 2009).

Over the period 1997-2007, in total 605 MRDs have been registered in England and Wales of which in only 104 (17%) cases solely MDMA was found in blood, whereas in the majority of the other cases cocaine was also found (Schifano et al., 2010). Since, a 69% decrease in MRDs in England and Wales was found between 2008 and 2012 (Handley & Flanagan, 2014). Across the UK, the incidence of MRDs has increased eightfold in only a short period (from 9 in 2010 to 76 in 2015) with the highest annual numbers found in England and Wales: from 12 in 1993 to 63 in 2016, which represents about one MRD per week (EMCDDA, 2016b; Newcombe, 2017; ONS, 2014). Total MRDs from 1993 to 2016 is 853 with an annual mean of 37 (Handley et al., 2018).

In 2017, in England and Wales, 56 cases out of 3,756 drug-related deaths were MRDs; in 35 MRDs (62%) MDMA was the only substance mentioned on the death certificate (no other drugs, but alcohol may also have been mentioned) (ONS, 2018b). For comparison: the similar figures (no other drugs, but alcohol may also have been mentioned) for deaths related to heroin and morphine, cocaine and amphetamine were 535, 119 and 39 cases, respectively. This corroborates with findings of King and Corkery (King & Corkery, 2010; King & Corkery, 2018) who concluded that, based on an index of toxicity - calculated as the ratio of the number of deaths in England and Wales and availability over the period 2003-2007 - the relative fatal toxicity of MDMA is close to that of amphetamine and cocaine/crack. The last year ecstasy use in 16–59-year-old household residents in England and Wales was 1.7% (around 550,000 users) with the majority of ecstasy users (68%) reported having taken the drug only once or twice a year, 26% more frequently, and 6% had used ecstasy more often than once a month (Home Office, 2018).

11.3.2 Scotland

In Scotland, 27 MRDs were reported in 2017, of which in three cases solely MDMA was involved (NRS, 2018). The number of MRDs in Scotland was 2-3 times higher than in the UK as a whole, although Scotland accounts for only about 8% of the population of the UK (5,373,000 vs. 65,110,000 inhabitants). The annual mean in Scotland was 20 MRDs over the period 2013-2017. The figures for deaths involving heroin and morphine, cocaine, alcohol and amphetamine were 364, 176, 90 and 32, respectively (NRS, 2018). However, it should be noted that the MDMA-category reported in the Scottish data is more broadly defined. The last year prevalence in Scotland in 2014-2015 among household residents (16-59 year-olds) was 1.3% (45,000 users) (ScG, 2016) and almost half of adults (45%) of last year ecstasy users reported that they had used once or twice per year.

11.4 Risk assessment of ecstasy related fatal incidents in the UK

In England and Wales, 56 MRDs were reported in 2017 of which solely MDMA was implicated in 35 cases (ONS, 2018b). Based on 550,000 last-year users of ecstasy, the number of 56 MRDs gives an estimate of 0.01% (one death per 10,000 ecstasy users) per year. Based on two ecstasy sessions per

year (one pill per session), the number of 56 MRDs gives an estimated risk of an MRD of 0.005% (one death per 20,000 ecstasy pills. MDMA was the only substance mentioned on the death certificate (no other drugs, but alcohol may also have been mentioned) in 54% (35 cases) of the MRDs (ONS, 2018b) so that the estimated risk for MDMA alone (per session) is 0.003% (35 / (2 x 550,000)).
In Scotland in 2017, 27 MRDs were reported of which three cases where solely MDMA was involved (NRS, 2018). According to the latest Scottish Crime and Justice Survey 2014/15 (ScG, 2016), nearly half (45%) of last-year ecstasy users (last-year prevalence of 1.3%; 45,000 users 16-59 year-olds) had used ecstasy 1-2 times per year. Based on 45,000 last-year ecstasy users, the estimated risk of an MRD in Scotland is 0.06% (1 per 1,700 users). Based on two ecstasy sessions per year (one pill per session) the number of 27 MRD's gives an estimated risk of MRD of 0.03% (one death per 3,300 ecstasy pills. As in 2017, in only three MRDs solely MDMA was involved (NRS, 2018), the estimated risk for MDMA alone (per session/per pill) is 0.003% (3 / (2 x 45,000)).

Table 9. Risk estimation based on the annual number of MDMA Related Deaths (MRDs) in England/Wales and Scotland (56 and 27, respectively), and the number of last year ecstasy users (550,000 and 45,000, respectively).

	Risk (%)	Risk	Nominator
MRDs			
England/Wales	0.01	1:10,000	Per user
England/Wales [1]	0.005	1:20,000	Per pill
England/Wales; solely MDMA [2]	0.003	1:33,000	Per pill
Scotland	0.06	1:16,600	Per user
Scotland [1]	0.003	1:33,000	Per pill
Scotland ; solely MDMA [2]	0.003	1:33,000	Per pill
Alcohol specific deaths [3]			
England	0.011	1:9,000	Per drinker
Wales	0.014	1:7,400	Per drinker
Scotland	0.021	1:4,900	Per drinker
UK [4]	0.03	1:8,200	Per drinker
UK [5]	0.3	1:820	Per heavy drinker
Other causes			
England/Wales; opiates [6]	0.35	1:285	
UK fatal road accidents [7]	0.036	1:28,000	

[*] RR: relative risk (fold higher risk) as compared with one pill in The Netherlands; [1] based on two sessions yearly where one ecstasy pill is consumed per session; [2] annual number of MRDs involving solely MDMA was 27 and 3 in England/Wales and Scotland, respectively; [3] direct consequence of alcohol misuse, such as alcoholic liver disease (ONS, 2017); [4] 7,697 alcohol specific deaths in 2017 in the UK (ONS, 2018d); [5] in 2017 in the UK, 12% of males and 8% of females was a frequent drinker (those who drank alcohol on at least five days in the week before being interviewed) (ONS, 2018a); [6] 1,164 opiates (heroin and morphine) specific deaths in 2017 in the UK (ONS, 2018c); [7] 1,792 fatal road accidents based on 50 million driving licenses.

11.5 Discussion

Table 9 shows that the risk for a MRD (per session) in the England/Wales and Scotland is 0.005% and 0.003% per pill, respectively. Compared to the fatality rate of heroin and morphine in the UK of 0.35%, the risk for a MRD (per session) in the UK is some 70-100 times lower. As indicated above, alcohol use cannot be well compared with ecstasy use with respect to a fatal outcome, because alcohol-related fatalities mostly result from prolonged excessive drinking (defined as more than 21 glasses per week for men and more than 14 glasses per week for women on the long-term). In the UK, 12% of males and 8% of females was a frequent drinker (ONS, 2018a). For fatalities, the overall risk of frequent/excessive alcohol user is some 12 times higher than the fatality risk of an ecstasy user (10,000/820 in the UK; cf. Table 9). It should be noted that a dose-incident relationship for the

reported MRDs cannot be described due to the lack of relevant data.

11.6 Limitations of this study (applies also to non-fatal incidents)

The risk assessment of non-fatal cases was based on data reported by the MDI. The MDI-data refer to self-report which is liable to bias, whereas shame and confusion in the patient may lead to incorrect and under-reporting (Monshouwer et al., 2016; Vreeker et al., 2017b). Probably, the bias due to shame applies in particular to the relatively innocent incidents, whereas for moderate and severe incidents the patient is (and peers are) more motivated to search medical treatment and to report all details. In addition, when crowded at the treatment facility the pressure may contribute to suboptimal registration of the cases. The pattern of ecstasy use in a variety of ecstasy users was used for the risk estimation per pill. The Dutch Central Bureau of Statistics (CBS) reported a last year and last month prevalence of use of 2.9% and 1.0%, respectively (CBS, 2019), indicating that most users (66%) use ecstasy less often than once per month which fits well within the median value of 4.0 sessions per year as used for present the risk estimation. The prevalence rates of 1-2 sessions per year as reported by the Crime Survey's for the UK (Home Office, 2018; ScG, 2016) reflect the ecstasy use pattern of household residents, not of party goers.

Another limitation may be the poor registration of MRDs in the Netherlands. Once a hospitalised patient does not survive a severe ecstasy intoxication, clinical toxicological diagnostics are immediately stopped for budgetary reasons (no refund from insurance) leaving the cause of death unresolved so that the case is not reported as MRD. A contributing factor here may be that the ToxScreen detects a collection of amphetamine-like drugs and is not specific for MDMA. For severe cases we assumed that the patients are routinely transferred to ED of the main hospital in the region. The coverage of the MDI for the Netherlands was estimated as 50% to 70%. Main reason is that three large academic hospitals (Utrecht, Leiden and Maastricht) did not participate in the MDI monitor.

11.7 Conclusion

Ecstasy use can undoubtedly be harmful and may even be fatal. The main pathophysiological mechanisms contributing to MRD and serious medical complications are hyperthermia, serotonin toxicity, and disturbances in salt and water balance.

Fatalities have been reported where MDMA is the only substance identified by toxicology tests. However, because of patterns of polydrug use among ecstasy users and the highly variable content of pills sold as ecstasy, many ecstasy-related fatalities are attributable to multiple drug toxicity. In other words, even when MDMA is detected post-mortem, one should also consider other contributing factors, especially multiple drug toxicity and pre-existing pathology, before to conclude that MDMA use was the cause of death. Whilst fatalities related to the use of ecstasy attract the attention of the media and the general public, deaths as a direct result of MDMA consumption appear to be relatively rare events given the extent of its use. Nevertheless, ecstasy cannot be considered a benign drug as there is evidence that its use can cause fatalities.

The present assessment results in an estimated risk of any adverse health effect in ecstasy users of about one in 500 pill consumptions. This rate refers to all ecstasy-related incidents, but mild ecstasy intoxications usually resolve after medical treatment via First Aid at the location itself. In contrast, serious incidents require treatment in hospital and/or intensive care (Lameijer et al., 2018). For moderate to serious incidents the estimated risk is one in 2,700 pill consumptions. In the Netherlands, non-fatal ecstasy intoxications are currently not increasing in number. Given its widespread use in the Netherlands, this number is relatively low and similar to the number of non-fatal intoxications due to cocaine.

The data available do not allow to describe a dose-incident relationship for ecstasy. Likely, this is not related to the adverse health effects of ecstasy, but to incomplete registration of ecstasy-related non-fatal incidents. Given the apparent lack of a dose-dependency in both the number of non-fatal and the number of fatal ecstasy-related incidents, the relative risk of one ecstasy pill cannot be compared with that of one alcoholic consumption. One may relate the health risk of overall ecstasy use with that of overall alcohol use (or 'risky' drinking). In absolute numbers, alcohol-related non-fatal incidents are 3-5 times higher than ecstasy-related incidents, but this probably due to the much higher prevalence of alcohol use. Per session of use (ecstasy or alcohol) the difference may be considerably larger.

For fatalities, the risk of an alcohol user cannot be compared with that of an ecstasy user, because alcohol-related fatalities (excluding road accidents) arise predominantly in heavy and long-lasting alcohol users. In contrast, ecstasy-related fatalities result from an acute effect. Moreover, ecstasy is usually consumed only for a limited number of years (some 10 years) in young adulthood.

Ecstasy users are frequently polysubstance users (Office, 2014; Scholey et al., 2004; Wu et al., 2009) which may explain the high proportion (31%) of non-fatal incidents following the combined use of ecstasy and other substances (Lameijer et al., 2018), which proved to be nearly two-fold more serious than the use of ecstasy alone. Like the non-fatal incidents, the number of MRDs is relatively low given its widespread use. Moreover, the fatal risk of ecstasy is substantially lower than those related to other Class A substances, like heroin and cocaine. The rate of ecstasy-related serious incidents and MRDs seems to decrease, but the use of ecstasy still implicates a significant health risk.
Cohort studies are needed that will allow studies of MRDs over time, and direct comparisons of mortality rates for different drug classes.

12 Dependence

12.1 Dependence and tolerance

Probably due to the preference of MDMA to act on the serotonergic system and less on the dopaminergic system, it is comprehensible that the abuse liability of MDMA is low compared to many other substances of abuse. MDMA (0.01-0.56 mg/kg/injection) substitutes for cocaine (0.003-0.3 mg/kg/injection) in baboons and rhesus monkeys trained to self-administer MDMA intravenously (Lile et al., 2005).

Some psychological tolerance has been reported in subjects who use high dose NDMA pills (Parrott, 2005) leading in some users to a consequent need for dose escalation and to develop a compulsive pattern of ecstasy use and taking more pills to get the desired euphoric effect. The subjective and physiological effects produced in humans by the second dose were lower than expected (Farre et al., 2015; Peiro et al., 2013). In contrast to amphetamine and cocaine, ecstasy shows no long-term physical dependence, though some low mood is commonly experienced after withdrawal.

In conclusion, MDMA does seem to have reinforcing properties, and if present anyway they appear to be significantly weaker than those of e.g. cocaine.

12.2 Treatment demand related to ecstasy dependence

Although presentation for treatment of ecstasy use appears relatively uncommon compared to the prevalence of its use in the general population, it does occur though ecstasy use is rarely the primary reason for entering specialised drug treatment. Ecstasy was reported by less than 1% (around 900 cases) of first-time treatment entrants in Europe in 2015 (EMCDDA, 2017) and Australia in 2009 (Roxburgh et al., 2011); in the Netherlands the yearly number of ‘primary’ cases was 110-120 cases (<1% of total first-time treatments) (Alderliefste & Damen, 2018; van Laar et al., 2019). In the UK, the number of first entries for ecstasy abuse is steadily decreasing since 2007-2008 (from around 2,400 to 939 entries in 2017-2018) (NDTMS, 2018). For comparison: this was 4% for amphetamines, 11% for cocaine/crack cocaine and 20% for cannabis (NDTMS, 2018).

12.3 Conclusion

Ecstasy retains little propensity for dependence or withdrawal reactions and a only small number of users seek help through treatment services.

13 Public health risk

13.1 Prevalence of use

13.1.1 World-wide

UNODC estimates that in 2016 the annual global past-year prevalence for ecstasy 0.42% (range: 0.18-0.66%) of the population aged 15-64 yrs. (some 11-28 million users). Western and Central Europe: 0.85% (range: 0.83-0.91%); USA: 0.89% (range: 0.89-0.89%) (UNODC, 2018). In 2016, about 21 million people (aged 15-64 yrs.) have used ecstasy (0.3% of the world population) which compares to the number of people who have used cocaine or amphetamines, but is less than the numbers for cannabis or opioids (UN, 2018).

13.1.2 Europe

In Europe, around 11.5 million Europeans (15–64 years) have tried ecstasy in their lifetime, around 2 million in the last year (Trautmann et al., 2013). The lifetime prevalence of ecstasy among young adults (15-34 yrs.) in Europe varies considerably between countries, from 0.1% to 12.2%, with a weighted European average of 5.7%, whereas last year ecstasy use in this age group ranges from 0.1% to 3.1%, representing about 1.8 million (1.3%) young Europeans (EMCDDA, 2015). It should, however, be noted that the prevalence of ecstasy use among clubbers and visitors of dance and festival events is much higher (up to 75%). Statistical surveys in Europe suggest a continued increasing trend in Europe, with five countries reporting higher estimates than in the previous comparable survey and nine reporting stable estimates (EMCDDA, 2017). For instance, France and Finland report large increases in 2014, whereas in the UK a small decrease was observed by 2015 (EMCDDA, 2017).
In 2016, the prevalence rates of ecstasy-use (%) in young European adults (15-34 yrs.) and adults (15-64 yrs.) was: (a) last year prevalence young adults: 0.3 to 7.4%; (b) in all adults: 0.1 to 3.6%; last month prevalence in young adults: 0.1-2.7%; (c) in all adults: 0.0-1.2% (EMCDDA, 2018b). The highest values were found in The Netherlands.

Table 10. Prevalence of use in some EU countries (van Laar et al., 2019)

Country	Year	15-64 yr.		15-34 yr.	
		Ever (%)	Last year (%)	Ever (%)	Last year (%)
Netherlands	2017	9.4	3.3	15.1	7.1
Ireland	2015	9.2	2.1	14.0	4.4
France	2014	4.2	0.9	6.9	2.3
Spain	2015	3.6	0.6	4.7	1.3
Finland	2014	3.0	1.1	5.6	2.5
Austria	2015	2.9	0.4	4.0	1.1
Norway	2016	2.7	0.6	5.5	1.6
Portugal	2016	0.7	0.1	0.9	0.2
Sweden	2013	-	0.5	-	1.0

13.1.3 USA

The US Monitoring the Future Study showed that in 2017 lifetime use of ecstasy was about 7% (representing 18 million people) and the last year use was 0.9% (NIDA, 2018). People age 18 to 25 years appeared to be the groups with the greatest use, at 3.5%, as found in the 2017 National Survey on Drug Use and Health: Trends in Prevalence of MDMA. To put overall ecstasy use in the US in perspective, in 2010 2.4 million persons (aged > 12 yrs.) currently used cannabis, whereas last month prevalence was 0.9 million (ecstasy), 0.6 million (cocaine) and 0.6 million (stimulants) (SAMHSA, 2011) and about 14.5 million had used ecstasy at least once and 2.4 million at least once in the previous year (SAMHSA, 2012). A national survey in 2014 estimated 609,000 people or 0.2% of the US population aged 12 or older had used ecstasy in the last month, with 6.8% reporting lifetime use (SAMHSA, 2015).

13.1.4 The Netherlands

According to the Health Survey / Lifestyle Monitor of the Dutch Bureau of Statistics (CBS) from 2016

380,000 Dutch people (15 to 65 yrs.) had used in 2014 ecstasy (2.8% of the population ≥18 years) and about 80,000 in the last month (0.6%). Use is highest in the 20-24 year age group (12.8% in 2016). Ever ecstasy use was four times higher among people with an HBO or university degree than low-skilled (4.2% vs. 1.1%) (van der Pol & van Laar, 2016). In 2017, last year prevalence was 2.7% of Dutch adults (370,000); last month use was 0,8% (100,000) (van Laar et al., 2019).
Total annual consumption of ecstasy in the Netherlands range between 4.1 and 5.7 million pills, with point estimates between 5.2 and 4.5 million pills (Trautmann et al., 2013). Frequent users account for 39-49% of these amounts while occasional and infrequent users ('chippers') account for respectively 31-37% and 20-24% (Trautmann et al., 2013). The last measurement of the prevalence of ecstasy use by the Bonger Institute in 2013, showed that past month prevalence was 40% among clubbers and 69% among party visitors. See also User characteristics, paragraph 13.2.
Based on figures from the Tax Information Investigation Service (FIOD), Customs and Police (data about seizures of precursors and drugs, and confiscated drug-related chemicals found in storage and production locations), Tops et al. (Tops et al., 2018) recently estimated that 194 million ecstasy pills are yearly consumed in the Netherlands, though - based on prevalence and user rates - an estimate of eleven million pills (17 times lower) seems to be a more realistic estimate (Peters, 2018b).

13.1.5 UK
The British Crime Survey for 2017/18 showed the last year ecstasy use in 16–59-year-olds in England and Wales was 1.7% (around 550,000 people). In people aged 16-24 years last year ecstasy use peaked to 6.8% in 2001/02, but decreased to 5.1% in 2017/18 (Home Office, 2018). The majority of ecstasy users (68%) reported having taken the drug only once or twice a year rather than frequently, and only 6% had used ecstasy more often than once a month (Home Office, 2018). As expected, the last year prevalence of ecstasy by those who had visited a pub or bar at least nine times in the last month (9%) was 23-fold higher than those who had not visited a pub or bar in the last month, and its prevalence also depended on the frequency of alcohol consumption (days per week): 0.5% (drinking less than once per month) vs. 3.5% (drinking at least 3 days per week) (Home Office, 2018). The last year prevalence in 2014-2015 (16-59 year-olds) was 1.3% in Scotland (ever use was 6.8%) (ScG, 2016) and in 0.8% in Northern Ireland (NACDA, 2016). Just over two fifths of adults (45.5%) of Scottish last year ecstasy users said that they had used once or twice.

13.1.6 Australia
Use of ecstasy in the general population had declined from 3.5% in 2007 to 3% in 2010. In 2010 the majority of Australians who used ecstasy reported using once every few months or less (Roxburgh et al., 2011). In 2017, last six months prevalence of ecstasy use is 10% (ever use 18%) and median days used was 3 (Karlsson & Burns, 2018).

13.2 User characteristics
13.2.1 Type of user
The use of ecstasy is especially popular at clubs, festivals, house parties and within the rave culture (electronic dance-music scene). Ecstasy is highly appreciated by young adults, particularly young males who are relatively high educated and employed. Last prevalence in low, middle educated and high educated Dutch users was in 2017 0.8%, 1.7% and 5.5%, respectively (van Laar et al., 2019). Ecstasy is used less frequently than other stimulants, typically less than once per week; most using ecstasy a few times a year (see Prevalence data, see paragraph 13.1).

13.2.2 Pills used throughout the year
Virtually all last-year ecstasy users (96%) usually use ecstasy only on weekends; the rest 4.0% used both on weekends and on weekdays, and use on average 1.2 pill per event (van Laar et al., 2019).
A somewhat older report from 2012 described the estimated yearly individual consumption of ecstasy pills in the Netherlands (mean value) in a sample of 801 users was 10, 57 and 285 ecstasy pills for infrequent, occasional and frequent users, respectively (Trautmann et al., 2013). The number of ecstasy pills per typical use day for the Netherlands was 2.19 pill (mean value; 2.00 median value; N=1,648) 2.0 pills for infrequent users, 2.4 pills for occasional users and 3.6 pills for frequent users

(Trautmann et al., 2013). Last year users consume 1.2 pill per session (van Laar et al., 2019). However, 'party goers' used an average of 1.8 ecstasy pill per day when 'going out' (Monshouwer et al., 2016; van Laar et al., 2019).
"Het Grote Uitgaansonderzoek 2016" (HGU 2016) showed that 46% of 4,905 young respondents (15 to 35 years old, recruited online who had at least once visited in the past year a party, festival, club or discotheque) had used ecstasy at least once in the past year (Monshouwer et al., 2016). Almost three-quarters (71%) of them turned out to be an "occasional user" who did not use ecstasy more than a few times a year, 18% had used ecstasy once a month and 9% a few times a month. On a day off on which they took ecstasy, that was an average of 1.8 ecstasy pill (Monshouwer et al., 2016). Nine out of ten users mentioned party's and festivals as the main location to use ecstasy, and 71% have used ecstasy multiple times in the last year; 18% used ecstasy once a month and 9% a few times a month. If taken, the average dose was 1.8 pill of ecstasy (Monshouwer et al., 2016). Almost half of Australian ecstasy using festival-goers reported double dropping i.e., consuming two drugs simultaneously, typically two ecstasy pills, at the last festival attended (Grigg et al., 2018).
Previous data also indicated the great popularity of ecstasy among outgoing youngsters: the last year use of ecstasy among frequent party and club visitors was around 60% in 2013 (Goossens et al., 2013). The latest Antenne survey (Nabben et al., 2018) shows that among 'party goers' ecstasy is the most popular substance with 66% last year use (clubbers 68%; festivalgoers 65%). About half of them (45%) used ecstasy 4 times a year; 35% 5010 times and 20% more than 10 times. A quarter (24%) reported that they used ecstasy too often or too many pills. In a more recent online survey performed in 2016 among Dutch adolescents and young adults (N=4,905 aged 15-35 yrs.) who have attended at least once in the last year a party, festival, club or disco showed that almost half of them (46%) have used ecstasy in the last year.
The Global Drug Survey 2015 (Szigeti et al., 2018) reported an average worldwide frequency of 8.0 times per year and an average dose of 1.5 pills per session. These estimates are close to the results of the Dutch Party Panel internet survey from 2016 among 637 'party goers' where an average dose of 1.5 pills per session and a use frequency of 8.8 times per year was found (Peters, 2018a). According to the latest Antenne survey from 2017 among Dutch clubbers/'party goers' , the average number of sessions is even higher, i.e. 9.3 sessions yearly. About half of them (45%) used ecstasy 4 times a year; 35% 10 times a year and 20% more than 10 times a year (Nabben et al., 2018). The proportion of occasional users i.e., those who used ecstasy only 1-2 days per year, was 21%. The median and mean number of days (sessions) ecstasy was used was 8.5 and 5.0, respectively (Nabben et al., 2018). Previous 'Antenne' surveys have been performed among students (Nabben et al., 2017), and visitors of pubs (Benschop et al., 2015) and coffee shops (Nabben et al., 2016) in the Netherlands who had used ecstasy in the last year. The aggregated results showed that about one-third (35-38%) of them were occasional users (1-2 days per year). Across the three groups, the use was on average 1.2 pills of ecstasy per session on 4.0 days per year (median values). The mean number of days ecstasy was used per year was 4.9 (visitors of pubs), 7.5 (students) and 5.4 (visitors of coffee shops).

13.2.3 Polydrug use

Though polydrug use is not unique to ecstasy users, a considerable part of ecstasy users are polydrug users (using multiple substances within a specific time period) (Scholey et al., 2004; Wu et al., 2009). In other words, few individuals use only ecstasy. They often use ecstasy in combination with other substances such as alcohol, cannabis, amphetamine, cocaine and GHB (Doekhie et al., 2010; EMCDDA, 2009).
The 2012 CSEW data show that in the UK ecstasy was commonly taken simultaneously with alcohol almost all of the time (95%) and with other illicit substances about half of the time (49%). Of the other illicit drugs, the most common co-intoxicant was cannabis (64%), followed by cocaine (44%) and amphetamines (18%) (ONS, 2013). In a large Australian sample of regular ecstasy users, 62% said they usually consumed more than five 'standard drinks' (equivalent to more than 6 UK alcohol units) when they took ecstasy (Kinner et al., 2012). However, heavy and frequent ecstasy users are significantly more likely to use other stimulants and psychedelics at higher intensities than lighter ecstasy users (Scholey et al., 2004). See also the section 10 about 'Non-fatal incidents' for reasons of polydrug use.
Virtually all ecstasy users (>98%) also use alcohol with an excess of binge drinking and a variety of

other drugs (Martins et al., 2005; Wu et al., 2006) and 46% of young ecstasy users while holidaying in the international dance resort of Ibiza also used cocaine (Bellis et al., 2003). An explanation for the high prevalence of polydrug use among ecstasy users may be that ecstasy is used to enhance a high from other drugs (e.g., alcohol, cocaine or heroin), to come down from a high on other drugs (e.g., methamphetamine, cocaine or heroin) or that other drugs are used to enhance the ecstasy high or to soften coming down off ecstasy (Boeri et al., 2008).
Finally, ecstasy users, who support healthy behaviour and jog regularly, recently complained that they had no alternative than to consume ecstasy which production is related to environmental pollution due to the dumping of chemical waste generated during MDMA production.

13.3 Availability of the product

Ecstasy is an illegal drug, but well available via Internet and drug dealers (street, clubs and festivals). The seller's home is mentioned most frequently in all European Member States to purchase ecstasy (Trautmann et al., 2013). In the Netherlands, one pill (tablet) costs 3 to 5 euro; € 25 per gram, but prices in Europe vary from €3 to €17. For comparison: in the Netherlands cannabis costs € 10 per gram (€2.50 per joint) and cocaine €40 - €70 per gram. In the UK, the price per tablet in 2016 was GBP 10. The time required to purchase ecstasy in the Netherlands was within one hour for half of users; others required more time (Trautmann et al., 2013). The number of pills usually purchased per occasion was 7-12 pills (Trautmann et al., 2013). In Belgium, 24% of 15- to 24-year-old Belgians were able to buy ecstasy in 2014 reasonably or very easily within 24 hours (EC, 2014).

13.4 Quality of the drug

13.4.1 Introduction

The scheduling of MDMA and MDA has led to a black market where contaminated or falsely represented ecstasy pills (tablets) are distributed. Indeed, ecstasy pills (1) frequently contain substances entirely different from MDMA, (2) the MDMA strength varies widely, and (3) the ecstasy pills are often adulterated and contain compounds that increase morbidity and mortality. Illustrative are the findings of Tanner-Smith (Tanner-Smith, 2006) who reported that overall, 39% of the pills were comprised of MDMA only, 46% only contained substances other than MDMA and 15% were mixtures of MDMA and other substances. According to the Trimbos Institute, the purity of ecstasy is now (2018) almost 98%.

13.4.2 Content of pills and contamination of pills

For instance, an American study analysed pills, collected from events across the United States from 2010 to 2015 and only 60% of the 529 samples collected contained MDMA (Saleemi et al., 2017). Some batches of pills marketed as ecstasy have been found to contain stimulants like caffeine MDA, ephedrine, amphetamine, or hallucinogens, like LSD, ketamine, pentylone, DOM or its 4-bromo analogue DOB (2,5-dimethyl oxy-4-bromoamphetamine) or 2C-B (4-bromo-2, 5-dimethoxyphenethyl amine), MDEA (3,4-methylenedioxyethylamphetamine), MDA (3,4-methylenedioxyamphetamine), or MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine) instead of ecstasy (Winstock & King, 1996). More unusual compounds detected in pills have included atropine, strychnine, metamphetamine and dextromethorphan.
Of the 223 participants, attending large electronic dance music festivals in the US, who indicated use of Ecstasy, Molly and/or MDMA/MDA, MDMA without a novel stimulant was confirmed in the oral fluid of 121 (54.3%) participants, 32% was negative for any psychoactive compound and 28.5% tested positive for MDMA plus at least one novel stimulant, like methylone, ethylone and butylone (Krotulski et al., 2018).
Partly due to the global supply shortage of precursors, like PMK, sassafras oil, isosafrole or piperonal the drugs that are sold as ecstasy contain no MDMA, but instead contain MDPV, mephedrone, methylone, ethylone (EMCDDA, 2015) which give a similar psychedelic effect, but may lead to serious accidents, because they are generally more toxic than MDMA. Occasionally, ecstasy pills contain 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA), other amphetamine derivatives, caffeine, opiates, or painkillers.
Powdered ecstasy ranges from pure MDMA to crushed pills with 30–40% purity or containing no MDMA at all (EMCDDA, 2015). The low content of ecstasy in pills is due to agents that are added to

dilute the drug and increase profits (e.g., lactose) and binding agents. The proportion of MDMA-like impurities and MDMA-content in ecstasy pills varies annually and by country, though the purity has increased since the 1990s.
The impact of increased strength of the pills is yet to be determined. Despite that in 2017 65% of pills on the Dutch market contained > 150 mg, no increase in ecstasy-related incidents were seen (and no MRDs in 2017) in the Netherlands (Lameijer et al., 2018). This corroborates with the latest figures of the Office for National Statistics in the UK covering all drug related deaths registered in 2017 in England and Wales which showed that MRDs fell slightly for the first time since 2010 (ONS, 2018c). The widespread publicity on high-strength ecstasy pills and safer drug use messages (sufficient water drinking and pill testing) may have been a contributing factor for this decrease.
The Netherlands has an efficient “Red Alert” system by which recreational drug users can receive an alert (‘app’) when there are especially dangerous drugs on the market.

13.4.3 Strength of pills

Recreational dose of ecstasy is usually 1-2 pills per event, with most individuals using the drug at weekends once a week or less because tolerance to its positive effects rapidly develops. The normal content of MDMA in a pill should be 60–120 mg to give an optimal effect, but the strength of ecstasy pills have varied over a time.
Since some years the strength of ecstasy pill has dramatically increased which is of concern because such ‘super strength’ ecstasy containing around 2-2.5 times the standard dose per pill (Drugscope, 2014) may lead to unexpected adverse effects which is of concern. Up to 2009, XTC pills contained on average 80-90 mg of MDMA. However, due to stricter legislation and more successful seizures, a shortage of MDMA-precursors arisen. Clandestine producers of MDMA search for alternative precursors of MDMA or simply produced ecstasy pills containing substances other than MDMA. As a result the ecstasy-market was flooded with pills containing either no or little MDMA or were contaminated with by-products. Examples of substances applied instead of MDMA are MCPP, pentylone, mephedrone and various other psychoactive hallucinogenic substances, which induced similar but more unpleasant and even more toxic side effects (Felgate et al., 1998).
In 2010, the quality suddenly turned: ecstasy pills again contained mainly MDMA i.e. the purity of the pills was very high, but the pills were 1.5 to 2 times stronger than before. In 2017, the average strength of ecstasy pills delivered to test centres in the Netherlands was 167 mg MDMA with strength up to 278 mg (a pill of 366 mg MDMA was detected in 2013), and 65% of pills contained more than 150 mg (van der Gouwe & Rigter, 2018) which is of concern. Similar trends are reported in other EU member states (EMCDDA, 2016c; Palmer, 2016; Spadari et al., 2016). The reason to produce such pills with such high strengths remains unclear. High strength pills are no more expensive than conventional pills. Perhaps a proportion of users have indicated they wanted stronger pills. Anyway, the high MDMA content found suggests that producers are having no difficulty acquiring the precursor chemicals necessary to manufacture the drug (EMCDDA, 2017).
Users have meanwhile become aware of the high strength pills so that they start dosing using a third to half of the pill and titrate further till the desired effect is attained. A recent report of GDS showed that more than half of respondents used a test dose when starting a new batch of ecstasy (25% of Dutch respondents) (GDS, 2019).
A risk with the high-purity crystalline product or high dosed pills is the difficulty in estimating the dose, bringing the user in the position that more than the desired amount of MDMA is consumed. Awareness campaigns in the UK have therefore advised to apply the ‘crush–dab–wait’ approach (Frijns & van Laar, 2013).

13.4.4 Adulterants

Notorious adulterants are p-methoxyamphetamine (PMA) and p-methoxy-methamphetamine (PMMA) which are similar in structure to MDMA. PMMA and PMA are widely considered the most dangerous adulterants in ecstasy pills, are substantially more toxic than MDMA (Steele et al., 1992). See also paragraph 13.4.
"Chemists" who manufacture MDMA in clandestine laboratories are usually no professionals and the illicit drugs are commonly produced in suboptimal facilities regarding specialized equipment which do not allow to attain optimal synthesis conditions. This will easily lead to incorrect synthesis and impure

final products i.e. containing toxic contaminants which could partly explain toxic reactions or even fatal incidents following ingestion of ecstasy reported in literature. For instance, according to David Nutt, producers in China started to use anethole as a precursor of MDMA when safrole was restricted by the United Nations in order to reduce the supply of MDMA. However, unfortunately from this precursor PMA is formed, which is much more toxic than MDMA. Other studies of ecstasy purity have been conducted in the past 10 years in the UK (Wood et al., 2011), and the Netherlands (Vogels et al., 2009).

13.5 Availability of proper information about the drug and its use

Harm reduction strategy has mainly focussed to inform users about risks and ways of minimizing risk, whereas the concept to provide illicit drug users with quality testing of their chosen drug is less well developed. To decide whether a pill is safe, users usually rely on the shape and imprinted logo of ecstasy pill they have taken before or word-of-mouth (Duterte et al., 2009). Pill-testing services are, however, a more reliable, legitimate and useful tool to reduce the harm of contaminated pills, because they decrease the consumption of potentially dangerous or unknown substances.
In the Netherlands, the Trimbos Institute provides since 1992 individual drug users with a free testing service to determine the identity and the strength of substance in drug samples. In the Netherlands, as well as in Austria, pill-testing services have received official recognition, but such services have met legal resistance in both the UK (King, 2015) and the US, as due to legislation, event organizers may be held liable for these services (Sullum, 2014).
Note that simple colorimetric tests provide no guarantee that the pill is safe; it only demonstrates that the pill contains XTC, but gives only very limited information of drug purity i.e. many potential contaminants show no positivity in such tests. However, drug testing on parties also use a database of already recognised pills (logo) which assists to identify ecstasy pills that have an unusually high drug content.

13.6 Ways of distribution

Ecstasy is usually purchased at the seller's home, in clubs and at (music) festivals by dealers or friends of the user (Nabben et al., 2018; Trautmann et al., 2013). Only 1% of respondents purchase ecstasy through the internet; the majority of respondents purchased from personal contacts, about half of the ecstasy users said that they were able to obtain the drug within one hour (Frijns & van Laar, 2013). In the Netherlands, ecstasy pills are routinely (44%) purchased by ordering (and delivery) via 'What's app' (Nabben et al., 2018).

13.7 Nature and magnitude of incidents (fatal and non-fatal)

In The Netherlands, the MDI collects data about 70% of incidents related to ecstasy use in The Netherlands. Except for the UK, no systematic data collection is performed. In other countries, EDs occasionally report ecstasy related incidents.

13.8 Risk for public order and safety

No specific ecstasy related risks for public order are anticipated. Ecstasy does not (or seldom) lead to violent behaviour.

13.9 Nuisance for citizens around sales and use

No specific ecstasy related risks for public order with respect to the purchase/sales and use of ecstasy have been reported and are not anticipated.

13.10 Effects on aggression and violence threshold in the user

Considering the empathogenic effects, ecstasy probably facilitates altruism and social behaviour and inhibits violent behaviour. While controlling for confounders, like family history of antisocial behaviour and lifetime psychiatric, alcohol and drug use disorders, ecstasy users in the US were more often engaged in violent and nonviolent crime than non-ecstasy users (Vaughn et al., 2015). This may be related to the concomitant use of other substances, notably including alcohol. For instance, virtually all ecstasy users (>98%) also use alcohol with an excess of binge drinking and a variety of other drugs (Martins et al., 2005; Wu et al., 2006), and polydrug use was highly associated with recent alcohol

abuse or dependence (Wu et al., 2006). Other studies showed low aggression levels in ecstasy users: the users' aggression scores following the use of ecstasy, alcohol and cocaine was 1.5, 2.3 and 3.1, respectively (Parrott, 2013). Some aggression may arise days after ecstasy was used, as following elevated mood on day 1, irritability arises in the comedown period after ecstasy use with few days of relatively low mood with sometimes signs of a clinical depression during the 'mid-week crash' (Curran & Travill, 1997; Parrott & Lasky, 1998). Considering that ecstasy enhances empathy (Parrott, 2013), it seems unlikely that ecstasy users show a high violent crime rate. A recent study of van Amsterdam provided no indications that ecstasy use was related with public violence (van Amsterdam et al., 2019). Case reports of an acute psychosis with aggressive behaviour following ecstasy use have rarely been described (Milas, 2000b).

13.11 Conclusion

Ecstasy does not predispose users to violence and users do not usually present problems for policing.

14 Risk's related to criminal involvement

14.1 Involvement of (organized) crime in production and trafficking

14.1.1 Introduction

The estimated size of the European illicit ecstasy market in 2013 was € 660 million euro (range: € 607 to €723 million) (EMCDDA, 2016d). In contrast to the use of illegal drugs which does not constitute a crime in legal terms, the possession, production and trafficking of MDMA (ecstasy) is illegal. It is obvious that the production and sales of ecstasy is highly profitable. For example, the illegal production cost of ecstasy is between €0.25 and €0.40 per pill (MoJ, 2001), but is sold to the European consumer for €5-10 per pill (EMCDDA, 2016b). Therefore, ecstasy use is linked to crime and there is evidence of the involvement of Dutch, Belgian, German and British organised crime groups (OCGs) in the production and trafficking of ecstasy. In 2016, the market for ecstasy amounts € 0.67 billion yearly (range € 0.61 to 0.72 billion) (EMCDDA, 2016b). The Trimbos Institute estimated in 2006 that seventy percent of the globally seized ecstasy pills (between 110 and 220 million) were of Dutch origin (van Laar et al., 2006).
More recently, Tops et al. (Tops et al., 2018) estimated in 2017 the Dutch share in the market of ecstasy (produced in the Netherlands) amounted 19 billion Euro world-wide (expressed as selling price). Based on an average profit of 15% of the total sales value of the final product related to heroin and cocaine (Kilmer & Reuter, 2009), Tops et al. estimated that (organised) criminals earned around 2.8 billion euro related to the production of ecstasy. Last year the production of ecstasy pills was estimated at one billion ecstasy pills with more than 80% produced for the export (Tops et al., 2018). Tops et al. (Tops et al., 2018) estimated that in 2017 the production in the Netherlands was 972 million MDMA-pills of 157 mg. This estimate was based on seizures of MDMA-precursors in 2017 (cf. Table 11).

Table 11. Estimated MDMA-production and consumption of ecstasy pills in the Netherlands in 2017 (Tops et al., 2018).

PMK seized	29,612 L
20% of total was seized (x 5)	148,060 L
MDMA produced in 2017 (x 1.2)	152,536 kg
Ecstasy pills produced (x 1/0.000157)	971 million ecstasy pills
Share Dutch market according to Tops et al. (20%) [#]	194 million ecstasy pills
Consumption in NL *	1.7 - 2.9 million ecstasy pills (0.4% - 0.7%)

[#] See also paragraph 14.2.1 below; * See paragraph 10.5: 360,000 users with median use days of 4.0 per year (1.2 pills per session) = 1.7 million pills; 360,000 users using 8 days per year = 2.9 million pills (Nabben, 2018).

14.2 Some remarks about Tops' report

14.2.1 Ecstasy use in the Netherlands

In their paper Tops et al. (Tops et al., 2018) estimated (based on "experts", not further documented) the yearly use of 37 million pills (18.5 million on festivals and 18.5 million at home and in pubs). On the basis of 390,000 adult Dutch ecstasy users who take 10 pills per year, Nabben estimated that a maximum of 3.9 million pills is consumed yearly (Nabben, 2018), Peters (Peters, 2018a) estimated the Dutch ecstasy use at 4.7 million pills yearly (8 sessions per year; 1.5 pills per session), while, based on sewage water data, Voogt et al. estimated an annual use of 18 million ecstasy pills in the Netherlands (de Voogt et al., 2018).

14.2.2 Export of ecstasy

Part of the ecstasy pills produced in The Netherlands may be exported to the European countries, as well as, Australia. Last year ecstasy users in 2017 in Europe was 2.6 million (EMCDDA, 2018c) people which would consume yearly in total 2.6 x 5 pills per year = 13 million ecstasy pills. In Australia last year use was 11% (2.5 million users) (Lee, 2019). This gives a consumption of 2.5 x 5 =

12.5 million pills. So, people in the EU plus Australia would consume (maximally !) some 25 million pills yearly.
Note that the ecstasy consumed in the USA and Canada is produced by Canadian illegal networks i.e., not imported from the Netherlands.

14.2.3 Production of MDMA according to Tops et al.
Tops et al. estimated that 29,612 L PMK was seized which would lead to a production in 2017 of 152,536 kg of MDMA, but the volume of 29,612 L PMK seems an overestimation.

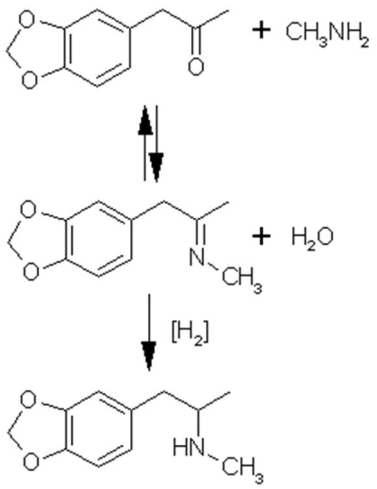
Some preliminary remarks

- PMK and PMK-glycidate are precursors only leading to MDMA
- Mono-methylamine and hydrogen gas are essential chemicals, not precursors
- Bulk chemicals, like starch, calcium carbonate and lactose, are used to produce any tablets (pills) and are unrelated to MDMA.
- 1 kg PMK-glycidaat = 0.75 kg PMK = 0.62 L PMK = 0.82 kg MDMA (= 0.97 kg MDMA HCl salt). This is simply calculated on molecular weight basis i.e., assuming full conversion in the two steps of synthesis. Tops et al. used factor 0.50 to calculate litres of PMK from kilograms of PMK-glycidate (not 0.62 as it should be).
- For MDMA-synthesis: per kg of MDMA one needs 0.16 kg of mono-methylamine.

Synthesis of MDMA

- Step I (imine condensation) is an equimolar reversible imine formation (occurring spontaneously) with a nucleophile (methylamine) reacting with a ketone (PMK)
- Step II (reduction of the imine) a hydrogenation (100 % saturation of the double bond) of the imine using H_2-gas plus catalysator.

In step I, methylamine is commonly used at least in 6-fold excess (1 kg methylamine per kg MDMA).



Reagent	Mol. weight (g/mol)	Density (g/ml)
PMK	177	1.2
PMK-glycidate	236	solid
safrol	162	1.1
Mono-methylamine	31	reactant
Methanol		solvent
Methylamine HCl	67	reactant
Isopropyl alcohol		solvent
MDMA	193	Final product
MDMA HCl salt	230	Final product

Under optimal conditions (in theory):
1 kg of PMK > 1.1 kg MDMA (1.3 kg MDMA HCl) > 1.3 times
1 kg of PMK-glycidate > 0.8 kg MDMA (1.0 kg MDMA HCl) > 1.0 times
1 kg of methylamine HCl > 2.9 kg MDMA (3.4 kg MDMA HCl) > 3.4 times

Under suboptimal conditions (DrugLabs; non-professional clandestine conditions) (Anonymous, 2007; Erowid, 2005):
1 kg PMK (0.833 L) > 0.3 kg MDMA HCl > 0.3 times = 0.25 times for MDMA
1 kg of PMK-glycidate > 0.2 kg MDMA HCl > 0.2 times = 0.17 times for MDMA
Methylamine is routinely used in 6 to 16-fold excess
1 kg methylamine > 1.2 kg MDMA HCl > 1.2 times = 1.00 times for MDMA

Tops et al. estimated that 29,612 L PMK was seized which would lead to a production in 2017 of 152,536 kg of MDMA, but the volume of 29,612 L PMK seems an overestimation.
The following corrections have been made (cf. Table 12):

- 16,946 L PMK (57% of total amount seized) has presumably not been fully converted to MDMA. Almost half (8,500 L PMK) was seized after November 1st, 2017. It is at least doubtful that it will be converted in MDMA in 2017.
- 8,828 L of PMK (52%) was derived from volumes of secondary chemicals (essential chemicals), like mono-methylamine, and simple chemicals suitable to produce the tablets (pills). PMK is a unique and expensive chemical which is only useful in MDMA-synthesis, whereas methylamine is not expensive (€ 1.70 per kg; PMK €1,300 per kg). As such, criminals have methylamine in stock for future production of MDMA, and should not be taken as parameter/predictor of MDMA-production in 2017. Therefore, methylamine was not used as parameter of MDMA production in contrast to the primer precursor PMK.
- Chemical waste should not be used to calculate MDMA production, because the estimates are doubtful i.e., content of MDMA in the solvents are not known and dilution is not known
- Tops et al. used the conversion value of 1.2 to calculate the amount of MDMA from PMK. Presumably, this factor is based on the relative molecular weight of MDMA (193) and PMK (177). However, it is very doubtful that the two steps of the MDMA-synthesis and the subsequent purification (crystallisation of MDMA HCl) is 100% efficient i.e., no loss of MDMA. Considering that MDMA is produced and purified under suboptimal conditions by unqualified chemists, the factor of 0.25 was used as conversion factor (PMK to MDMA HCl) (Anonymous, 2007; Erowid, 2005).

Table 12. Estimation of MDMA-production and consumption of ecstasy pills in the Netherlands in 2017 (Tops et al., 2018), corrected.

	Current estimates (L)	Tops et al. (L)	%
PMK cat 1	1,373	1,373	100
PMK cat 2	376	376	100
PMK cat 3	1,500	1,500	100
PMK cat 4	7,725	16,946	45
PMK cat 5	4,695	9,415	50
Total	15,670	29,612	53
20% of total was seized (x 5)	78,345	148,060	53
Minus 20% seized (no longer available for market)	62,676	127,113	53
MDMA produced in 2017 (x 0.25) *	15,670 kg	152,536 kg	10
Per pill: 157 mg MDMA			
Ecstasy pills produced (x 1/0.000157)	100 million	971 million	10
Share Dutch market according to Tops et al. (20%)	20 million	194 million	10

* Tops et al. used conversion factor 1.2; MDMA HCl is produced, not MDMA free base.

The figure of 971 million pills produced in the Netherlands in 2017 is not a reliable figure. Among

others because of the following case. According to the verdict of the Court of Appeal in 's-Hertogenbosch on 24 April 2015 (RechtNL, 2015), a group of criminals was arrested who had in the period from 1 June 2004 to 30 May 2006 (almost 2 years) produced 3,910 kg MDMA in Hechtel-Eksel (Belgium) and Liessel (The Netherlands). This production relates to 25 million ecstasy pills in two years, 12.5 million per year. This would represent (only) 1.3% of the volume estimated by Tops et al. (971 million), and implicate that some 80 criminal groups with this size of MDMA-production are currently active in The Netherlands which seems doubtful.

- **Anyway, whatever figure is correct, the production of MDMA in the Netherlands is huge and deserves to be tackled with high effort.**

The extent of ecstasy related organised crime is not exactly known, but seems substantial. OCGs are particularly important for ecstasy trafficking in western Europe, notably the UK, Germany, Spain and other countries with large consumer markets. OCGs tend to cooperate internationally with each other and use their common capacities for drug production and share supply channels. For example, groups supplying ecstasy and amphetamine produced in the Netherlands and Belgium are also involved in the cannabis and cocaine market (EMCDDA, 2016b), and illegal synthetic drug production facilities in the Belgian-Dutch border region and Poland are owned by Dutch criminal organizations (Tops et al., 2018).
A limited number of studies indicate a large involvement of Dutch criminal organizations in Belgium (Boerman et al., 2017; KLPD, 2012; Tops et al., 2018). It has been claimed that Dutch criminals are involved in 90% of the production locations in Belgium (KLPD, 2012). Another example is that pre-precursors are imported in Belgium and further exported to the Netherlands (KLPD, 2012).
Figures from the federal police show that the number of offenders with Dutch nationality involved in the production of synthetic drugs increased from 5% in 2012 to 18% in 2017, with the largest increase in 2013 (13%), whereas the share of Belgian offenders seems to be decreasing (De Middeleer et al., 2018). Many suspects of synthetic drug production have antecedents for producing cannabis and often belong to the southern Dutch caravan (gipsy) community (KLPD, 2012). Since 2012, there was an increase in the involvement of outlaw motorcycle gangs in the ATS production (specifically ecstasy, amphetamines and (to a lesser extent) methamphetamines) in the Netherlands (Boerman et al., 2017). Dutch top criminals who are known as leading figures in criminal organizations active in the production of synthetic drugs, also often perform management positions in outlaw motorcycle gangs (Boerman et al., 2017; De Middeleer et al., 2018; Tops et al., 2018).

Illegal activities such as the production and sales of illicit drugs, smuggling and prostitution contribute to the national income of a country. It is difficult to obtain reliable estimates of the size of these activities, but the total contribution of illegal activities to the national income of the Netherlands between 1995-2008 is estimated to have increased from 1.8 billion euro in 1995 to almost 3.5 billion euro in 2008, equalling 0.6% percent of gross national product (GNP). The main illegal sector is drugs, which accounted for over half of the total income from illegal activities in 2001, but it went down in 2008 to less than 40%, whereas finding illegal employment rose from about 10% to 33% in the same period (Kazemierk et al., 2012). A revision of these data in 2010 resulted in an estimate of illegal activities of 2.6 billion euro (0.4% of gross national income) (Rensman, 2010). Cannabis related illegal activities have the largest share with 40% of added value in BNP; prostitution 20%, and hard drugs (heroin, cocaine, ecstasy and amphetamine) 15% (Rensman, 2010). In 2015, the estimates are considerably higher (cf. Table 13). It is not clear why the data of Kamphuis deviates that much from those of Tops who estimated that (organised) criminals earned around 2.8 billion euro related to the production of ecstasy (17 times more) (Tops et al., 2018). Note that the 17-fold difference was also found in Tops et al. estimation of yearly consumed ecstasy pills in the Netherlands (see 11.1)

Table 13. Financial profits of illegal activities in 2015 in euro (source: CBS) (Kamphuis, 2018).

Illegal activity	Amount (million Euro)	Share (% of total)	R
Production, trafficking and sales of ecstasy	160	3.3	1.0
Production, trafficking and sales of cannabis	2,900	60.4	18

Production, trafficking and sales of heroin and cocaine	460	9.6	2.9
Illegal prostitution	393	8.2	2.5
Fencing, the handling of stolen goods	336	7.0	2.1
Illegal temporary employment through employment agencies	300	6.3	1.9
illegal gambling	137	2.9	0.9
Smuggling and sales of illegal cigarettes	104	2.2	0.7
Illegal copying of software, games, movies and music	47	1.0	0.3
Total	4,800	100	-

14.2.4 Different routes of MDMA synthesis and precursors used

Safrole is the key starting material to synthetize MDMA and related drugs. Three other compounds i.e. iso-safrole, piperonal and 3,4-methylenedioxyphenyl-2-propanone (PMK) are precursors of PMK that have been produced starting with safrole. Many illicit syntheses start with PMK and produce racemic MDMA. The four precursors noted above are listed in Table I of the United Nations 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The corresponding EU legislation is set out in Council Regulation (EEC) No 3677/90 (as later amended), which governs trade between the EU and third countries (EMCDDA, 2015).

The simplest method to synthetize MDMA and MDA is from the commercially available ketone PMK as starting compound. The more clandestine synthesis start with safrole (often from sassafras oil) from which PMK is prepared. Obviously, the more steps in the synthesis, the more the volume of waste products (solvents used for purification, reaction by-products formed in each step) which put a heavy burden on the environment. For instance, due to stricter law enforcement the general access to safrole and piperonal has decreased dramatically. Since, piperonal is for instance synthetized from vanilla or piperonal, although this synthesis route results in a more contaminated MDMA as final product (Gallagher et al., 2012). Furthermore, the final product may become contaminated if the intermediate and final products are not adequately purified. As such, the rigorous regulation of PMK and piperonal may have led to a heavier environmental pollution by criminals as - due to global shortage of PMK - they were obligated to use more synthesis steps or apply suboptimal routes in the illegal synthesis of MDMA. See also below ‘Environmental damage’.

14.2.5 Environmental damage

During the production of MDMA and other synthetic drugs a large amount of chemical waste is generated, which is dumped by the producers in a variety of illegal ways. The amount of waste depends on the production method, the substances used and the quality of the production process (van Geffen, 2012). Since the ban of the precursors PMK and BMK, they are no longer imported from China and Russia, but produced in so-called conversion labs. The increase in the amount of waste is partly due to the use of new precursors and pre-precursors, which necessitated an extra step in the production process, requiring more chemicals (Vijlbrief, 2012). Estimates vary, but Europol estimates that for the production of 1 kilo of MDMA, 6 to 10 kilos of liquid waste is released (EMCDDA, 2016a).

Since 2010, the number of MDMA-related dumps or synthetic-drug waste dumping in the Netherlands has increased. In 2010 the national number of dumps was 35, this doubled in 2012 and in 2014 172 dumps were reported. After a small decrease in 2015 (N=161) the increase continued to 206 dumps in 2017 (Schoenmakers et al., 2016; van den Besselaar & van Grootel, 2017; van Laar et al., 2019; van Laar & van Ooyen-Houben, 2016). The southern provinces Brabant and Limburg form the 'epicentre' of illegal dumps. In the period 2010-2014, 56% of the total of 446 registered drug waste dumps was found in North Brabant; Limburg follows with 22% (N=100) of the dumps. At the end of 2018, ten dumps were found within nine days. The figures are probably an underestimation, because not all dumps are detected, not all discovered dumps are reported to or unambiguously registered by the police.

Most of the 446 dumps in the period 2011-2014 were found in the countryside (84%), followed by industrial areas (8%) and residential areas (4%); in the remaining 4% the type of location is unknown. An increasing amount of drug related chemical waste is also found in Belgium. are also produced in Belgium and that more and more drug waste dumping is being found (De Middeleer et al., 2018; Janssen, 2015; van der Wiel, 2016).

Spapens concluded in 2011 that OCGs were able to adapt to some extent to the methods and tactics used by the Dutch police enforcement, but that the main explanation for the continued production of MDMA was that criminal groups are each time replaced by new ones (Spapens, 2011).

14.2.6 Costs of environmental damage

Some drugs such as amphetamine and cocaine, but not MDMA, can be efficiently removed by the water purification plant. The costs of illegal dumping largely depends on the type of dumping (disposed in barrels, directly in the sewer system or in trenches). In Baarle-Nassau (the Netherlands), a waste water purification plant had to be shut down twice because of large drug dumps which costed each time 80,000 to 100,000 euros. Estimated costs vary therefore from €4,000 to €80.000 per dumping. Some municipalities (e.g. Bergen op Zoom, The Netherlands) consider to allow 'criminals' to dump the chemical waste on official waste delivery points for free and anonymously.
Another form of environmental damage occurs in the rainforests in Cambodia which are destroyed to harvest the roots of the rare sassafras tree. Safrole is made from these roots, an important raw material for MDMA (MacKinnon, 2009).

14.2.7 Violence

Conflicts in the underworld are regularly accompanied by brute force, and in recent years criminals have also been more openly opposed to law enforcement officials that manifest in threats and arson of public buildings (e.g. the town hall of Waalre, The Netherlands).

14.2.8 Acquisitive crime

ecstasy users are more likely to be normally employed than users of heroin, cocaine and amphetamine (Rogers et al., 2009) and usually pay their ecstasy purchases from their own income rather than to commit acquisitive crime. At a local level, supply of ecstasy is prominently, though not exclusively, based within the night club and festival environment. For illegal websites in the cyberspace which sell ecstasy, arrests and market closures are hardly effective and produce only temporary results as the digital drug trade is redirected to other sellers and markets (Ladegaard, 2019).

14.3 Other risk factors

14.3.1 Undermining

There is emerging concern about 'undermining' (influencing politics with a criminal intent or the intrusion of the underworld (OCGs) to the upper world). Main activities of criminals who try to infiltrate in the upper world and influence local decision making (processes) are: threatening and bribing of local administrators and civil servants (Struiksma et al., 2017).
Using digital surveys six groups of civil servants were questioned: mayors, aldermen, councillors, civil servants working for public order and security, clerks and municipal secretaries (Struiksma et al., 2017). A total of 11,385 people were approached, of which 3,959 responded. Of mayors, civil servants working for public order and security and aldermen 24%, 12% and 11%, respectively reported they had been threatened by persons with a criminal intent. For example: most of the mayors who had been threatened indicate that they have been threatened once or twice in their current position in the past five years (62%). The rest was more often threatened, most of them up to five times. Drug trafficking (40%) and money laundering (28%) were mentioned most often as cause of threatening mayors and aldermen. Bribery with a criminal intent occurred much less often (1-2%). Of members of the town council, 39% suspect that there was criminal infiltration in their municipality. The number of cases reported by the 3,959 respondents was 237 cases of threat, 40 cases of bribery and 94 cases of infiltration.
Another form of infiltration is 'criminal beneficence' in the form of financial gifts and charity by criminals to gain social respectability and credibility (Bruinsma et al., 2018). In fact, it is an elegant or charming form of bribery.
The interference of the lower world on the upper world also manifests itself through investments of drug profits in real estate and companies. For instance, Dutch criminals started to invest in real estate in Belgium. Already in the nineties, some members of the Amsterdam crime scene (part of them is in the meantime liquidated) settled in a wealthy residential area in Neerpelt (N-Belgium). Investments are also made in commercial projects. For example, criminals recently tried to take over catering

establishments in North Brabant, the Netherlands (van Nimwegen et al., 2017).
In 2016, 476 investigations were carried out into undermining by organized crime where drugs were primarily involved. In 174 cases, this involved synthetic drugs (101 investigations in 2015) (van Laar et al., 2019).

14.3.2 Money laundering

Money laundering is preceded by a form of crime, like drug trafficking. The revenues from drug trafficking and drug sales must be laundered to a large extent. About 80% of these revenues must be laundered, the rest is used to buy precursors or pay the dealers. In the Netherlands drugs and fraud are the most important crimes to trace money laundering and *visa versa*. So, drug trafficking is interwoven with money laundering. It was always difficult to tackle (prosecute) drug criminals through illegal money laundering. However, since 2001, money laundering has been an independent criminal offense in which conviction of a fundamental offense ('gronddelict'), such as drug or human trafficking, is no longer necessary. In other words: for a conviction of money laundering, it is no for example no longer necessary to prove first drug trafficking.
In the past, most investigations by the police into synthetic drugs did not include a financial investigation, so that the criminal property of suspects was not further investigated, nor was the way investigated in which this wealth was put away or laundered.

Table 14. Crime rates 2014-2016 in the Netherlands. Opium law cases registered at the Prosecution (CBS, 2019; van Laar et al., 2019).

Type of crime	2015	2016	2017
Drug crimes	17,880	18,565	15,950
Hard drugs	7,565	7,585	7,015
Soft drugs	9,445	10,110	8,000
Drug crime (other)	870	870	935
Money laundering	570	620	700

Since 2015, the rate of drug crimes have decreased, but more hard drug offenses than soft drug offenses have been recorded. The hard drug crimes usually involve the possession of hard drugs; in the case of soft drug crimes it is usually the cultivation of cannabis (van Laar & van Ooyen-Houben, 2016). Of the 9,613 hard drug delicts registered in 2017 by the prosecution, 210 (2%), 3,185 (33%) and 6,218 (65%) were related to production (mainly synthetic drugs), trafficking (95% related to cocaine) and possession of hard drugs (amphetamines, cocaine and ecstasy, and less so opiates) (van Laar et al., 2019).

15 Current legal status

According to international drug treaties, the selling, possession and use of MDMA is world-wide illegal. Some examples are Australia*:* prohibited (S9), Brazil: prohibited (Class F), Germany: authorized scientific use only (Anlage I), New Zealand: Class B, The Netherlands: List 1, UK: Class A, US: Schedule I, UN: Schedule I.
Chemical analogues of MDMA (e.g. MDA) retaining similar pharmacological properties and pre-precursors of MDMA are illegal, as well.

15.1 International drug treaties

The major goals of the international treaties are to protect public health and societal wellbeing by reducing the harmful use of illicit drugs and to facilitate access to these drugs for medical and scientific purposes. The international drug control treaties include:

a. the Single Convention of 1961 (mainly plants: cannabis, coca and opium)
b. the 1971 Psychotropic Drug Treaty (mainly synthetic psychoactive drugs)
c. the 1972 amendment to the Single Convention
d. the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (mainly precursors)

The 1988 Convention stipulated how the drug control treaties have to be interpreted since 1961; namely, that member states were required to criminalize the possession, use, manufacture and sale of prohibited drugs while allowing for their legitimate use for medical and scientific purposes. Production of scheduled substances for medical and scientific purposes has been supervised by the International Narcotics Control Board (INCB) and its role is to ensure that there were sufficient quantities of these drugs available for medical use while minimizing their diversion for non-medical use. The INCB has also been charged with ensuring the compliance with the treaties and criticized members. For example, the Netherlands for not enforcing criminal penalties for cannabis use and sales; Switzerland for trialling heroin substitution in treatment of opioid dependence; Switzerland, Germany and Australia for the establishment of supervised injection facilities; the legalization of medical and recreational cannabis use in the United States; Bolivia's decision to legalize coca leaf cultivation for traditional use; Uruguay's decision to legalize cannabis (Hall, 2018).

15.2 Human rights

It has been argued that cognitive liberty gives an individual the right to consume illicit substances, except in those cases where it gives a high risk of causing harm to others (Walsh, 2016). Cognitive liberty, or the "right to mental self-determination", is the freedom of an individual to control his or her own mental processes, cognition, and consciousness. Note that cognitive liberty is not a recognized right in any international human rights treaty.

16 Risk assessment and critical considerations

16.1 Dutch ranking study

An expert panel has previously scored the adverse risks of ecstasy. Mean scores for risks given by the Dutch expert panel for ecstasy (MDMA) on a scale from 0 (no risk) to 3 (highest risk) are depicted in Table 15.

Table 15. Mean scores for risks given by the Dutch expert panel for ecstasy (MDMA) on a scale from 0 (no risk) to 3 (highest risk) (van Amsterdam et al., 2010).

	Toxicity	Dependence	Social risk	Total risk
At individual level (user)	1.3	0.6	1.2	1.06
At population level	1.3	0.6	1.1	1.03

Based on these scores, the overall harm of ecstasy was substantially lower than that of cannabis, ketamine and GHB. Similar results were obtained by Nutt et al.

16.2 Commission Garretsen

In 2011, the 'Expertcommissie Lijstensystematiek Opiumwet' (ELO; 'Commission Garretsen') advised the minister of Justice and the Minister of Health, Welfare and Sport, to maintain listing XTC on List 1 (i.e. classifying MDMA as a hard drug) (ELO, 2011). The argumentation was as follows: "As regards MDMA, better known as XTC, the committee concludes that investigations show that damage to the health of the individual in the long term is less serious than was initially assumed. But the extent of the illegal production and involvement of organised crime leads to damage to society, including damage to the image of the Netherlands abroad. This argues in favour of maintaining MDMA on List 1."

The "precautionary principle" suggests that, in the absence of knowing for certain, "experts" should argue that ecstasy be avoided. However, there is a large amount of evidence indicating that ecstasy is not leading to dramatic health damage or loss of lives. Under laboratory conditions, single-dose administrations of MDMA (75 or 125 mg) are safe with 'good drug effects' and little acute and subacute adverse effects in 166 healthy subjects, e.g. body temperature >38°C in only 19% of the subjects (Vizeli & Liechti, 2017). Under similar conditions, low doses of MDMA had little effect, whereas moderate doses increased body temperature by around +0.4°C, and higher doses caused a mean increase of +0.7°C (Parrott, 2012). On the other hand, ecstasy used as a party drug is not quite an innocent drug (cf. paragraph about incidents).
It is not known what impact, if any, the classification of MDMA as Class A has on criminal activity. Downgrading of MDMA to a lower risk class would reduce the maximum sentence for possession, production or supply. However, in Amsterdam possession of five or less ecstasy pills is not prosecuted. Separation of MDMA from other Class A drugs in the UK (and elsewhere) could have health and societal benefits through separating drug markets and reducing 'one-stop-shop' drug dealers that encourage heroin and crack cocaine/cocaine use has been suggested, but is not certain.

16.3 Other countries

A popular statement is that governments should consider international examples such as Portugal and Switzerland, which have used decriminalisation in combination with law enforcement measures as efficient policy in drug regulation. Internationally, there have been in the past some calls in various countries to regulate MDMA.
In 2015, a Melbourne pharmacist (Joshua Donelly) and a leading doctor (Prof. David Penington) proposed that Australians should be able to purchase ecstasy in their local pharmacy to curtail the harm caused by contaminated black-market pills (Donelly, 2015). This has been advocated before on the 2nd Australia21 roundtable on Illicit drugs in 2012 (Douglas et al., 2012) and in New Zealand in 2015 (SMC, 2015).
In Canada, Perry Kendall, B.C.'s top health official, asserted in 2015 that the risks of ecstasy are overblown, and that its lethal dangers only arise when the man-made chemical is polluted by money-

hungry gangs who cook it up. That's why the chief provincial health officer is suggesting the risks of black market ecstasy could be mitigated, for example if it were legalized and potentially sold through licensed, government-run stores where the product is strictly regulated from assembly line to check-out. According to Kendall: “And if it (ecstasy) were to be regulated for recreational use, then it certainly should be strictly controlled and one hypothetical mechanism might be like we use for liquor stores, only I would suggest it would need be stricter and more stringent than we currently have for liquor stores." (Stafford, 2012).

In 2009 the UK government’s Advisory Committee on the Misuse of Drugs (ACMD) was asked to provide a report about Ecstasy/MDMA. After consulting with experts in the fields of medicine, neuroscience and the criminal justice service, the ACMD concluded that Ecstasy/MDMA would be more appropriately placed in Class B, rather than Class A (Nutt, 2009b). Despite these recommendations being made after extensive examination of peer-reviewed evidence the then Home Secretary disregarded the advice, saying to change the drug’s classifications would be to “send the wrong message”.

In the UK, regulation of ecstasy is also a topic of interest. For example see the website of The Independent dated 2015 (Saul, 2015). Using a scientific rationale, the British government's former top drug adviser, Prof. David Nutt, claimed that taking ecstasy was likely to be safer than horse riding (Nutt, 2009a). Steve Rolles of the Transform Drug Policy Foundation advocated a pharmacy model for ecstasy in 2009 (Rolles, 2009).

17 Economic costs

17.1 Burden for industry

Legal chemical companies suffer from the higher bureaucratic burdens that are being introduced to regulate raw materials from MDMA more strictly.

17.2 Estimations in the Netherlands

In the Netherlands, no budget is associated with the drug policy documents and there is no review of executed expenditures. In 2006, the results of a study that aimed to estimate overall drug-related public expenditures in the Netherlands was published (Rigter, 2006). This study estimated that in 2003 total drug-related public expenditures represented 0.5% of gross domestic product (GDP). Most of the expenditures were attributed to law enforcement (75%) and the remainder to treatment (13%), harm reduction (10%) and prevention (2%). The total drug policy spending estimate in 2003 in the Netherlands was 2,185 million Euros. Allocation to functions amounted to 42 million Euros for prevention, 278 million for treatment, 220 million for harm reduction and 1,646 million for enforcement (Rigter, 2006).

17.3 Estimations international

Legalising cannabis in the UK would raise taxes worth hundreds of millions of pounds and produce large savings for the criminal justice system, a private analysis for the Treasury has concluded (Morris, 2015). The research drew heavily on a study by the Institute for Social and Economic Research (ISER) at the University of Essex, which calculated an annual windfall of between £500m and £800m to the Treasury if cannabis was treated in the same way as tobacco.
The department of Economic and Financial Affaires agreed that regulating and taxing cannabis had the potential to generate notable tax revenue of € 450-700 million.

It pointed to research concluding that legalisation could have a small impact on the NHS costs. The research speculated on a range of outcomes between a saving for the health service of € 14 million and a cost of € 112 million.

- € 16 million to the police
- € 21 million to the courts
- € 8 million in community sentences
- € 2.6 million to the probation service
- € 2 million to prisons

However, any extra spending is likely to be outweighed by annual savings of between € 48 million and € 128 million to the criminal justice system, the Treasury said. If people were no longer charge for possession of cannabis, there would savings of € 16 million to the police, € 24 million to the courts, € 8 million in community sentences, € 2.6 million to the probation service and € 2 million to prisons. It also suggested that the cost of dealing with more serious drugs offences would drop as users switched to the legal market.

18 Reputation damage

In the second half of the nineties, when exports of ecstasy to the United States only seemed to increase (in 2000, it was claimed that 80% of ecstasy pills seized in the US originated from The Netherlands), the American authorities revolted. They even threatened at the end of 2000 to put the Netherlands on a black list. Prime Minister Kok was furious and immediately summoned the top of the public prosecutor's office and the police to demand measures. From that moment on, the detection went at full speed to combat the spread of illicit drugs, including ecstasy. The note “Samenspannen tegen xtc”, containing a strategic plan, appeared in May 2001 and was a direct result of serious threats from the US. By far the largest part of the financial means (€205 million) (TK, 2001) went to activities against drug trafficking. Thanks to this and other Dutch initiatives from 2001-2006, the relationship with the US improved, so that the Netherlands disappeared from the 'Majors List' (a list of the most important countries from where drugs are smuggled to the US). Countries on this list are at risk of (economic) sanctions (Neve et al., 2007).

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