Literature Review and Assessment Report on MDMA / Ecstasy

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Contents

Executive Summary

This paper reviews the international and New Zealand literature on the evidence on the risk of harm associated with 3,4, methylenedioxymethamphetamine [MDMA], an amphetamine-type stimulant (ATS). The information presented addresses the criteria which the Expert Advisory Committee on Drugs [EACD] must take account of when considering the appropriate classification of a substance, under section 4B of the Misuse of Drugs Act 1975.

The use of MDMA is undoubtedly harmful. High doses and context of use (i.e. where heat, excessive continued physical activity, lack of water or over-re-hydration occur) may result in death. Nonetheless, fatalities are low given the relatively high prevalence in New Zealand. As context is particularly relevant in mediating MDMA-related harm, risks may be minimised by adopting remedial measures, e.g. appropriate re-hydration.

While there are some acute adverse events requiring presentation and admission to hospital following ingestion of 'ecstasy', New Zealand data do not indicate an increase in hospital presentations and admissions. However, neither do data presently differentiate between different ATS's, thus specific details are difficult to track.

The evidence of ecstasy abuse and dependence is limited, despite increased lifetime and last year prevalence. Ecstasy users rarely present in drug treatment with ecstasy as their primary substance use problem. Nonetheless, dependence and abuse issues may be masked by a propensity for polydrug use. A significant proportion of frequent ecstasy users drive under the influence of ecstasy.

There is little consistent evidence for severe, chronic negative effects of MDMA, particularly in casual, infrequent users or abstinent former users. There is, however, evidence of small deficits, i.e. in relation to verbal memory, even at a low dose. As ecstasy has been prevalent in New Zealand for a relatively short time, long-term negative effects cannot be discounted.

Ecstasy use is not generally associated with public disorder, violence or risky behaviour, i.e. not to the level associated with alcohol, amphetamine and other stimulants, e.g. methamphetamine ('P').

Ecstasy is associated with illegal activities, organized crime and criminal groups. Hence it is coupled with a range of secondary harms, e.g. risk of marketplace-violence, criminal conviction, poisoning from contaminated pills. These may be exacerbated by barriers to harm reduction information / practices, e.g. pill content testing and information for consumers.

Literature and research on ecstasy in New Zealand are under-developed. Quantitative and survey data predominate, particularly regarding prevalence and use patterns. There is inconsistent collection of ecstasy-specific hospital, and abuse / dependence data. There is very little qualitative research.

Introduction

This review will follow the convention adopted by the Ministry's review of MDMA for the EACD (Ministry of Health, 2003). Thus a distinction is drawn between studies in which it is known that MDMA (i.e. methylenedioxymethamphetamine or N-methyl-3,4-methylenedioxyphenylisopropylamine) was administered, and data concerning the use of 'ecstasy'. The latter term is reserved for street drugs, which are accepted to be frequently of unknown composition. As Holland (2001.) observes, all illegal substances are of unknown chemical makeup and purity. Consequently, the purchase of Ecstasy, whether at a dance party or from a dealer or under other circumstances, precludes the possibility of knowing the exact nature of the substance, thereby increasing the risk of harm.

Readers of the present review may wish to bear this distinction in mind. The literature discussed is varied, drawing on clinical, scientific research and observations of the effects of MDMA in laboratory settings, as well as on survey data and anecdotal observations of the consequences of the use and effects of Ecstasy in recreational drug use contexts. As research on the latter suggests, there is both considerable variation in the content and purity of ecstasy (e.g. Camilleri & Caldicott, 2005) and on users' knowledge of determining the content of what they have purchased and how it will affect them (e.g. Johnston et al., 2006). Thus in actuality 'ecstasy' (as opposed to MDMA) may be seen more as a concept than as a specific or discrete substance. In this sense it becomes a product or brand in the drug market place, with its users as making choices aligned with lifestyle (e.g. the dance party scene, music, clothes) as much as with experiencing or desiring a specific drug effect (e.g. Rhodes et al., 2003; Furlong & Cartmel, 1997).

This ambiguity, however, is not restricted to research on the marketplace and illegal purchase. Data produced through controlled scientific research are similarly ambiguous, with various scientists, researchers and physicians holding differing and often opposing views on issues as diverse as neurotoxicity (e.g. Baggott & Mendelson, 2002; Ricaurte et al., 2000) and the politics of therapeutic use (e.g. Sessa & Nutt, 2007).

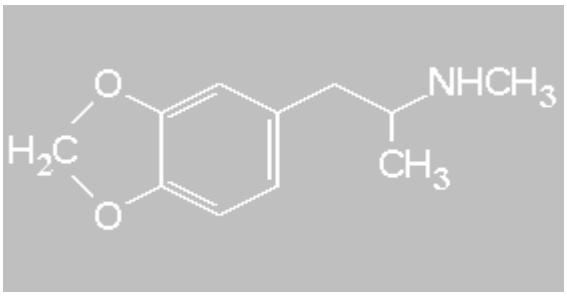
The present review aims to place the major data streams concerning 'ecstasy' (both international and domestic) in the context of risks and harms. Alternatively, one might take a leaf from Holland's (2001) treatise, thus describing what follows as an assessment of the literature concerning the 'risks and benefits of MDMA'.

1.0 Substance identification, mechanism of action and production

The following information and diagram previously reported to the EACD (Ministry of Health, 2003) provides a convenient starting point for this section.

MDMA ($C_{11}H_{15}NO_2$) is an N-methyl analogue of the 'parent' compound MDA (3,4-methylenedixoyamphetamine). Its chemical structure is shown in Figure 1. In its base form, MDMA is a white, musty-smelling oil, with a searing, bitter taste.

Figure 1: Chemical structure of MDMA



There are a number of unknowns about MDMA, for example its precise LD50 (i.e. the lethal dose by which 50% of those administered it are killed),[1] whether it is excreted in breast milk (Toxinz Poisons Information, 2009) and even its full mechanism of action. Concerning lethality, in lieu of a specific LD50, Gable (2004) proposes a dose of 2g / kilo, for an average 70 kg human, having no previous tolerance, with a range of lethal dose as between 150-1250g for an adult. By dividing the latter by the 'effective dose', he extrapolates a measure of lethality, which is then comparable with other substances. This yields an index of lethality for various substances, with lethality increasing as the figure decreases. In this example he proposes figures for Heroin (6), Alcohol (10), Methamphetamine (10), Cocaine (15) and MDMA (16).

Regarding MDMA's mechanism of action, Fleckenstein et al., (2007) comment that despite the lack of clarity it is generally considered that the primary relevant pharmacological characteristic of the drug is its affinity for serotonin reuptake transporters (SERTs), which are protein pumps on the axon's (thread-like extension of the nerve cell) cell wall, i.e. part of the serotonergic neuron. These remove serotonin from the synapse to be recycled or stored for later use. MDMA inhibits the reuptake of serotonin into this pump, along with reversing the action of the transporter so that it begins pumping serotonin into the synapse from inside the cell.

While the serotonin system is primarily impacted upon, levels of the neurotransmitter dopamine are also increased because the MDMA molecule fits into the dopamine reuptake transporters, reducing clearance of synaptic dopamine. Moreover, high

[1] For obvious reasons this is not known for humans, thus comparisons are made with animal models and known dosage regimes. For a useful comparative table see R.S. Gable, (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction, 99*, pp 689-90.

serotonin levels also trigger release of additional dopamine. The elevated synaptic dopamine levels produce a speedy feeling, and the sense of imminent anxiety (Thomas, 2002).

MDMA's unusual empathic/entactogenic (i.e. 'to touch within'; Nichols, 1986) effects have been hypothesized to be at least partly the result of the release of oxytocin (McGregor et al 2008; see also Young, 2007). Oxytocin is a hormone commonly released following such events as orgasm and childbirth, which is thought to facilitate bonding and the establishment of trust. It is proposed that MDMA causes this release by indirectly stimulating 5-HT1A receptors, with evidence derived from studies conducted on rats (McGregor, Ibid.).

The Ministry's previous report to the EACD (Ministry of Health, 2003) noted the multistage production process of MDMA, including the requirement of a full laboratory set-up and that the process is considerably more complicated than methamphetamine production, with a level of laboratory experience required (National Drug Intelligence Center [NDIC], 2000). Although there are more than 20 chemical recipes for MDMA, clandestine laboratory operators commonly use only seven methods—misreported as 'only one' by the previous review (Ministry of Health, 2003:2)—of which six use safrole or isosafrole as precursor chemicals; the other uses piperonal (NDIC, Ibid.). Safrole, extracted from the root-bark or the fruit of sassafras plants, is a colourless or slightly yellow oil, and is the primary precursor for all manufacture of MDMA. Numerous synthetic methods are described in the literature to convert it into MDMA via different intermediates (Milhazes et al., 2007).

In a successful production process, the resulting MDMA is a nearly 100 percent pure powder with a distinctive licorice scent (NDIC, Ibid.). The powder is pressed into pills with identifying designs or symbols, such as marketing logos or other images from popular culture, which may imply a degree of standardization or quality (Schloenhardt, 2007). However, these tablets often contain adulterants, diluents, other psychoactive substances (e.g. MDA, methylamphetamine, ketamine, BZP) and varying amounts of MDMA (Australian Crime Commission [ACC], 2009). Thus there is the potential for considerable variation in pill content, including purity. For example an Australian study reported 68% of pills tested at a rave (outdoor dance party) and 89% of pills submitted to police over a six-month period contained MDMA (Camilleri & Caldicott, 2005; see section 2.4.5 for further details).

MDMA is related to both the amphetamine family of psychostimulants, and to the hallucinogen mescaline (Budavari et al., 1996; Eisner, 1994).[2] Although most often identified as a hallucinogenic stimulant or amphetamine-type stimulant (ATS), some have argued that the drug's unique pharmacological profile justifies its own classification as an "entactogen" (see above; Nichols, 1986). Though reference to MDMA's hallucinogenic qualities / categorization is common (e.g. Ministry of Health, 2003; Schloenhardt, 2007; Toxinz Poisons Information, 2009), other sources dispute this characteristic, arguing instead that hallucinations are not *typically* associated with 'ecstasy' (e.g. Shulgin and Nichols, 1978; Liester et al., 1992; Green et al., 2003), but rather manifest as a rare negative side effect. The latter view was

[2] For a detailed description of MDMA's family tree see B. Eisner, (1994). *Ecstasy: The MDMA Story* (2nd ed.). Berkeley: Ronin Publishing, Inc. Appendix I, pp 139-161.

adopted by the recent United Kingdom review of MDMA / 'ecstasy' (Advisory Council on the Misuse of Drugs [ACMD], 2009).

As the previous report to the EACD noted (Ministry of Health, 2003) MDMA is sometimes confused with related chemical compounds, such as ethylenedioxymethamphetamine (EVE) and dioxymethylamphetamine (DMA) (Sweetman 2002). The *Australian Standard Classification of Drugs of Concern* also notes MDMA is closely related chemically to phenethylamines like 4-bromo-2,5-dimethoxyamphetamine (DOB), 2,5-dimethoxy-4-methylamphetamine [DOM], 3,4-methylenedioxyethylamphetamine (MDEA), paramethoxyamphetaminamine (PMA) and trimethoxyamphetamine (TMA) (refer also to ACC, 2009).

1.1 Current Classification

MDMA is currently classified as a Class B controlled drug under Part 1 of the Second Schedule of the Misuse of Drugs Act 1975. Previously it was in Class B, Part 2, with classification being revised following the EACD's recommendation to the Minister in 2004.

2.0 Overview and Analysis of International Literature on MDMA/Ecstasy

This section considers the international literature on MDMA/Ecstasy, commencing with a brief description of its early history. This is followed by a discussion of patterns of use, specific effects, public health risks, contemporary research aligned with therapeutic value, risk of mortality, potential for dependence and international experiences concerning legal classification.

The medical and therapeutic uses of MDMA are then examined, given their initial overlap with its recent history (i.e. 1970-1984). Following this epidemiological data on recreational use and those generated by enforcement agencies via seizure statistics and intelligence reports are discussed. The section concludes with a general consideration of drug effects (e.g. pharmacological, psychoactive, toxicological) and a specific assessment of harms and risks.

2.1 History

MDMA was first synthesized in 1912 by chemist Anton Kollisch, working for German pharmaceutical company Merck. Although the common myth is that the company was looking for appetite suppressants, in fact it was aiming to develop haemostatic substances (i.e. to stop abdominal bleeding) and wanting to evade an existing patent for the compound hydrastinine. As such, MDMA was an intermediate compound, its discovery essentially an accident on the route to methylhydrastinine, with Merck not interested in its properties (Freudenmann et al., 2006). On December 24, 1912 Merck filed two patent applications that described the synthesis of MDMA and its subsequent conversion to methylhydrastinine (Wikipedia, April, 2009). Received in 1914, the patent has subsequently expired, which means MDMA can no

longer be patented (Holland, 2001; ACMD, 2009). The latter also notes that MDA (methylenedioxyamphetamine, and analog and metabolite of MDMA) was patented by Smith Kline French and tested on humans as an appetite suppressant in 1958, although subsequently abandoned due to its psychoactive properties. She suggests this is the likely source of the myth regarding MDMA's original application (Holland, Ibid.).

Little work was done on MDMA between 1912 and 1953 with Holland (Ibid.) noting it only appears twice in the literature during that time, the first in 1927 when Merck's chemists were evaluating adrenaline-like substances in safrole, an MDMA precursor (Freudenmann et al., 2006). In 1953 the US Army Chemical Center funded secret behavioural and toxicological testing of psychotropics, including MDMA, in search of 'brainwashing' weapons. Performed at the University of Michigan using animals, these were declassified in 1969 and published in 1973 (Hardman et al., 1973; Holland, 2001; Wikipedia, 2009, April [Holland misreports the first author as 'Hartman']). Holland (2001) notes the earlier recreational use of MDA (circa mid-1960's amongst the San Franciscan hippy subculture) and the death, in 1952, of a human subject through inadvertent overdose, during a study of MDA conducted at the New York State Psychiatric Institute.

MDMA followed its analog cousin into the streets in the early 1970s after the US criminalisation of MDA in 1970, the first confirmed sample being seized and identified by Chicago Police that year (Sreenivasan, 1972). In the mid-1970s, research biochemist Alexander Shulgin learned of MDMA's unusual effects from his students, one reportedly overcoming his stutter as a result of use. Intrigued, Shulgin re-synthesized MDMA in 1976 (having first done so in 1965—other sources including Wikipedia [2009, April] propose the later date, 1976) and tried it himself (Shulgin & Shulgin, 1991). He and colleague David Nichols subsequently produced the first published study on the drug's psychotropic effect in humans. They described an "altered state of consciousness with emotional and sensual overtones" that can be compared "to marijuana, to psilocybin devoid of the hallucinatory component" (Shulgin & Nichols, 1978).

2.1.1 Early Therapeutic Use

Shulgin's interest in MDMA, including its therapeutic value, increased. He began sharing his knowledge with friends, among whom, were a number of professional therapists. One of these, psychotherapist Leo Zeff, had used psychedelics in his practice. Zeff developed such enthusiasm for MDMA that he came out of his semi-retirement to promote its use. He subsequently traveled widely, both around the US and occasionally to Europe, training other psychotherapists in its use (Shulgin & Nichols, Ibid.; Bennett, 2005). Among underground psychotherapists, MDMA developed a reputation for enhancing communication during clinical sessions, reducing patients' psychological defenses, and increasing capacity for therapeutic introspection. Coupled with the drug's relatively short duration of action, for many it was considered the ideal tool in standard therapeutic practice (Grinspoon & Bakalar, 1986; Adamson & Metzner, 1988). Prior to its criminalisation in the mid 1980's, anecdotal reports suggested up to 4000 therapists in the United States had been

introduced to MDMA through Zeff and colleagues (Shulgin & Shulgin, 1991; Sessa, 2007) and that many of these had achieved successful results (Stolaroff, 2004).

Eisner (1994) notes that despite therapists' belief in its efficacy, there was concern that attention might be drawn to MDMA, and fear this would increase the likelihood of criminalisation, blocking further research. Thus, while many held strongly positive views of its therapeutic efficacy (e.g. Beck 1986), very little research, and no rigorously controlled trials were ever conducted to examine MDMA's therapeutic potential before it was criminalised. This latter event occurred with a rapid increase in recreational MDMA use, particularly in Texas in the early 1980's, resulting in the emergency classifying of the drug in Schedule 1 (alongside heroin and cocaine) by the DEA in 1985, with the scheduling confirmed in 1988 (TheDea.org, 2003).

Despite continued illegal use by some therapists, there was a hiatus in legal MDMA human research until Charles Grob initiated an ascending-dose safety study in healthy volunteers (Liester et al., 1992). Subsequent legally approved MDMA studies in humans have included research in the U.S. in Detroit (Wayne State University), Chicago (University of Chicago), San Francisco (UCSF and California Pacific Medical Center), Baltimore (NIDA-NIH Intramural Program), and South Carolina, as well as in Switzerland (University Hospital of Psychiatry, Zürich), the Netherlands (Maastricht University), and Spain (Universitat Autònoma de Barcelona) (Multidisciplinary Association for Psychedelic Studies [MAPS], 2009; see section 2.5.1 for further details)

2.2 Patterns of use and abuse

International data suggest that the use of 'ecstasy' is considered broadly recreational by users, rather than as a drug of dependence or daily use (Measham et al., 2001; Measham, 2004). However, one of the confounders in determining specific patterns of use for ecstasy is that users commonly also take other drugs simultaneously. This phenomenon of polydrug use is fruquently reported, for example in Canada (Gross et al., 2002), Portugal (Palha & Esteves, 2008), the U.K. (Riley et al., 2001), Germany (Daumann et al., 2004) and Brazil (Dalgalarrondo et al., 2004). The latter contextualized use inversely against religious affiliation (i.e. the greater the religious affiliation, the less likely individuals were to use substances and to polydrug use). Polydrug use also has implications for determining evidence of neurotoxicity and cognitive dysfunction, both phenomena said to be associated with MDMA use (Gouzoulis-Mayfrank & Daumann, 2006). These and other issues (e.g. the implications of specific drug synergies with MDMA; Daumann et al., 2004) are discussed below (see section 2.3.2.3).

Nonetheless, in experienced users a tendency to increased dosage has been noted (Parrott, 2005), along with increasing use of certain other drugs, particularly hallucinogens and other stimulants (e.g. LSD, psilocybin, cocaine) as opposed to non-stimulants like alcohol and cannabis. Hence there are implications for tolerance and cross-tolerance (Scholey et al., 2004). In the latter study, comparing novice ecstasy users (used 1-9 times) with moderate users (10-99 times) and heavy users (+100 times) the heavy user group took significantly more ecstasy tablets on each occasion. A confounder, however, concerns pill purity, with the suggestion that increasing use

per occasion may reflect higher rates of adulteration of illegally purchased tablets, something evidence from the U.K. suggests is a more recent phenomenon. Thus, to achieve the desired effect more pills per occasion are required (Forensic Science Service, 2008a & b; see also Dalgarno, Appendix IV).

Having noted the general tendency to non-daily use and the difficulties posed by polydrug use for determining effects specifically attributable to ecstasy, there is clinical evidence of tolerance for some of the psychological actions of MDMA. In considering animal models, which support the notion of tolerance, there is evidence that rats exposed to high doses of MDMA show temporary tolerance to serotonin-releasing and behavioural stimulant effects of subsequent doses of MDMA (Baumann et al., 2008; Brennan & Schenk, 2006).

Further issues concerning abusive patterns of use involve specific contexts of use, for example, in association with sexual activity and with driving. Regarding the former, there is evidence for the inappropriate use of MDMA during sexual activity (Palha & Esteves, 2008), with these authors noting its employment as a sexual aid, but that chronic use has the potential for deteriorating sexual function, as well as exposing users to risky sexual practices including sexually-transmitted disease and unwanted pregnancy.

There is equivocal evidence of MDMA's effects on driving, with both improvements and impairments associated observed (e.g. Kuypers et al., 2006; Kuypers & Ramaekers, 2008). In the U.K., however, cases of MDMA-impaired driving are reportedly rare (Association of Chief Police Officers, 2008). In a U.S study (Cottler et al., 2001) use in dangerous circumstances (including driving and operating machinery) was the most commonly reported abuse criterion according to the DSM-IV (45% of users). However, it was also the least reliably reported symptom (k= 0.37). (Driving is discussed in greater detail below; see sections 2.3.2.3 and 3.2.2.2).

The above notwithstanding, epidemiological and police seizure data from the UK indicate that despite ready availability of ecstasy in the illegal market and falling prices (e.g. Schifano et al., 2006), use has remained relatively stable since 1996 (British Crime Survey, 2008).

2.3 Specific Effects / Physical harms

This section covers acute and lingering subjective effects as reported by users, as well as clinically assessed effects and negative side effects. In general, effects are numerous and varied, relating to both direct toxicity—including death resulting from a single tablet (Rogers et al., 2009)—and with behaviours contextualising use, such as energetic dancing for long periods. Ecstasy-related presentations to Emergency Departments are typically associated with polydrug use. For example, U.K. data suggest 80% are associated with alcohol, 24% with cocaine and 21% with ketamine (Dargan, 2008, in ACMD, 2009).

2.3.1 Acute Effects

One means of defining MDMA's acute effects is to divide them into positive and negative, with further divisions between affective states (e.g. euphoria / dysphoria) and physiological events, and degrees of severity.

2.3.1.1 Positive subjective effects

The sought-after psychotropic effects are generally consistent and predictable amongst users, being noted within 30-60 minutes of ingestion, reaching a plateau lasting 4-6 hours and concluding with a 'comedown' period of several hours. This latter may involve fatigue and other minor effects, some of which might last up to a few days. A composite of these effects, self-reported by users at the following dance / rave cultural internet sites (TheDea.org, 2003; The Vaults of Erowid, 2009; DanceSafe, 2009) includes the following:

- euphoria;
- decreased hostility and insecurity;
- increased feelings of intimacy with others;
- feelings of empathy towards others;
- ability to discuss anxiety-provoking topics with markedly increased ease;
- a strong sense of inner peace and self-acceptance;
- feelings of insightfulness and mental clarity;
- intensification of sensory experience, particularly proprioception (sensory data providing a sense of the body's position), hearing and touch.

Other sources note the lack of a predisposition to violence by those affected by MDMA, the retention of a sense of contact with reality and increased concentration (Ramaekers et al., 2006). Regarding lack of aggression, Iverson (2008) suggests this may be due to MDMA acting principally on serotonin pathways and not dopamine. Neither is there a common association with 'bad trips' (Green et al., 2003) although an earlier study (Davison & Parrott, 1998) described a 'bad trip' incidence of approximately 25% in their sample. Occasionally panic attacks may ensue (Whitaker-Azmitia & Aronson, 1989). Finally, while hallucinations may occur, these have been described in the literature as rare and an adverse side effect (Creighton et al., 1991; Davison & Parrott, Ibid.).[3]

2.3.1.2 Less-severe physiological effects

Less affective than physiological effects include:

- decreased appetite;

[3] Interestingly, during the preparation of this review the author spoke casually with an experienced 'high end' user (a business person claiming the phrase **M**anaging **D**irector **M**ergers and **A**cquisitions was common parlance for MDMA in some financial circles) experienced in consuming powdered 'ecstasy'. This person reported hallucinations as not uncommon. However, whether the powder was *definitely* MDMA was unable to be confirmed.

- short-term memory loss.

Common side effects self-reported by users include:

- urinary retention (hyponatremia, see below);
- mydriasis (abnormal pupil dilation);
- increased physical energy;
- increased heart rate and blood pressure;
- increased mean body temperature;
- trisma (lockjaw);
- bruxia (involuntary teeth grinding);
- gurning (projecting the lower jaw forward, usually caused by higher doses);
- nystagmus (rapid, uncontrollable eye movements).

Commonly self-reported lingering side effects (i.e. following primary subjective effects) include:

- several hours of restlessness, sometimes accompanied by residual euphoria;
- fatigue;
- a period of general malaise, normally resolving within a few days.

2.3.1.3 Serious acute effects

There are several acute serious effects of MDMA, often resulting from the context and environment in which the drug is used recreationally, i.e. constant physical exercise (dancing) in a hot, crowded space with reduced access to liquids/water. Some of these effects, depending on severity, are potentially fatal; they include:

1. Hyperthermia
2. Hyponatremia
3. Dehydration
4. Aggravation of underlying health conditions
5. Serotonin syndrome

1. Hyperthermia

Hyperthermia (or hyperpyrexia) is an excessive and unusual elevation of set body temperature greater than or equal to 41.1 °C (Wikipedia, 2009, May). Ingesting MDMA may precipitate the condition through a number of contextual, environmental factors including an intemperate environment, lack of hydration or lack of rest from physical activity, e.g. dancing. Dance culture information site TheDea.org (2003) describes the complications of malignant hyperthermia as the most common causes of death and injury, usually in association with 'raves' (which often involve all-night marathon dancing) and dancing at conventional clubs. Potential overexertion/hyperthermia-related events include disseminated intravascular coagulation, rhabdomyolysis, hepatoxicity, and renal failure (Ferrie & Loveland, 2000). Hyperthermia is a poor prognostic indicator and aggressive cooling is required

(Jordan & Hampson, 1960; Chan et al., 1994; Toxinz Poisons Information, 2009). These risks can be greatly increased by mixing drugs, particularly other stimulants.

Occasionally reported and sometimes secondary to hyperthermia is acute liver failure (hepatitis). However, this may also result from direct idiopathic (of unknown cause) hepatotoxicity from the drug. It may also re-occur if ecstasy is taken again (Devlin & Henry, 2008).

2. Hyponatremia

'Water Intoxication' or hyponatremia is also a relatively common cause of MDMA-related death. It has been suggested (TheDea.org, 2003) incidences of this adverse event may be the direct result of public awareness of heatstroke-related deaths leading some users to consume large amounts of water out of fear (over eleven litres in one case [Balmelli et al., 2001]). Increasing blood volume reduces blood sodium concentrations, resulting in sodium leeching into the water-engorged gut. This produces a difference in osmotic pressure, causing body tissues, including the brain, to take on water and swell (Cherney et al., 2002). While most organs cope with this, the brain, being encased in the skull, can be exposed to increased intracranial pressure due to swelling. This can crush the brain stem or result in a cerebral hemorrhage.

Other researchers propose that MDMA may cause some people to suffer from idiopathic antidiuretic hormone secretion (Matthai et al., 1996), thus kidneys retain water, aggravating excessive water intake (Smith et al., 2005; Devlin & Henry, 2008). In terms of numbers, a recent U.K. study noted nine published case reports of fatal hyponatremia between 1997-2002, all in women aged between 16-21 (probably due to female's lower ratio of body water to body mass). They also noted twenty-four case reports of non-fatal hyponatremia (Rogers et al., 2009).

3. Dehydration

Given the typical activities associated with the dance and club scenes (i.e. prolonged dancing), profuse sweating, increased activity, tachypnea (increased respiration), and hyperthermia not uncommonly lead to significant body-fluid depletion. While those suffering dehydration require management, before managing patients it is important to exclude the possibility of hyponatremia as fluid administration may potentially be fatal in such cases (Toxinz Poisons Information, 2009).

4. Aggravation of underlying health conditions

There is also the possibility that underlying health conditions, e.g. cardiovascular problems, such as heart disease may be exacerbated by some of the effects of MDMA. An example, dramatically reported at the time, involved the death of a young woman who suffered a cerebral hemorrhage after taking a single MDMA pill (The Associated Press, 2002). Some, however, have questioned whether the blood pressure increase caused by MDMA would be sufficient to produce such an outcome (see TheDea.org [2003] and further discussion of skewed media reporting concerning MDMA below, section 2.4.6). Nonetheless, on rare occasions use of amphetamines, cocaine and MDMA can lead to intracerebral and subarachnoid haemorrhage (Gledhill et al., 1993; McEvoy et al., 2000).

5. Serotonin syndrome

A final specific effect of MDMA concerns serotonin syndrome. Silins et al. (2007) note that due to the potential for synergistic reactions between MDMA and many commonly prescribed antidepressants with serotonergic potential, health professionals need to be better informed of risks of this condition. This is increasingly the case with a rise in prescribing of antidepressants. They argue that research on other MDMA-related harms, e.g. debates on neurotoxicity (e..g. Gouzoulis-Mayfrank & Daumann, 2006), memory deficits (e.g. Reneman et al., 2006) and the relative merits of animal versus human models of research (e.g. de la Garza et al., 2006) has overshadowed research on serotonin syndrome, which can be fatal.

In their recent Australian study Silins et al. (2007) reviewed the literature on the syndrome as a means to constructing a clinical hierarchy of risk. Following Gillman (2006), they define serotonin syndrome as "a drug-induced toxic state caused by an excess of serotonin within the central nervous system." The condition is characterized by a cluster of autonomic signs, neuromuscular changes and altered mental status (Dunkley et al., 2003), with its most likely clinical presentation indicated by rapid onset, usually within twenty-four hours of the introduction of a serotonergic substance (Birmes et al., 2003). Gillman (2005) notes that MDMA has clinically relevant serotonergic potency, with a large dose releasing significant amounts of serotonin in the synaptic cleft. As a consequence there can be an 80% loss of brain serotonin within four hours of intravenous use (Green et al., 2003).

Parrott (2002) suggests due to many ecstasy users' perceptions that early serotonin syndrome symptoms are within the normal range of expected drug reactions, patients frequently present to emergency departments with more advanced symptoms. As the syndrome develops these include hypervigilance, agitation, tremor, exaggerated reflexes, muscle spasm starting in lower limbs generalizing with increasing toxicity, fever, sweating, dilated pupils, rapid heart rate and breathing. Subsequent developments include shaking, shivering, clenched jaw; in severe cases, development of fixed rigidity impairing breathing, can lead to raised carbon dioxide levels in blood. Confusion, rigidity, and body temperature above 38.5C indicate life-threatening toxicity (Dunkley et al 2003; Gillman, 2005).

Since the 1980's only few MDMA-induced fatalities fitting serotonin syndrome criteria have been reported (Mueller & Korey, 1998; Vuori et al., 2003), with it being recognized that the relative frequency of MDMA-related fatalities to use is low (White & Irvine, 1998; Hegadoran et al., 1999; Gowing et al., 2002; Kinner et al., 2005). Nonetheless the extent of acute, non-fatal consequences of MDMA's use is less easy to determine due to less serious cases not being published and to patients in this category accessing varied sources of treatment (White et al., 1997; Stafford et al., 2005).

In summarising their hierarchy of risks, Silins et al. (2007) propose the following:

i. serotonin re-uptake inhibitors (SSRI's, SNRI's, TCA's) are less likely to induce serotonin syndrome when used with ecstasy;
ii. high, repeated doses of stimulants like methamphetamine, cocaine and amphetamine, when used with ecstasy, intensify serotonin release and increase the risk of serotonin syndrome;
iii. 5-HTP and L-tryptophan (serotonin precursors) should be expected to influence the course of serotonin syndrome when used with ecstasy;
iv. MAOI's (including RIMA's) are most likely to produce serious increases in serotonin when used with ecstasy;
v. comparatively little is known about the impact of St. John's Wort, LSD, anti-migraine drugs and lithium, i.e. there appears to be only limited evidence of practitioners screening, (e.g. Friedman et al., 2001), however, consequences of use are potentially serious;
vi. there is emerging evidence of deliberate combining with ecstasy—both pharmaceutical drugs and supplements (Tong & Boyer, 2002; Copeland et al., 2006; Stafford et al., 2006); that the consequences can be serious (Vuori et al, 2003); that the practice is not uncommon (i.e. anecdotal evidence from ecstasy-use websites, [e.g. Bluelight, 2009]); that likely legal combinations with ecstasy include SSRI's, MAOI's, 5-HTP, St. John's Wort (Copeland et al., 2006) and that combined illegals include cocaine and amphetamine (Degenhardt et al., 2005; Stafford et al., 2006).

2.3.2 Long-term consequences of use

The issues discussed in this section may generally be subsumed under the rubric of neurotoxicity. They include arguments concerning the complimentarity of animal and human models of research, psychopathology and cognitive deficits.

2.3.2.1 Neurotoxicity

Numerous authors have noted the controversy surrounding the extent of MDMA's neurotoxicity (e.g. Grob, 1998; Holland, 2001; Lyvers, 2006; Sessa & Nutt, 2007). Research has focused on a profound loss of serotonin axons (thread-like extension of the nerve cell) in animals (mice, rats, monkeys, and baboons), and dopamine axons in some species/dosing regimens, though the cell body itself is not destroyed (Molliver et al., 1990). Research suggests hyperthermia is a key factor linking many of the disparate findings. Evidence of this comes from studies indicating that animals given MDMA can avoid neurotoxicity if hyperthermia is avoided (Yuan et al., 2002). While the exact mechanism of toxicity is unknown, it is likely that the metabolic breakdown of MDMA or a metabolite of it may react with the local antioxidant supply thereby reducing antioxidant levels, with resultant axon damage. Thus suggested sources of *oxidative stress* include MDMA's capacity to increase metabolic activity, its metabolites or metabolites of dopamine (also released by MDMA). Bonson (2004) has commented that one puzzling aspect in preclinical MDMA research, however, is the discrepancy found between significant serotonergic changes and inconsistent behavioural deficits.

In consideration of the above, ecstasy information site The.Dea.org (2003, May) observes that for practical purposes, the role of hyperthermia in both neurotoxicity and MDMA death/injury makes rave/dance party settings more potentially dangerous than home usage.

Research related to neurotoxicity includes early rat studies on the pharmacology of MDMA, which found elevated serotonin levels and damaged serotonin neurons, i.e. those releasing serotonin in the brain (Green et al 2003); similarly for non-human primates (Hatzidimitriou et al., 1999). Despite the relatively higher dosages than would typically be taken recreationally, these early studies raised concerns that humans might suffer similar nerve cell damage. One study, published in the Journal *Science*, that controversially produced extreme results was subsequently retracted when it was discovered that rather than being administered a typical recreational dose of MDMA, its animal (monkey) subjects had received relatively high doses of methamphetamine (Ricaurte et al., 2002; note also the retraction subsequently printed in the same journal, *Science* [2003] 301:1479). More recently a non-human primate study using dosing similar to that seen in humans showed no effect (Fantegrossi et al., 2004).

Further criticisms of studies on MDMA neurotoxicity include concern over whether the alterations in serotonergic systems can be defined as 'neurotoxic', given MDMA does not consistently affect non-serotonergic markers of cellular damage, e.g. silver staining or glial fibrillary acid protein (GFAP). Moreover, MDMA's non-linear pharmacokinetics strongly influences serotonergic damage, as does ambient temperatures (discussed above). There is also the issue of complimentarity between animal and human models (Bonson 2004).

2.3.2.2 Animal studies and general critique

A common criticism of the animal studies indicating serotonin neuron damage concerns the relatively higher dose than humans would recreationally use (Green et al., 2003). Nonetheless it is accepted by other researchers that heavy users of ecstasy may approach these dosage levels (e.g. Jansen & Forrest, 1999), though Jansen (1999) expresses reservation about high dose self-administration studies due to most recreational human use of MDMA being non-dependent. There are other issues, however, that make direct comparison between animals and humans problematic. While the strategy itself (known as 'inter-species scaling') is a well used technique based on comparison of relative sizes of animals to determine, for example, toxicity, for the technique to work the mechanism by which the drug is toxic must be a simple one, not the case with MDMA. Additionally, the high doses animals receive in experiments (as much as 50 mg/kg compared with an effective dose for humans of 2mg/kg; [The.Dea.org, 2003]) may also be administered by injection. The lead author of the problematic study noted above (i.e. Ricaurte et al., 2002) had previously reported that injecting MDMA could triple its neurotoxicity over oral dosing (Ricaurte et al., 1988).

The criticisms of the work done on MDMA's neurotoxicity, some specific to human studies, take in a range of problems. These include publication bias, selective reporting of outcomes and interdependence of some outcome measures producing

confounding, particularly where other substances are concerned, i.e. polydrug use, especially that involving alcohol and also cannabis (Rogers et al., 2009).

More specific problems involve the methodologies and technologies employed to determine serotonin neuron damage. Thus neuro-imaging may be used to measure damage in living tissue, using radioactive tracers to bind to the serotonin reuptake sites. Here a reduction in tracer binding indicates reduced numbers of serotonin nerve terminals consistent with the serotonin nerve terminal damage in non-human primates (Hatzidimitriou et al., 1999). Such studies are however, potentially problematic, with a number of possible confounders, e.g. the use of other drugs and effects of residual MDMA in the brain could reduce tracer binding thereby mimicking terminal damage. The literature is further complicated with the use of differing tracers having differing characteristics. This makes difficult comparisons between studies. Bearing these limitations in mind, the following may be said:

- there is a dose correlation with a reduction of tracer binding in various brain regions of MDMA users (McCann et al., 1998;[4] Reneman et al., 2001; Burchert et al., 2003; McCann et al., 2005);
- these studies suggest women might be more affected than men (Buchert et al., Ibid);
- there is evidence from some studies suggesting the reduction of binding tended to be less or not present in ex-users (McCann et al., 2005);
- a recent U.K. study using state-of-the-art tracer has found no difference between ex-users and controls (Selvaraj et al., 2009).

In summary, therefore, serotonin-imaging data suggest that while MDMA may alter tracer binding to nerve terminals, the phenomenon has short-term implications and is not permanent (ACMD, 2009).

MDMA also interacts with the brain's dopamine system (Johnson et al., 1986). However, no evidence of negative impacts on this system has been found. This distinguishes MDMA from other stimulants including cocaine and methalymphetamine, where clinically relevant negative consequences are seen on impulse control, planning and attentional (as opposed to memory) processes (Volkow et al., 2001a & b).

2.3.2.3 Psychopathology and cognitive deficits

[4] Jansen and Forrest's critique (1999) of McCann et al. (1998) highlights the difficulties facing those undertaking research on the neurotoxicity of MDMA using human subjects, specifically the problems of polydrug use and cross-sectional studies, and the importance of differentiating between research on MDMA vs ecstasy. They comment: "ecstasy may contain one or more of various substituted amphetamines, including MDMA, amphetamine, ephedrine, ketamine, tilatamine, or other compounds…what these investigators [McCann et al., 1998] have shown is a difference in serotonin transporter activity between a group of individuals who thought they had taken MDMA in the past, compared with a group of people who said they had never taken MDMA before." See Jansen, K.L.R., & Forrest, A.R.W. (1999). Toxic effect of MDMA on brain serotonin neurons. *Lancet, 353*(9160), 1270.

As with the research reported above, links between MDMA use, psychopathology (e.g. depression, anxiety) and cognitive deficits (e.g. verbal learning and memory) are as yet not clearly defined.

The difficulties alluded to here may be noted in research where MDMA is seen to be associated with depression. Acutely, there is a typical pattern of MDMA-associated depressive symptoms following weekend recreational use, termed the 'mid-week crash' (Parrott & Lasky, 1998). Associated feelings are generally mild and quickly resolve. However some users reportedly take selective serotonin reuptake inhibitor (SSRI's) antidepressants to mitigate effects (Farre et al., 2007).

Concerns have been raised regarding chronic use leading to clinical depression through changes in brain serotonin function, but evidence is equivocal—most studies do not find significantly increased levels of clinical depression in current / ex-'ecstasy' users, though combined evidence (e.g. Rogers et al., 2009) suggests there is a small but significant exposure effect. One study (Rosier et al., 2005) found rating scale depression scores for MDMA users slightly elevated compared with non-users, with this being most marked in those with a specific genotype of the serotonin reuptake site; however, the effect did not reach the threshold of clinical significance for depression even in the most affected group. The recent U.K. report on MDMA (ACMD, 2009) also noted a suggestion that MDMA can acutely lift mood of those suffering clinical depression, but that due to the drug scheduling of MDMA research in this area was being discouraged.

Research focusing on MDMA's links with depression is further hampered by polydrug use (see also above, section 2.2) and in many cases the methodology deployed. Daumann et al. (2004) considered cross-sectional designs problematic and as a consequence introduced a longitudinal component to their study, which sought self-rated information from recreational ecstasy users (with matched controls), on a range of psychological complaints. At both baseline and in follow-up, they observed that the self-reported psychopathology was mostly associated with regular concomitant cannabis use. The ecstasy users who had abstained from cannabis use at follow-up were comparable with those abstaining from ecstasy. Additionally, higher levels of obsessive-compulsive behaviour, interpersonal sensitivity, depression, anxiety, phobic anxiety and paranoid ideation were significantly correlated with the duration of regular interim cannabis use. Gouzoulis-Mayfrank and Daumann (2006) note that, while many drugs associated with poly-use may behave synergistically with MDMA, there is an added complexity with cannabis in that while it is a well recognized risk factor in neuropsychiatric disorders, cannabinoids have neuroprotective actions and they have been shown to (partially) block MDMA-induced neurotoxicity in laboratory animals.

Regarding cognition, there are a number of issues that have made it difficult to determine whether the chronic use of MDMA results in residual cognitive deficits in humans. These include (after Grant, 2004):

i. the variety of neuropsychological tasks employed;
ii. ability to define performance deficits in the context of specific cognitive processes;
iii. relating performance deficits to serotonergic function;

iv. MDMA user heterogeneity regarding gender, duration, amount of use, drug purity, drug abstinence periods and ability to monitor abstinence;
v. lack of clear criteria for MDMA regarding abuse vs dependence;
vi. polydrug use.

As with depression, polydrug use, context and amount of use are particularly significant. Gouzoulis-Mayfrank and Daumann (2004) report that in a longitudinal study following 30 moderate and 30 heavy users, deficits in learning and memory were closely related to extent of previous ecstasy use. These authors noted a failure to improve even after prolonged abstinence. Similarly, Halpern (2004) and Halpern et al. (2004) compared non-use with moderate MDMA use and heavy use, while controlling for alcohol and other drug use. In this study, MDMA users as a whole performed worse than non-users on most cognitive performance tasks in a variety of domains, though rarely reaching statistical significance. However, moderate users showed no differences from non-users, while heavy users showed numerous significant deficits, particularly regarding mental processing speed and impulsivity. Halpern (2004) describes unusually "pure" frequent MDMA users (largely reporting 60+ lifetime episodes of use) as having residual cognitive deficits despite adjustments being made for cofounders, concluding therefore that MDMA itself, rather than some other factor, was responsible for the deficits.

Furthermore, Rogers et al. (2009) note a small but significant negative effect on cognitive and psychomotor function. These authors carried out a meta-anaylsis of over 100 studies assessing observational data on recreational use. They examined studies comparing polydrug-users with MDMA users and MDMA users with drug-naive controls. However, despite their significant findings they acknowledged that mean scores of 'ecstasy'-exposed cohorts were still within the 'normal range'. Former 'ecstasy' users commonly showed deficits matching or exceeding current users, with statistically significant differences most apparent in relation to memory impairment and on focused but not sustained concentration. They also noted that self-rated measures by participants gave bigger effects than objective measures, suggesting a degree of self-concern amongst volunteers, which they proposed might bias research findings in such studies.

An additional area of ambiguous cognitive deficits involves driving while affected by MDMA. Evidence suggests the drug improves some aspects of driving and impairs others. This contrasts significantly with alcohol, which impairs on all measures and leads to impulsivity (Ramaekers et al., 2006). In written evidence to the ACMD (2009), however, the Association of Chief Police Officers (2008) commented that cases of MDMA-affected driving were rare in the U.K. Having acknowledged this, Curran (2008) described a study in which human volunteers were administered an 80 mg dose of MDMA which revealed a word-recall deficit (one or two words out of a list of 20) similar in magnitude to the effect of alcohol found at the U.K. maximum BAC when driving (80mg / 100ml).

Finally, in a prospective Dutch study (Schilt et al., 2007) a group of young people likely to use 'ecstasy' were tested on a range of measures prior to any use, then re-tested after two-to-three years. Those having used 'ecstasy' were found to have a significant reduction in performance of verbal memory, i.e. fewer of the 'ecstasy' users improved than did the controls. However, the ACMD (2009) review of this

study noted that absolute level of scores was very high in all tests and did not differ between users and non-users, Moreover, the ACMD (2009) was presented with conflicting interpretations regarding the potential clinical relevance of the data, with no significant changes observed in all tests and 'ecstasy' users in some tests 'improving' more than non-users. Further criticism of the Dutch study (Schilt et al., 2007), a related study (Schilt et al., 2008) and others like it (e.g. Bedi & Redman, 2008), criticized methodology (non-randomization, sampling bias, confounding) as well as challenging as speculation the notion that negative cognitive effects might increase with age (Krebs et al., 2009). The latter commented on "over twenty years of repeated studies looking for brain damage in ecstasy users [where] we see very few consistent findings and little consideration of pre-existing psychiatric factors that may influence young people to repeatedly risk criminal penalties in order to experience MDMA-mediated feelings of love and empathy" (Krebs et al., 2009:877).

2.4 Risks to public health

Quantifying risks to public health from any substance is difficult and, as the critique of the findings reviewed thus far indicate, ecstasy is no exception. Inconsistency of findings, methodological problems and the lack of longitudinal and epidemiological data complicate matters. In terms of risks and harms, public health data will typically rely on case reports, with these likely to focus on adverse events, particularly fatalities, thereby skewing data further. In the case of MDMA/ecstasy, particular and serious adverse effects have been discussed above (section 2.3.1.3). These involve hyperthermia and hyponatremia, although a hierarchy of risk might promote idiopathic reactions to MDMA as a first order risk (personal communication with Dr John Fountain, New Zealand Poisons Information Centre). Also of concern is serotonin syndrome, particularly given elevated levels of contemporary antidepressant prescribing. As shall be seen, however, severe or fatal adverse events are relatively rare where ecstasy is concerned.

Regarding more general factors, the present section will discuss risks to public health by considering availability and harms relative to population base, general incidence of ecstasy-related problems (social and medical), comparing MDMA with the risks posed by other drugs, considering seizure and production data, purity, examining media response to ecstasy use and, societal harm.

2.4.1 Availability and harms relative to population base

The European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) (2008) report provides a useful picture of MDMA/ecstasy's availability in that part of the world. It notes an estimated 9.5 million European adults (3% on average) have tried ecstasy, with about 3 million (0.8%) having used in the last year.[5] There is

[5] While the World Drug Report (2008) notes the same number of 3 million Europeans having used in the last year, it reports this proportion as 0.2% of the population aged 15—64. See United Nations Office on Drugs and Crime (UNODC). (2008). *2008 World Drug Report*. Vienna: United Nations Office on Drugs and Crime, p 164. Note also the comments on page 21 of this review regarding a change in UNODC data collection from 2008 to 2009, and that respective data for these two reports are not directly comparable.

considerable variation between countries (0.3%-7.3%) lifetime prevalence, but with most rates in the range 1.3%-3.1%. Use last year ranged from 0.2% to 3.5%, with more males than females reporting use on all measures (EMCDDA, 2008). The report notes ecstasy was more common among young adults (15-34 years), with lifetime prevalence estimates between 0.5%-14.6% and use in the last year 0.4%-7.7%. Even higher estimates prevail for the age group 15-24, with lifetime use ranging from 0.4-18.7%, though most estimates are reported in the 2.5%-8% range.

Despite Europe's ecstasy-using population being similar in numbers to those consuming amphetamines, very few ecstasy users present at treatment facilities, this figure being less than 1% of all drug presentations where ecstasy was reported as the primary drug. Countries reporting higher rates (i.e. ranging from 0.5%-4%) include France, Italy, Hungary, the United Kingdom and Turkey (EMCDDA, 2008). This provides a very basic picture of the extent to which (mostly less severe) adverse events from use impact on public health.

Using figures from 2007, the World Drug Report (United Nations Office on Drugs and Crime [UNODC], 2009) reports global ecstasy use numbering between 12 and 24 million individuals, with annual prevalence ranging between 0.3% and 0.5%. The report notes the difficulties in assessing all data, that consequently its previous reports are not directly comparable, and that this lack of clarity is reflected in presented data.[6] The highest prevalence figures are for Oceania (3.6%-4.0%) despite having the fewest users in absolute numbers. By comparison, Asia has the highest estimated number of users (3.6 to 13.6 million) aged between 15-64. In both these areas use is increasing. The report notes that given Australia's large population relative to Oceania, its figures tend to drive the data from this area, but also that due to New Zealand's legal market for BZP (for the period covered by UNODC's 2009 report) the latter's increased 'ecstasy' figures may be inflated (UNODC, 2009:159).

North America is estimated to have 2.6 million users, with an annual prevalence of about 0.9%, similar to Western and Central Europe. In the latter use appears to be largely stable, to slightly declining since 2004, principally in developed countries. Use in North America is described similarly, while in South America use is still increasing. Globally use is trending up (UNODC, 2009:156-7).

The Australian Crime Commission's (2008) report claims that despite a decline in MDMA seizures, Australia has the highest per capita use of ecstasy in the world, with the drug being the second most popular illegal drug behind cannabis. In 2007 3.5% (0.6 million) Australians used ecstasy in the previous 12 months, while lifetime prevalence is 8.9% of the population or 1.5 million people. Moreover, use in Australia has increased (ACC, 2009) while globally there is a trend in developed nations is to stabilized use (UNODC, 2009). A similar trend to Australia is observed in New Zealand, with Wilkins and Sweetsur (2008c) reporting an increase in the general population (15-45 years) from 5.4% in 2003 to 8% in 2006.

[6] For comparison with the subsequent data, the following figures are from UNODC's 2008 report. In 2006 there were approximately 2.4 million users in North America (0.8% of the population). Figures for Oceania and Asia were 3.2% (Australia 3.5%; New Zealand 3.9%) and 0.1% respectively. United Nations Office on Drugs and Crime (UNODC). (2008). *2008 World Drug Report*. Vienna: United Nations Office on Drugs and Crime. See also footnote note 3.

While the figures above provide an indication of use levels, a greater sense of perspective on the extent of public health risk may be gained from the proportion of users suffering adverse events. This is difficult, however, given lack of information on consumption levels and dose-response relationship between tablet intake and increased risk of overdose. There is also the problem of accurately estimating actual numbers of users, and the reliance on case reports, rather than larger data sets (case reports for the U.K. were discussed above, e.g. regarding hyponatremia, section 2.3.1.3).

Bearing these issues in mind, U.K. data give some indication of relative risks for MDMA/ecstasy. An early attempt at calculating risk of fatality (Gore, 1999), proposed a 25-fold range for estimating ecstasy-related deaths amongst 15-24 year olds in the U.K., this being one in 2,000-50,000 users. More recently the ACMD (2009) combined a Home Office report (2006a) estimating U.K. user numbers, and data from the U.K. General Mortality Register. The Home Office (2006a) data suggested 1.2 million users consumed approximately 60 million tablets annually.[7] When combined with the General Mortality Register data, and using Gore's (1999) calculation, this suggests the risk of death per person and per tablet is one in 39,000 and one in 1.8 million respectively, if either all deaths mentioning 'ecstasy' are mentioned, or only those deaths solely mentioning 'ecstasy' are noted.

2.4.2 Fatal toxicity compared with other drugs

Further data from the U.K. aimed to quantify MDMA's intrinsic fatal toxicity (T) in comparison to other drugs (ACMD, 2009). Three separate measures (i.e. T1, T2, T3) were indexed against mortality data during the period 2003-2007, where ecstasy was mentioned on death certificates. The mortality figures were divided by, respectively:

T1 number of users of a given drug;
T2 seizures by law enforcement agencies;
T3 estimates of the market size for given drugs in England and Wales.

Data were subsequently normalised such that for each of the three scales above (T1, T2, T3) heroin = 1,000. Table 1 below indicates the relative toxicities:

Table 1. Indices of fatal toxicity (T) for the period 2003-2004 (U.K.)

Drug	T1	T2	T3
Heroin/opiates	1,000.0	1,000.0	1,000.0
Cocaine	10.9	163.0	92.0
MDMA	4.6	118.0	99.0
Amphetamine	5.0	95.0	106.0
Cannabis	< 1.0	2.0	< 1.0

[7] Sessa and Nutt (2007) citing NCIS put this figure at 100 million per annum. See National Criminal Intelligence Service. (2001). UK Threat Assessment 2001, produced by the National Criminal Intelligence Service, cited in Sessa, B., & Nutt, D. (2007). MDMA, politics and medical research: Have we thrown the baby out with the bathwater? *Journal of Psychopharmacology, 21*(8), 787-791.

Source: ACMD (2009:18)

In the above example amphetamine, MDMA and cocaine have roughly similar levels of fatal toxicity. This is considerably lower than for heroin. As noted above (section 1) Gable (2004) had previously produced an index of lethality wherein he proposed the following figures, Heroin (6), Alcohol (10), Methamphetamine (10), Cocaine (15) and MDMA (16), with descending numbers indicating increased lethality. His estimations for cocaine and MDMA are relatively comparable with those seen in Table 1.

There are of course other metrics by which to compare the harms of drugs, both clinical and non-clinical. The DSM-4R (Michael & Tasman [Eds.], 2004) criteria of abuse and dependence are discussed elsewhere (sections 2.2 and 2.7). Additionally, an extension of a drug harms analysis could logically comprise multiple dimensions, thereby incorporating a broad range of societal harms. This has been attempted by Nutt et al., (2007) and is discussed below (section 2.4.7.1).

2.4.3 Seizure and production data

Seizure data offer a further perspective on consumption and therefore another metric by which the potential harm posed by specific drug may be gauged. The UNODC (2008) notes that overall consumption is difficult to assess and can only be estimated. It comprises three components: global seizures of ATS end-products (i.e. drug seizures); ATS-related chemical precursor seizures; and ATS consumption. The following model determines production data: average seizure rates for either precursors or finished ATS's are estimated at 10%; the average consumer of the ecstasy 'group' (MDMA, MDA, MDEA/MDE) uses three times a week, consuming an average of 90 mg of active ingredient per episode. The UNODC divides ATS's into two groups, the amphetamine group and the ecstasy group, with the latter comprising approximately 11% of overall production, in 2006 ranging between 87—120 metric tonnes (UNODC, 2008).

The EMCDDA (2008) notes the relative importance of Europe as both consumer and marketer of ecstasy, with over 20,000 seizures intercepting nearly 14 million tablets in 2006. The Netherlands reported the highest seizure quantity (4.1 million tablets), followed by the U.K, Turkey, France and Germany. Both the EMCDDA (2008) and the UNODC (2008) notes the stable to declining market for ecstasy, with both quantity and numbers of seizures reducing during the period 2001-2006. Europe accounted for 43% of the ecstasy seized in 2006, with 34% seized in North America (UNODC, 2008). In Australia the weight of MDMA detections decreased from 5234 kilograms in 2006-7 to 213 kilograms in 2007-8, though this is reportedly due largely to a single record detection in 2006-7, while the number of detections remained stable (113 in 2006-7 vs 116 in 2007-8) (Australian Crime Commission [ACC], 2009).

2.4.4 Purity and pricing

As discussed elsewhere in the present review, there is no guarantee that 'ecstasy' purchased illegally is pure or in fact contains any MDMA at all. Given the relative popularity of 'ecstasy' as a recreational drug the adulteration of street-purchased tablets with impurities or other psychotropics must rate as a potential and significant risk.

In Europe, of the ecstasy tablets analysed in 2006, most contained MDMA or other ecstasy-like substances (e.g. MDEA, MDA) as the only psychoactive present. Seventeen European countries reported this as the case in over 70% of all tablets analysed, with Spain and Poland being exceptions. In these countries amphetamine or methamphetamine was frequently found in ecstasy tablets, along with analogues of MDMA.

Regarding purity, most countries reported typical ranges between 25-65 mg of MDMA, although the overall range was significant (9-90 mg). Additionally, high-dose ecstasy tablets (e.g. over 130 mg) were reported in Belgium, Denmark, Germany, France, Netherlands and Norway, with high-quality MDMA powder also becoming available (EMCDDA, 2008). Of Canadian samples tested between 2001-7, those comprising MDMA as the sole substance detected declined from 69% to 3% (UNODC, 2008). In Australia, nearly half of police detainees (via surveys and urinalysis) self-reporting MDMA use in the previous 48 hours tested negative, with 34% testing positive for methylamphetamine (ACC, 2009).

The Australian drug report (ACC, 2009) also noted a trend to domestic production of MDMA in clandestine labs, commenting also on potential hazards. These include the use of highly toxic, flammable and explosive substances, which can be ingested, absorbed through the skin or inhaled, resulting in nausea, chest pain, eye and skin irritations, burns and death.

Regarding price, In Australia data suggest this has remained relatively stable over the last few years. Nationally prices have ranged from $10-$60 per tablet/capsule. Bulk purchases (1000 or more MDMA tablets) ranged between $7-$30. In Europe, prices are reported as varying considerably, with the Netherlands and Poland relatively cheap at US$4.40 and $3.50 / tablet respectively, while Norway and Iceland at US$43.90 and $33.80 respectively, represent the expensive end of the market. In the U.S. by comparison a single tablet is reported as costing $25 (UNODC, 2009:271-272 for global price schedule). As a detailed example, the ACMD (2009) reports that U.K. prices have fallen in recent years, with single tablets available for as little as £2.30 and most commonly sold in batches of 3-5 for £10. By comparison MDMA powder costs £30-£40 per gram (see also Dalgarno, Appendix IV). Measham and Moore (2009) suggest that powder may have greater kudos due to its higher price.

2.4.5 Pill testing

The data above suggest that the issue of pill purity is one having a bearing on public health. This is particularly the case given what appears to be a decline in the 'quality' of street-purchased 'ecstasy'. In the U.K., for example, there is evidence that over the past decade the average content of MDMA in pills has reduced from 100 mg to 40 mg. As noted previously, this may in part explain why there has been an increase in

the numbers of pills consumed per occasion. Thus data show considerable variation in pill contents (Forensic Science Service, 2008a & b). Data from Australia have also been discussed, for example regarding negative test results for almost 50% of police detainees who self-reported taking what they thought was MDMA (ACC, 2008).

Thus in Australia, as elsewhere, there is evidence of pill adulteration, both in terms of impurities and alternative psychotropics. Regarding the latter, Quin et al. (2004) report the three most commonly detected substances in seized Australian (Victoria) pill samples were MDMA, methylamphetamine and ketamine. These authors note that for the period they report on, MDMA content of pills ranged between 1% and 70%. Other studies suggest that ecstasy users are concerned about the purity and content of pills they consume (White et al., 2005). In some cases there is good reason for concern, with potentially lethal psychoactives contained in pills sold as ecstasy. This has previously been documented in South Australia, where toxic side effects, hospitalisation and eleven reported fatalities between 1995 and 2003, resulted from the recreational and unintended consumption of paramethoxy-amphetamine (PMA; Caldicott et al., 2003; Johnston et al., 2006).

Consequently there is a level of interest among dance party enthusiasts and users of MDMA and other 'dance party' drugs, for knowledge about, and testing kits for the drugs they purchase. Johnston et al. (2006) have reported significant levels of interest in determining pill content, with 84% of a sample of 810 regular ecstasy users claiming they had made some attempt to discover the contents of the drugs they had purchased. While many asked friends or dealers about their pills, at least 20% had purchased pill-testing kits. Of these, 75% reported they would not take a pill if it was 'unknown' (i.e. produced no reaction in a reagent test).

However, while testing kits may provide a basic guide to the contents of pills, it is recognised that they have their limitations (Winstock et al., 2001), e.g. kits only indicate what the *main* ingredient in a pill is, and alternative means of pill content verification such as pill comparison charts may not match the pills available on a given occasion (Camilleri & Caldicott, 2004). Indeed, Winstock et al. (2001) argue that kits' ability to identify relevant substances is too limited and that in any case the colour coding of reagent tests requires interpretation which is too subjective to be safe. They argue, therefore, that pill testing is an example of harm minimisation gone too far, and that other, simpler techniques such as the use of educational material, would be more successful.

2.4.6 Skewed media reporting and portrayal of drug use

Some commentators (Forsyth, 2001; Holland, 2001; Taylor, 2008) have noted the tendency of media to skew their reporting of drug-related items and stories, with ecstasy being a prominent example. This, they argue, is not helpful in educating users about risks, as biased reports undermine legitimate messages. During the 1990's in Scotland, for instance, while every MDMA-related death was reported, fatalities due to other drugs were much less likely to be, e.g. diazepam—1 in 50 and amphetamine—1 in 3 (Forsyth, 2001). Others (e.g. TheDea.org, 2003, May) have proposed that by accentuating the risks faced by ecstasy use at parties, users may respond inappropriately, for example by drinking too much and thereby risking

hyponatremia due to being overly concerned about the effects of hyperthermia. Taylor (2008) notes the impact on users of negative stereotyping and the promotion of simplistic discourses, which undermine broader more inclusive discussion around harms and the means by which these might be addressed.

2.4.7 Societal harms

There is a range of other harms which impact on broader society. These may be characterized by a more socially orientated comparison of MDMA with other drugs; its impact on public order including associations with criminality and violence; the use of MDMA in drug facilitated sexual assault (DFSA); and the consequences for users, their affiliates and society of the prohibition / criminalisation of MDMA possession and use.

2.4.7.1 Social harms comparison of MDMA with other drugs

Nutt et al. (2007) have approached the issue of relative drug harm using a broader perspective than solely medical criteria. They argue that present classification systems are non-rational and that their methods generally are neither specified nor transparent. Consequently confidence in classifactory systems' accuracy is reduced and health messages are undermined. These authors developed a nine-matrix categorization of harm using an expert Delphi procedure with two separate rating groups.[8] Their nine categories were developed through the expansion of three principal factors determining harm associated with drugs with potential for abuse:

- physical harm to individual users caused by the drug
    - acute
    - chronic
    - intravenous

- potential for dependence
    - intensity of pleasure
    - psychological dependence
    - physical dependence

- effect of the drug use on families, communities and society
    - intoxication
    - other social harms
    - health-care costs.

The resultant matrix was applied to rank twenty drugs commonly used recreationally in the U.K. according to relative harm, including five legal drugs (alcohol, khat, solvents, alkyl nitrates and tobacco). The top five substances—in descending order of

[8] The Delphi technique, to gain consensus of expert opinions, is a commonly used method for the production of clinical guidelines. For example see Meijer, R., Ihnenfeldt, D., Vermeulen, M, De Haan, R, Van Limbeek, J. (2003). The use of a modified Delphi procedure for the determination of 26 prognostic factors in the sub-acute stage of stroke. *International Journal of Rehabilitation*, 26(4), 265-270.

harmfulness—were: heroin, cocaine, barbiturates, street methadone and alcohol. Ecstasy was ranked 18 out of 20, with the authors noting the correlation between their rankings and harm classification by the U.K. Misuse of Drugs Act (1971) was not statistically significant (Nutt et al., 2007:1050).

2.4.7.2 Public order

Associations between behaviours such as drug taking, and violence and criminality (e.g. Baumer et al., 1998) provide a means by which to assess the impact on public order of, in the present case, MDMA use. While the bigger picture will take in the significance of global drug trafficking and organized crime (e.g. UNODC, 2009), considering domestic crime statistics provides a context for individual behaviour.

Brownstein and Goldstein (1993) suggest three principal pathways by which drugs may influence criminal behaviour: the *psychopharmacological*, i.e. through disinhibition and impaired judgment; the *systemic*, i.e. drug-related crime is a consequence of negative interactions aligned with illegal drug markets; and the *economic*, with pressure to commit acquisitive crimes deriving from the need to meet the high cost of repeated drug use. In this regard, Hendrickson and Gerstein (2005) analysed data from the U.S. data from the Arrestee Drug Abuse Monitoring system (ADAM). They found ecstasy use to be less prevalent among young male arrestees than young men in general. Moreover, while ecstasy use was positively associated with aspects of drug market participation, it was negatively associated with violence and property offences. New Zealand data relevant to this issue are discussed below (section 3.2.2.3).

2.4.7.3 Drug facilitated sexual assault (DFSA)

A further specific example of drug-associated public disorder concerns the use of drugs to facilitate sexual assault (DFSA), i.e. the use of so-called ‘date rape drugs’. Du Mont et al. (2009) suggest there is evidence this phenomenon is not uncommon. In their sample of 977 consecutive sexual assault victims suspected of being drugged, they found that 20.9% met criteria of DFSA. Victims were more likely to have presented at a large urban care centre for assessment, to be employed, and to have consumed either over-the-counter medications, street drugs or alcohol in the 72 hours prior to the assault. Compared with other victims of sexual assault, subjects in this sample were four times more likely to have consumed alcohol. Another recent study (McCauley et al., 2009) also reports a strong association between DFSA and substance use, particularly alcohol. In their study (n=396) ‘club drugs’ were undifferentiated (they included MDMA, CHB, Ketamine, Rohypnol, Methamphetamine and hallucinogens) and had the smallest proportion of use (3.3% of the sample). Similarly, an earlier study (Scott-Ham & Burton, 2005) reported a strong association with alcohol (46% of 1014 cases). In this study there were three cases (i.e. 0.3%) of unreported MDMA detected, suggesting ‘ecstasy’ may have been used to ‘spike’ subjects’ drinks. Similar data come from Gee et al. (2006) who found one case of unreported MDMA consumption in their sample of 120 DFSA victims.

Most commonly reported locations for contact with assailants prior to drugging include pubs, clubs and establishments where disposable income is required to buy drinks (Gee et al., 2006). Prominent reported symptoms of DFSA include total amnesia, loss of consciousness, drowsiness, confusion and dizziness or light-headedness (Du Mont et al., 2009). It is the prevalence of these symptoms and the association with the above noted venues, however, that prompts Jansen and Theron (2006) to argue against the inclusion of MDMA as a likely date rape drug. Their arguments are discussed in greater detail below (section 3.2.2.3), along with New Zealand research on other associations between MDMA / ecstasy use and crime.

2.4.7.4 MDMA / ecstasy and drug policy

There is a long-standing argument concerning the effectiveness or otherwise of various drug policies and their conceptualization of and impact on drug problems. Although detailed analysis of it is beyond the scope of the present review, a brief discussion will illustrate harms at the intersection of policy and 'ecstasy' use.

Goldstein and Kalan (1990) note the polarized nature of the debate, with extreme positions placing drug policy as either a matter of law enforcement or health, and preferred options being either prohibition or legalization. They comment that while benefits of drug use and individual freedoms must be weighed against harms to users, their affiliates and wider society, any analysis will carry implicit biases reflecting social, political and religious views. Bearing this caveat in mind, a benchmark analysis by MacCoun and Reuter (2001) identifies forty-eight drug harms, of which thirty-six derive from policy, typically associated with prohibition. Prominent among the latter are drug users receiving penalties that are more damaging than their drug use behaviours (imprisonment, fines, stigma, loss of employment, loss of access to social capital and resources, e.g. education, welfare etc.); economic and social resources wasted on failed prohibition; unfair negative impact on family and affiliates; racially-biased policing; undermining of the rule of law due to perceived unfairness of sanctions; and barriers to research, education and treatment (e.g. see below, section 2.5 regarding therapeutic value) (MacCoun & Reuter, 2001:60).

The perception of policy-driven or 'secondary' harms is further mediated by types of drugs and their legal classification, i.e. users of drugs perceived as less harmful or 'soft' are more likely to be seen as suffering a greater range of harms from policy. Historically the classic drug in this category has been cannabis. Since the late 1980's, however, the rise of the rave music scene and concomitant use of club drugs, particularly ecstasy, has seen youth make what they believe to be rational choices about substance use irrespective of substances' legal classification (Parker et al., 1998; Parker et al., 2001). This in turn has led to a split in domestic drug policies from the status quo of global prohibition, with some countries looking for alternative ways (broadly subsumed under 'harm reduction') to mitigate drug harms, including those generated by policy.[9] Portugal, for example, decriminalized all drugs in 2001

[9] The Harm Reduction movement was initially a response to the early phase of the HIV/AIDS epidemic of the 1970's and early 1980's, and the realization that all pathways to infection (including those associated with illicit drug use) could be better engaged with through treatment and education. Its scope has now broadened to capture all drug use, with an emphasis on health rather than solely enforcement. However the definition of 'harm reduction' is often contested. See Wodak, A., &

(see Greenwald, 2009). On the other hand the Netherlands has, since the 1970's, incorporated the notion of 'soft' and 'hard' drugs into policy, initially with cannabis but more recently ecstasy, with the justification being to separate the 'soft' drug market from its more harmful cousin marketing 'hard' drugs such as heroin and cocaine. The Dutch example offers both a rationale for an alternative policy intervention against ecstasy harms and a demonstration of how harms are mediated by politics and ideology, rather than exclusively by drugs and drug use.

Uitermark and Cohen (2005) argue that ecstasy use in the Netherlands is relatively unproblematic, that lifetime use at the turn of the century was 2.9% and has now stabilized at approximately 1% of the general population. More recent data generally confirm this with 2006 European averages for lifetime (2.8%) and last year (0.8%) use being similar to Dutch figures (EMCDDA, 2008). Use last year figures for the age group 15-34 at (2.7%), however, show the Dutch to be slightly higher than the European average for this group (EMCDDA, 2008).

Of greater relevance to the discussion of ecstasy harms is the impact of the drug's classification in the Netherlands (Schedule 2), where it is considered 'hard' if possessed for sale / trafficking but 'soft' if possessed for use only, with the latter group of consumers not prosecuted (Uitermark & Cohen, 2005). In this regard a comparison with U.S. consumption (Table 2) under strict prohibition (Schedule 1) shows that attempts to emphasise the harms and risks of ecstasy use through prohibitive policy have had little impact on consumption.

Table 2: Comparing Ecstasy Use Rates Under Two Policy Regimes: Harm Reduction (Netherlands) and Prohibition (United States); Age >12, percentages of last year use by age group

Age	U.S.	Netherlands
12-17	2.4	0.9
18-25	6.9	5.6
26-34	1.4	1.9
>34	0.1	0.2

Source: Uitermark and Cohen (2005:69)

In noting the lack of significant differences in terms of simple prevalence between the two regimes, Uitermark and Cohen (2005) outline the harm reduction measures allowable in the Dutch system. They note the 1980's implementation of pill testing by the 'Adviesburo Drugs', leading to: pills being colour-coded, measured and numerically tagged; on-site testing at raves allowing harmful adulterants to be notified immediately, with consumers being able to feed back to dealers; the system was expanded, becoming funded by the Ministry of Health; and, most importantly, the Drug Information Monitoring System (DIMS) enabled health organisations to keep an eye on the markets for products which would otherwise be unregulated.

Saunders, B. (1995). Harm reduction means what I choose it to mean. *Drug and Alcohol Review, 14*(3), 269-271.

The initially informal network of harm reduction organisations developed into a coherent 'care regime' engaging with large-scale events, ultimately formalised by government involvement, with the Ministry of Health's position being that "In Dutch drug policy preventing problems during the use of drugs is just as important as preventing use itself. This is the principle of damage or harm reduction." Uitermark and Cohen (2005:68). As the latter comment (Ibid.), the result of this position is that three lines of action become paramount:

i. educating youth;
ii. manipulating the setting of drug use;
iii. regulating the market.

Overall then, the Dutch harm reduction strategy seeks to inform but not encourage, without frightening or sensationalising negative consequences of use. Uitermark and Cohen (2005) observe that use remains but that injuries or problems are rare. Nonetheless, they also note that more recently Dutch policy has come under increasing pressure to abandon the approach described above, both from near neighbours (e.g. France and Germany) and particularly from the U.S., whose Drug Enforcement Agency commented on the need to reintroduce "law enforcement solutions" as opposed to "the health aspect of addiction" which it sees as resulting in a "flurry of harm reduction measures [being] introduced throughout the Netherlands" (Drug Enforcement Agency, 2003). The impact of policy on harm reduction (minimisation) in New Zealand, for example pill testing and education, is discussed in greater detail below (section 3.2.3).

2.5 Therapeutic value

The early therapeutic use of MDMA was discussed above (section 2.1.1). While there was evidence of value in psychotherapy (e.g. Greer & Tolbert, 1986; Holland, 2001) much of the early research was criticized for its lack of scientific rigor, i.e. reliance on self-reports. For a critical review of the controversies surrounding this early work see Pentney, (2001). Despite the problem of MDMA's illegal status, since it was scheduled in the U.S. in 1985 more formalized research into therapeutic value has occurred, albeit at a slower pace than might otherwise have occurred.

2.5.1 Contemporary therapeutic research

The earlier work focused on psychotherapy, with research in this area continuing. Doblin (2002) has outlined a clinical plan for the treatment of post-traumatic stress disorder (PTSD) using MDMA. The project was based on a pilot dose-escalation study, described by Doblin at that time (2002:5) as "the world's only on-going study of the efficacy of MDMA-assisted psychotherapy". Although the study originally planned to treat 29 subjects with chronic PTSD secondary to a sexual assault, political pressure forced its closure before it was completed, at which time only six women had been treated. However, preliminary results found that low doses (between 50-75 mg) were psychologically and physiologically safe for all subjects (Bouso et al., 2008).

Sessa (2007) likewise comments on the difficulty of carrying out research on illegal drugs in a therapeutic context. He asks the medical profession to consider the usefulness of MDMA in a dispassionate and open-minded debate, noting that there are currently several new double-blind, randomised controlled trials either underway (e.g. PTSD trials by Mechael Mithoefer; and J.H. Halpern [Harvard Medical School], the latter with terminally ill patients; both studies in the USA) or pending (other PTSD trials in Spain, Switzerland and Israel) which are revisiting MDMA's therapeutic efficacy and therefore place in modern psychiatric practice.

In expanding on these concerns, Sessa and Nutt (2007) argue that the criminalisation of MDMA has potentially undermined the development of a valuable therapeutic tool. They note there is significant work done on researching the effects of drugs associated with negative mood and depression, and therefore question why similar work is not being carried out on a drug (i.e. MDMA) that has marked interactions with 5HT and an association with elevated mood. They also observe that the concerns regarding potential neurotoxicity of MDMA are based on scientific research that relies on high-dose (e.g. 120 mg plus) frequent use of MDMA, a phenomenon irrelevant to the proposed clinical use of the drug (i.e. low dose; possibly 50-75 mg). They site research (e.g. Halpern et al, 2004) showing that where 'pure' users of MDMA (i.e. controlling for polydrug use) were isolatable, moderate, infrequent users showed no clinically significant differences from non-users.

A review of contemporary issues concerning psychotherapy (Parrott, 2007) concludes that while there are possibilities for use in this context there are also a number of issues requiring clarification. The author noted MDMA can generate positive, life-enhancing and affirmative cognitions which may endure beyond treatment. However, the affective power of MDMA may also produce negative mental states, a phenomenon which psychiatric individuals are more prone to. Additionally, while setting, intention and expectancy were found to be crucial for positive outcomes, explanations for proposed MDMA-assisted therapy were all psychodynamic, thus a neurochemical model is needed (Parrott, 2007).

In response to concerns raised by Parrott (2007), Johansen and Krebs (2009) offer a neurobiological argument for strengthening research in this area. They note the use of supportive medications in exposure therapy for anxiety disorders and that some of these (e.g. SSRI's and benzodiazepines) may actually interfere with the extinction learning that is the aim of treatment. Furthermore, they remark that on-going randomised trials with MDMA for treatment-resistant anxiety disorders may benefit from three mechanisms associated with the drug: first, MDMA's increasing of oxytocin levels (see section 1, e.g. McGregor et al., 2008) may strengthen the therapeutic alliance; second, MDMA increases ventromedial prefrontal activity and decreases amygdala activity, which may improve emotional regulation and decrease avoidance; and finally, given MDMA increases norepinephrine release and circulating cortisol levels, it may facilitate emotional engagement and enhance extinction of learned fear associations. Consequently Johansen and Krebs (2009) argue MDMA's combination of pharmacological effects could, in a clinical setting, facilitate a balance of activating emotions while maintaining a sense of safety and emotional control, as previous case reports of MDMA-assisted psychotherapy have maintained.

Finally, in a non-pschotherapeutic context, there is evidence indicating that MDMA may be effective in treating Parkinson's. This comes from animal research (mice) where recently discovered trace amine associated receptors (TAAR's) represent attractive potential mediators of certain aspects of movement control. In this research Sotkikova et al. (2008) explored the role of the newly discovered receptor TAAR1 and the actions of antiparkinsonian drugs. ATS's were noted to be surprisingly effective at high doses and MDMA at low doses markedly enhanced the effects of dopamine derivatives (e.g. L-dopa).

2.6 Potential for death

This issue has been adequately covered above in the sections dealing with specific acute effects (section 2.3.1.3), availability and population based harms (section 2.4.1), and those discussing toxicity (sections 1; 2.4.2 and 2.4.6).

In summary, acute fatal affects derive from idiopathic responses of individuals to recreational doses; the effects of hyperthermia and hyponatremia; the effects of serotonin syndrome, possibly as a consequence of a synergistic reaction with antidepressant medication or polydrug use; and death due to underlying and/or undiagnosed medical conditions. There is also the possibility of death from adulterants such as paramethoxyamphetaminamine (PMA), as occurred in South Australia (e.g. Caldicott et al., 2003; Johnston et al., 2006), though of course technically this is not an MDMA-related death but rather derives from the use of an illegal and therefore unregulated drug. Authors including MacCoun and Reuter (2001) and Wodak and Saunders (1995) would argue adulterant-related deaths are a result of poor drug policy.

However, irrespective of the culpability of drugs or policy, each of the fatal events described above is rare, as indicated by section 2.4.1 on comparative risk at a population level, with an average of twenty deaths per annum reported in the U.K. since the turn of the century (Sessa and Nutt, 2007). Other fatal consequences, e.g. hyperthermia and hyponatremia, are at least in part a result of the context of use, i.e. prolonged intense activity in a hot environment, possibly without adequate rehydration, or too much of it. Overall, therefore, the likelihood of death as a consequence of the direct ingestion of MDMA is considered to be low. As a final comparison, Sessa and Nutt (2007) observe that annually in the U.K. (2001 figures) approximately 7,000 deaths were attributed to alcohol related causes and 106,000 to tobacco.

2.7 Ability to cause physical and psychological dependence

As was the case with the previous review for the EACD (Ministry of Health, 2003), there remains a lack of clarity around MDMA's potential to cause dependence. Additionally it should be born in mind that the instrument commonly used to determine dependence (presently the DSM-IV-R) does not have a specific set of criteria for MDMA. This is a matter noted by Cottler and Grant (2006:167), with the point being made that "a generic 'drug abuse / dependence diagnosis' does not exist—rather criteria must be met for each individual substance". Moreover, in the case of

MDMA, although the drug is assessed separately from hallucinogens, in some studies (e.g. Cottler et al., 2001) diagnostic criteria for hallucinogens have been included to accommodate the substance's hallucinogenic characteristics. As discussed above, however, this is also potentially problematic given the lack of agreement over MDMA's hallucinogenic qualities (e.g. Shulgin and Nichols, 1978; Nichols, 1986 Liester et al., 1992; Green et al., 2003).

Cottler et al (2001) comment that a number of early studies both in the U.S and Australia suggested ecstasy had few negative health effects (eg. Peroutka et al., 1988; Solowij et al., 1992; Moore 1993; Beck and Rosenbaum 1994) and was therefore relatively benign. Thus, where dependence was addressed in the literature it was considered uncommon (eg. Peroutka 1989; Steele et al. 1994; Green et al. 1995). In part this was due to the rapid reduction of the positive effects with repeated use, thereby intensifying negative effects such as anxiety and teeth grinding (e.g. Chesher 1990; Beck and Rosenbaum 1994). Nonetheless others (e.g. Hall & Hando, 1993) warned that if the dominant route of administration changed (i.e. from infrequent oral doses) the self-limiting nature of use might also alter.

Two subsequent studies (Merrill, 1996; Topp et al., 1997) seemed to confirm this, the latter noting 83% of a sample of 185 regular ecstasy users reported significant tolerance, with 56% claiming they used double what they initially took to achieve the desired effects. This study was noteworthy as it confirmed problems with ecstasy did exist. For example, a previous study by Solowij et al. (1992) had reported that only 2% of their 100 subjects felt they had at some time 'been dependent on ecstasy'. The study by Topp et al. (1997) also presented data on each DSM-IV criterion and it identified the need to determine DSM reliability, underscoring the issues noted at the beginning of this section (i.e. Cottler & Grant, 2006). Overall, Topp et al. (1997) reported diagnoses of 48% of subjects for dependence and 36% for abuse.

Other studies of note include Schuster et al. (1998) and Jansen (1999). The former interviewed a representative sample of 3021 14-24 year olds in Munich, Germany. Lifetime prevalence for ecstasy use was 4% for males and 2.3% for females. Approximately half had used more than five times, with the typical pattern (about half the sample) varying between once a month and twice week, and 17% reporting use on three or more days per week. The authors proposed, therefore, that approximately 20% of those using ecstasy at least once are likely at some stage to reach DSM-IV diagnosis for dependence. By comparison Jansen's (1999) research described case studies of three high-frequency, high-dose users who were described as feeling they had lost control over their use despite awareness that it was causing them problems.

Cottler et al. (2001) report similar data regarding similar DSM-IV diagnoses for dependence and abuse, with 52 (30%) of their sample of 173 (mean age 19.3 years) reporting ecstasy use more than five times. Of this sample, 43% met criteria for dependence, and 34% met criteria for abuse. The authors reported acceptable test-retest reliability, with data being collected twice over five days using blinded interviewers, and participants advised that the second interview was to test interviewers.

There are, however, a number of confounders with the studies noted above, most of which have already been discussed previously in other contexts. First, there is the

issue of pill content or purity. As is always the case, unless specifically tested, what participants actually ingested is speculation. In this regard Jansen and Forrest's (1999) comments are apposite (see footnote note 4). A similar problem pertains to the issue of polydrug use. For example, in the case of Cottler et al. (2001), along with ecstasy, proportions of their sample had lifetime use (>5 times) of alcohol (100%), cannabis (98%), tobacco (87%), hallucinogens (67%), stimulants (64%), cocaine (50%), opioids (50%), sedatives (40%) and nitrous oxide (39%) respectively (recall the mean age of this sample was 19.3 years). Additionally, their recruitment protocol included payment ($20 to $50 per subject). Collectively, and particularly given Cottler and Grant's (2006) comments about the present version of the DSM's lack of specificity concerning substance-related diagnoses, one must consider research in this area with caution.

There is other research that further implies the need for caution regarding dependence diagnosis. Von Sydow et al.'s (2002) prospective longitudinal examination of self-reported symptoms of depression among ecstasy users found that despite a 1% diagnosis of dependence at baseline, there were high follow-up rates of spontaneous cessation. The authors concluded that despite the existence of ecstasy use disorders, these may well be relatively transient and youth-specific, with only a small proportion of users going on to experience chronic problems. Measham (2004) makes a similar observation, where she notes the decline of ecstasy and cocaine use in 21st century Britain and a rise in sessional alcohol use. She suggests the longer term significance of contemporary patterns of consumption is mediated by the broader context of socio-economic and cultural change. This relates to "the pursuit of pleasure, the boundaries of leisure, and physical transgression in early 21st century leisure time/space" (Ibid:309).

Very recent data, this time from an American national survey of adolescent drug use (Wu et al., 2009) provides some support for relatively low levels of dependence but also evidence of further increases in use among a large sample (n=55,286) of 12-17 year olds. As with other research, MDMA was classed as a hallucinogen. In this study the overall prevalence of Hallucinogen Use Disorder (HUD) was low (<1%) despite over a third of MDMA users (38.5%) reporting symptoms. However, a greater proportion of MDMA (11%) users were diagnosed as hallucinogen-dependent than users of other hallucinogens. Additionally, the authors report that in the U.S. despite a decline in MDMA use to 2003, prevalence subsequently increased, though had plateaued by 2008.

Issues raised by the latter findings notwithstanding, Iverson (2008) suggests that, unlike amphetamines and cocaine, there is little evidence for long-term dependence on MDMA. He does note evidence of withdrawal (e.g. low mood) that appears to be relatively common but suggests compulsive use is uncommon. In this regard, Jansen's (1999) case study concerned three individuals who not only were polydrug users, but who had each experienced significant life trauma. In reviewing available evidence the U.K's Advisory Council (ACMD, 2009) suggested that MDMA's differential effects might be explained by the substance's acting principally on brain serotonin and less on brain dopamine function. In support of this they noted U.K. statistics for drug treatment seekers of 1% for ecstasy, compared with 3% for amphetamines and 11% for cocaine (ACMD, 2009).

Nonetheless, despite these final comments it is appropriate to conclude this section by acknowledging the earlier Ministry report on MDMA (Ministry of Health, 2003) and its observation that there is a risk of dependence with all drugs repeatedly self-administered. It seems very unlikely that MDMA / ecstasy should be any different.

2.8 International classification

2.8.1 United Nations' drug control conventions

MDMA is listed as a Schedule I substance under the 1971 United Nations Convention on Psychotropic Substances, along with its 'parent' compound MDA, and the chemically related substances DMA, DOB, DOM, PMA and TMA.

This scheduling requires that dealings with MDMA at a national level must be prohibited, except for scientific and very limited medical purposes. Schedule I status reflects an assessment by the World Health Organization Expert Committee on Drug Dependence that MDMA is a substance whose liability to abuse constitutes an especially serious risk to public health, and which has very limited (if any) therapeutic utility.

2.8.2 Other countries' classification of MDMA

i. In the United States, MDMA is a Schedule 1 substance under the Controlled Substances Act (since emergency scheduling in 1985).

ii. In the United Kingdom, MDMA has been classified as a Class A drug under the Misuse of Drugs Act since 1977. This classification has remained, following the rejection of the recommendation of the government's Advisory Council on the Misuse of Drugs (ACMD, 2009) to down grade MDMA to Class B.

iii. In the Netherlands, MDMA is for practical purposes a Schedule 1 drug (under the Opium Act) where there is evidence of trafficking, and a Schedule 2 drug where there is evidence for possession for personal use (Ministry of Health. 1995; Uitermark & Cohen, 2005).

iv. MDMA is also a highly controlled substance in Australia. For example, MDMA is a Schedule I substance under Queensland's Drugs Misuse Act Regulations, Victoria's Drugs, Poisons and Controlled Substances Act, and South Australia's Controlled Substances (Prohibited Substances) Regulations. Similarly, in the Australian Capital Territory, MDMA is listed in the same category of substances as heroin and LSD, under that jurisdiction's Drugs of Dependence Act and Drugs of Dependence Regulations.

3.0 Relevant New Zealand Qualitative and Quantitative Research on MDMA/Ecstasy

Compared to the developed international literature, there is relatively little New Zealand research on MDMA / ecstasy or research that is published locally. For example, a search in the New Zealand Medical Journal (key terms: MDMA ecstasy) returns only six articles between 1999-2009. Obviously local research is published internationally (e.g Boden et al., 2006). In general, however, what exists is predominantly quantitative in nature and survey orientated, tending to focus on prevalence and use patterns, for example Massey University's SHORE studies (e.g. Wilkins & Sweetsur, 2008c; Wilkins et al., 2009). Other data streams include those generated by enforcement (Police and Customs), the two longitudinal studies (Dunedin and particularly Christchurch's Health and Development Study), the Institute of Environmental Science and Research (ESR), the Ministry of Health's periodic surveys (e.g. Ministry of Health, 2007), the National Addiction Centre, and research carried out by academics and health professionals. These sources are considered below under categories of prevalence, health data and general research.

3.1 Research examining prevalence of MDMA / ecstasy in New Zealand

New Zealand drug use prevalence surveys have been conducted since 1990. Initially research involved telephone surveys undertaken by the Alcohol and Public Health Research Unit attached to the University of Auckland (Wilkins et al. 2002). Since 2005 surveys under the Illicit Drug Monitoring System (IDMS) have included interviews with 'key informants' having personal experience of drug use, the most recent being Wilkins et al. (2009), which is discussed below. These data are augmented by other relevant research.

In 2008 Wilkins et al. (2009) interviewed 135 frequent ecstasy users (at least monthly use over the previous six months). Subjects participated in an in-depth, hour-long face-to-face interview using a structured questionnaire. Recruitment was carried out in the three main centres (i.e. Auckland, Wellington and Christchurch), with subjects being predominantly male (62%) and pakeha (87%; 8% Maori; 1% Pacific Islander), over 16 years of age (mean age 23), and having resided at the site location for the previous 12 months. Sampling was purposive (targeted) and supplemented by 'snowballing' (affiliates contacted by respondents).[10]

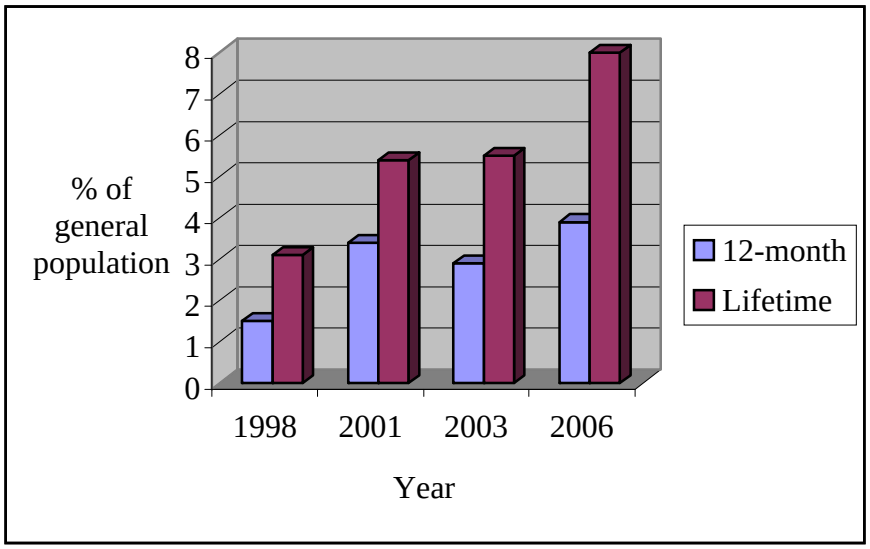
Their results, indicating stable to increasing access to ecstasy, were consistent with earlier research (Wilkins & Sweetsur, 2008c) comparing general population lifetime and 12-month prevalence of ecstasy data from 1998 to 2006 (Figure 2, following page).

In the later study (Wilkins et al., 2009) respondents described current availability of ecstasy as either 'easy' (46%) or 'very easy' (32%). In comparing present availability with earlier data (i.e. Wilkins and Sweetsur, 2008c), Wilkins et al. (2009) noted

[10] Wilkins et al. (2009:72) note that 198 subjects felt competent to comment on the price, purity and availability of ecstasy, including 99% of frequent ecstasy users, 34% of frequent users of methamphetamine (n=46) and 14% of frequent injecting drug users (n=19).

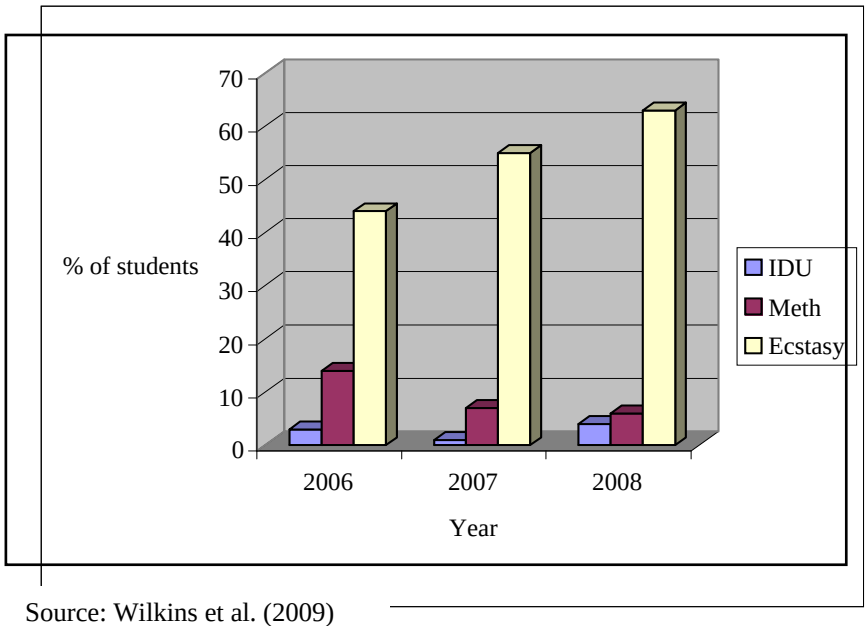
respondents perceived a further increase in availability, trending to statistical significance (p=0.0590). This perception of the increasing popularity of ecstasy is corroborated by other New Zealand research. In her recently completed qualitative study of the Wellington clubbing scene Hutton (submitted, 2009) found the use of ecstasy to be commonly accepted and prevalent among her small sample (n=26), with 21 respondents (80%) reporting use. Moreover, in other research concerning provision of harm reduction information on alcohol, ecstasy was noted by participants in the study to be a popular (university) student drug and one for which more information should be available (Hutton, 2008). In Figure 3 the prevalence of ecstasy among the student population relative to their use of other illegal drugs (i.e. methamphetamine and intravenous drugs) is evident in data from Wilkins et al. (2009).

Figure 2: Lifetime and 12-month ecstasy use in the general population, aged 15-45 years.



Source: Wilkins and Sweetsur (2008c)

Figure 3: Proportion of students reporting use of ecstasy, methamphetamine and intravenous drugs.



Source: Wilkins et al. (2009)

The above data are interesting as seizure figures supplied by the National Drug Intelligence Bureau (NDIB), for the years 2004 to 2008, suggest that the actual amount of ecstasy intercepted has been declining, particularly at New Zealand's borders, thereby implying decreased availability (Table 3).

Table 3: Incidents and quantities of ecstasy tablet seizure for years 2004-2008

Year	2004	2005	2006	2007	2008
Incidents	186	144	125	95	89
Quantity (tablets)	115,256	28,736	8,769	3,123	15,207

Source: Supplied by NDIB (2009)

In explanation, drug intelligence officials speculate that individuals and organisations trafficking in ecstasy are finding new ways to import the their product and that as yet these methods have not been discovered by Customs (personal communication with Les Maxwell, Strategic Analyst, NDIB). Wilkins et al. (2009) also report this view. Further, occasionally shipments destined for New Zealand are intercepted prior to their arrival here. This occurred in 2004 when Belgium authorities seized 55,000 MDMA tablets that were ultimately intended for New Zealand (NDIB, 2004).

Supporting evidence for the contention that ecstasy is getting into New Zealand by means as yet undetected comes from comparing Customs seizure incidents and quantities, with those by Police (Table 4). Data indicate that while in recent years, seizure and ecstasy quantity figures for both Customs and Police have declined, the

Table 4: Comparison between Customs / Police incident and quantity seizures for years 2004-2008.

Year	2004		2005		2006		2007		2008	
	Customs	Police	Customs	Police	Customs	Police	Customs	Police	Customs	Police
Incidents	65	121	41	103	25	100	15	80	12	77
Quantity	50449	64807	17507	28736	4484	8769	390	2733	121	15086

Source: Supplied by NDIB (2009)[11]

relative difference for Customs is much greater. This is particularly evident with seizure incidents, where 2008 figures for Customs are just 18% of what they were in 2004. By comparison, in 2008 Police seizure incident figures had only declined to 63% of their 2004 levels. While other factors will doubtless have contributed to this difference (e.g. the numbers of Police in comparison with Customs officers), the increase in quantity of pills seized in 2008, coupled with the data provided by Wilkins et al. (2009) suggests the domestic ecstasy market is being met to some extent. Moreover, as was discussed earlier, figures from the World Drug Report (2009) suggest that as is the case in Asia and South America, the prevalence of ecstasy in Oceania is increasing.

The reference to Asia is significant, as the international supply of ecstasy has also been changing in recent years, a factor discussed by Uitermark and Cohen (2005) in their analysis of the changing Dutch market. While the Netherlands has traditionally been one of the main global suppliers of ecstasy (along with Belgium), Asia has increasingly become a source, especially for relative neighbours like New Zealand. In this regard the NDIB (2004; 2008) notes the increasing shift of supply from the Netherlands and Belgium in favour of Hong Kong and China. They report (NDIB, 2004) that for the previous year 82% of the total ecstasy seized originated from these two countries.

Other data impacting on the market and prevalence concern price. Both the IDMS surveys and enforcement have commented on this. Wilkins et al. (2009) report the following median (mean) prices per pill: 2006 - $60 ($59); 2007 - $60 ($55); 2008 - $60 ($56). Thus they note that the mean price for a pill fell between 2006 and 2008, and that the difference trended towards significance (p=0.0767). Fifty-five percent of frequent users reported that the price for ecstasy had been ‘stable’ over the previous six months.

Nonetheless, by comparison NDIB data on price indicate considerable variation, with this likely being dependent on the purchaser’s place in the market. They offer the following figures (Table 5).

Table 5: Current ‘Street’ prices for MDMA in New Zealand

[11] In reviewing the NDIB *Annual Reports* (2005, 2006, 2008) it becomes apparent that there is considerable disparity between figures stated in these compared with 2009 raw data supplied by the NDIB (i.e. Tables 3 and 4). Generally the latter are significantly higher, in the case of 2004 by a factor of more than two (e.g. the 2005 *Report* records 45,387 pills seized for 2004, compared with 115,256 (Table 3). There are also disparities between reports. As the NDIB could not be contacted to provide clarification, it was decided to use the (generally) higher and more recent data initially provided upon request. These agree with those also reported by Wilkins et al. (2009:81), with the exception of the 2007 figures, which from the NDIB data are reported as 3,123. Wilkins et al. (2009) report 4,123 for this period.

Quantity	Price per unit
1 tablet (Street)	$45-$85
1tablet (Wholesale)	$20-$30
50-500 tablets	$32-$33 per unit
1000 tablets	$18-$27 per unit
2000+ tablets	$23 per unit
10,000+ tablets	$21 per unit

Source: NDIB (2008)

In their 2008 Report the NDIB also reference the IDMS price data noted above. However, as Wilkins et al. (2009) do not report their raw data it is unclear where their respondents were placed in the market. This would be useful information as one may speculate that a person with greater involvement in an illegal drug market (as a dealer, importer or manufacturer) would have greater knowledge of the substances concerned, and would therefore be able to provide more accurate data.[12]

The issue of 'expert' knowledge as opposed to 'general experience' is particularly relevant with regard to purity of street ecstasy. As has been mentioned throughout this review, pill 'contamination' or adulteration with either other psychotropics or non-psychoactive compounds is a significant health issue with potentially fatal consequences (e.g. Caldicott et al., 2003; Johnston et al., 2006; see sections 2.4.5 on pill testing and 2.6 'Potential for death'). This matter is discussed below in the section considering research aligned more with health and risk (section 3.2).

With further regard to prevalence Wilkins et al. (2009) note that in their sample, while 48% of frequent drug users considered 'about the same' number were using over the past six months, 44% considered that 'more' people they knew were using. This perceived increase in user numbers was statistically significant ($p=0.0281$) for the year 2006 compared with 2007.

A further metric of prevalence concerns the time taken to purchase drugs. Of frequent drug users, 27% reported that in 2008 they could purchase ecstasy within one hour or less. Wilkins et al. (2009) note that the proportion of their sample claiming to be able to do this had increased from 19% in 2007. The increase was not statistically significant. A further 13% of the 2008 sample could obtain ecstasy within a day, a similar proportion to previous years.

In terms of reliability of supply, 36% of frequent drug users reported there was 'always' a supply, while 42% described supply as 'mostly' available. Wilkins et al.'s (2009) data suggest there has been no change in availability by this metric across the years 2006-2008.

A final comment on prevalence pertains to use in the general population (15-45 years). Wilkins and Sweetsur (2008c) note a statistically significant increase in lifetime prevalence ($p=0.0019$) between 2003 (5.5%) and 2006 (8%). A similarly significant increase was noted for lifetime prevalence of ecstasy: 2001 (5.4%)

[12] Discussion was sought with Dr Chris Wilkins, first author of the 2009 IDMS report and SHORE Drug Research Team Leader, as part of the present review. He declined a formal interview. However, he was prepared to offer published papers.

compared with 2006 (8%) (p=0.0003); and 1998 compared with 2006 (3.9% vs 8%; p=0.0019). Moreover, figures for 'last year use' showed a significant difference between 1998 and 2006 (1.5% vs 3.9%) (Wilkins & Sweetsur, 2008c).

Two further data sets add detail to the picture of ecstasy use in the general population. 2003 data were collected by SHORE and analysed by Public Health Intelligence, the Ministry of Health's epidemiology group (Ministry of Health, 2007). These, deploying a computer-generated telephone survey of 8095 respondents aged 13-65 years, note the concentration of use within certain age groups, e.g. 13-17 (1.5%); 18-24 (11.3%); and 25-34 (6.7%). The study describes ecstasy as New Zealand's third most popular drug after cannabis and the amphetamines.

By comparison, the Christchurch Health and Development Study (CHDS) reports on a longitudinal inquiry following 1236 children born in Christchurch in the mid-1970's. At present the cohort has been assessed up to age 30. Although not having yet conducted an in depth analysis of ecstasy use, CHDS researcher John Horwood, providing comment on previously published drug use data (Boden et al., 2006) (personal communication; see also Appendix III) advised that to this age approximately a third of the cohort had ever used ecstasy. Use peaked in the early to mid 20's (22-25) with up to 20% of the cohort reporting use in a given year. Although most use was occasional, a maximum of 4% of the cohort were regular users (at least monthly) and 1% reported weekly or more frequent use.

Taken collectively, therefore, these data (i.e. CHDS; Ministry of Health, 2007; Wilkins & Sweetsur, 2008c) suggest a significant level of use in New Zealand, especially amongst those aged 17-34. Use may in fact be higher than what is claimed by Wilkins et al. (2008c). Commenting on an earlier SHORE analysis, known as the 'National Drug Use Survey' (i.e. Wilkins et al., 2002), Boden et al. (2006) observe that due to it being based on retrospective reports derived from cross-sectional data, there may be an underestimation of lifetime use of illegal drugs. Thus the prevalence figures for ecstasy reported in the present review should be viewed as a lower limit of use.

3.2 Ecstasy-related harm in New Zealand

There is an array of means by which to gauge harms related to ecstasy use. These include the negative impact on users' health, economic and social opportunities; impact on their affiliates; and on the wider society. Additional factors include associations with criminality and the impact of the quality of the drugs users are consuming. As previously discussed, some of the factors result from direct consumption of substances by drug users, while other harms are mediated by the context of use including the physical and social environment. The latter may also be mediated by society's views of substance use, including policy (MacCoun & Reuter, 2001). These issues are discussed below with reference to New Zealand data and research practices.

3.2.1 Physical and psychological health

Wilkins et al. (2009) describe a number of physical problems commonly reported by frequent ecstasy users. These included insomnia (67%), blurred vision (51%), heart palpitations (27%), and teeth problems (23%). Some of these events were statistically more likely to have been experienced in 2008 compared with 2007, for example, blurred vision (51% vs 37%, p=0.0276) and vomiting (29% vs 15%, p=0.0399). Two percent of frequent users in this sample reported overdosing on ecstasy in the previous six months (Wilkins et al., 2009). It is not clear from this study, however, what the severity of the overdoses were. Having noted this, 5% of frequent ecstasy users reported visits to Accident and Emergency Departments during the previous six months.

Other data potentially offering an insight into acute adverse events associated with ecstasy use include those from hospital presentations admissions. In New Zealand, however, definitive data per drug are difficult to access, a point acknowledged by the previous report to the EACD on MDMA (Ministry of Health, 2003). Issues are compounded by different reporting practices from individual hospitals and different admission protocols regarding time spent in ED's following presentation, but prior to either being admitted or leaving the hospital (personal communication with Dr Paul Quigley, Emergency Medicine Specialist, Wellington Hospital).

A further problem exists in that MDMA is not typically differentiated from other ATS's at presentation. Thus determining exactly which substance may be responsible for the presentation is left up to either the attending medical staff (via assessing symptoms) or accepting the explanation of the patient (personal communication with Dr John Fountain, New Zealand Poisons Centre, Otago University). These issues notwithstanding, the following data on pscyhostimulant poisoning were provided by Analytical Services, Ministry of Health (2009):

Table 6: Number of publicly funded hospital discharges with a primary diagnosis of T43.6 Poisoning by psychostimulants with potential for use disorder. Excludes short stay ED events.

	Total	**00-**	**05-**	**10-**	**15-**	**20-**	**25-**	**30-**	**35-**	**40-**	**45-**	**50-**	**55-**	**65-**	**70-**
1999/00	36	2		3	9	5	5	6	3	2			1		
2000/01	96	4		4	21	32	10	10	12	2	1				
2001/02	61	3	1	4	15	13	8	10	2	3	1	1			
2002/03	52	2	1	2	12	8	8	8	7	2	2				
2003/04	67	5	4	2	15	15	11	7	4	3	1				
2004/05	61	4		2	12	9	7	17	5	4	1				
2005/06	54	5		3	17	10	6	6	5	1		1			
2006/07	67	9		5	14	12	2	7	9	4	1	3	1		

2007/08	48	2	1	7	14	3	4	9	2	5	1		
2008/09	40	4			9	4	1	9	7	1	3		2

Source: Analytical Services, Ministry of Health (extracted July 8, 2009)

It will be seen from Table 6 that the bulk of admissions occur in the age groups 15-40, with presumably naive poisonings in earlier age groups. In the previous report to the EACD (Ministry of Health, 2003) it was noted that there were 109 publicly funded stimulant-related hospitalizations between the years 1996-1998, with a rise from 18 in 1996 to 46 in 1998. As the present data indicate (Table 6) this increase appears to have stabilized.

A further set of hospital data derives from a study reported by Theron et al. (2007), who examined overdose presentations at Auckland Hospital Adult Emergency Department through the years 2002-2004. They sought to compare 'Party Pill' presentations with other substances, including 'ecstasy'. These authors noted 'ecstasy' presentations (n) and the percentages (%) these comprised of total admissions for the following years: 2002 (n=46; 3.23%); 2003 (n=53; 3.87%); 2004 (n=38; 2.86%). They claim a monthly consumption of 200,000 tablets, thus the numbers above represent a small proportion of the hospital's annual burden of presentations. The authors also note that five of the ecstasy cases had co-ingested party pills and further comment that in the years reviewed, ecstasy presentations had not reduced, as had been suggested might occur with the introduction of party pills into the market.

In returning more generally to harms, Wilkins et al. (2009) also referred to a number of psychological symptoms resulting from ecstasy use, experienced by their 2008 sample of frequent users. These included strange thoughts (64%), anxiety (43%), visual hallucinations (28%), short temper (27%) and sound hallucinations (27%).

Regarding harm to different areas of their lives, frequent ecstasy users in the 2008 sample reported ecstasy's impact on 'energy and vitality (52%), 'financial position' (50%) and 'work and study life' (44%). Compared with 2006, in 2008 frequent ecstasy users were statistically significantly less likely to report harms to 'life opportunities' (9% vs 18%, p=0.0365) and 'home life' (10% vs 21%, p=0.0251) as a consequence of their ecstasy use (Wilkins et al., 2009).

Frequent ecstasy users in Wilkins et al.'s study (2009) were asked to identify the main drug types contributing to problems they had experienced. These were named as alcohol (57%), ecstasy (22%) and cannabis (15%). Specified problems for ecstasy users included loss of memory from the previous night (67%), reduced work or study performance (61%), being under the influence and behaving in a way they subsequently regretted (55%) and taking sick leave or cutting classes (53%). It is interesting to note that of Wilkns et al.'s (2009) three drug-type groups (ecstasy users, methamphetamine users and IDU's), only the ecstasy users identified a main drug (i.e. alcohol) *other than* the drug defining their inclusion in the study. This recognition of alcohol as a significant problem is also identified in Hutton's (submitted, 2009) study of ecstasy users in the Wellington club scene. While she notes alcohol is a

commonplace substance among her sample, her participants also described it as a source of stress in the clubbing environment.

3.2.1.1 Dependence

Drug dependence is a further indicator of problematic substance use and in the case of the present review, an important indicator of public health, legal and policy response to the use of ecstasy. However, as discussed above (section 2.7) the evidence for this is equivocal, with research having to engage with numerous confounders, including polydrug use and the problematic place of ecstasy in the DSM-IV nosological (disease classification) data set (Cottler & Grant, 2006). Perhaps as a means of avoiding the latter, Wilkins et al. (2009) employed a short item dependence scale (SDS) (i.e. 'severity of dependence scale'; Gossop et al., 1995) to identify levels of dependence within their sample. In their study those scoring four or more on the combined questions received a diagnosis as drug dependent.

Diagnostic questions and ecstasy users' responses are as follows:

i. felt out of control of their drug use – 2% felt this 'often' and 11% 'sometimes';
ii. feeling anxious about missing a dose – 15% (sometimes); 1% (often); 1% (always);
iii. extent of worry about drug use – 33% (sometimes); 2% (often); 1% (always);
iv. extent of wishing they could stop – 8% (sometimes); 3% (often);
v. how difficult finding it to go without drugs – 15% (quite difficult); 1% (very difficult);

Overall, Wilkins et al. (2009) report that in their 2008 sample of frequent ecstasy users 7% were classified as dependent, compared with 84% of IDU's and 63% of methamphetamine users.

To some extent this level of dependence (which arguably is not supported for the general population by treatment statistics—see below) should be expected as the sample reported on by Wilkins et al. (2009) is a relatively high-use, high-frequency one. Nonetheless, a level of support for dependence in ecstasy-using populations does come from the CHDS study, with approximately 3.2% of the Christchurch cohort meeting DSM-IV criteria for illegal drug dependence (other than cannabis) by age 25. The majority of those meeting dependence criteria were users of MDMA or other hallucinogenic type substances (Boden et al., 2006). Again, however, the caveat here is that these substances were not differentiated (the latter authors refer to 'hallucinogens' and 'Amphetamine-type stimulants; Ibid:159). As will be seen, when one examines New Zealand treatment data, ecstasy's profile in drug treatment presentations is remarkably low. This perhaps underscores the problems noted above regarding the generic application of the DSM-IV to specific substances with which it is presently not specifically nosologically aligned (e.g. Cottler & Grant, 2006).

A further means of gauging the effects of drug use on individuals is to examine the reasons people choose to use drugs. While some of these are positive, for instance

pleasure and social enhancement (e.g. Duff, 2008), other motivations may be aligned with pathology or the need to alleviate depression, stress, economic deprivation, social exclusion and mental health problems. Additional factors influencing the decision to use drugs or not may include availability and price (Wilkins & Sweetsur, 2008b). These factors are also mediated by policy, including the prohibition of drugs. While the latter may not be successful in eliminating drug use it may establish barriers to use through inducing fear of legal sanction, high prices and reduced availability (Wilkins & Sweetsur, 2008a). As discussed above, however, policy may also contribute to drug harm, for instance, through undermining the credibility of law, erecting barriers to treatment and education, facilitating unsafe use practices, promoting the growth of dangerous illegal markets and racist policing (Health Select Committee, 1998; 2003; Wilkins & Scrimgeour, 2000; MacCoun & Reuter, 2001). These and related issues are discussed below (section 3.2.3) in the context of New Zealand data.

While most of each of Wilkins et al.'s (2009) three samples expressed the desire to 'get high' (ecstasy users [95%] vs methamphetamine [95%] vs IUD's [85%]) there was also a negative discourse around dependence, i.e. 'because I am addicted': ecstasy users (23%) vs methamphetamine (58%) vs IUD's (79%). Not surprisingly, however, the trends noted above regarding dependence are reflected in these responses, i.e. that substantially fewer ecstasy users felt addiction was a major driver of their use.[13] Additionally, 19% of ecstasy users answered yes to the question: 'have you ever suffered from any form of mental illness in your life?' (Wilkins et al., 2009). Further, the latter's data revealed that 4% of frequent ecstasy users were currently receiving treatment or medication for a mental illness. This statistic is of interest given concerns raised over concomitant use of ecstasy and antidepressants noted above (i.e. regarding serotonin syndrome [section 2.3.1.3]; Silins et al., 2007).

In relation to mental health problems, Wilkins et al. (2009) reported that 9% of frequent ecstasy users had unsuccessfully sought help in the previous six months. As with the data noted above concerning problematic drug use, unlike the other two drug user groups, ecstasy users commonly sought assistance with drugs other than the one (i.e. ecstasy) for which they had been recruited into Wilkins et al.'s (2009) study, e.g. principally cannabis (53%) and alcohol (31%).

Unlike the other two groups, in fact, the frequent ecstasy users are not reported by Wilkins et al. (2009) to have had any problems specifically with ecstasy, which required drug treatment. This very low level of self-reported problematic use requiring mediation by treatment is corroborated by other New Zealand data. In response to questions on this matter, the Medical Director of Dunedin's Community and Alcohol Drug Service [CADS] advised that in his ten years as a consulting psychiatrist in that organisation he could not recall a single case in which a client had presented with ecstasy as their principal drug of concern (personal communication with Dr Gavin Cape, July 16 2009).

[13] One should also recall the comments noted above (Rogers et al., 2009; section 2.3.2.3) regarding the tendency to over-estimation by those self-reporting dependence symptoms. Having noted this, data from NZ-ADAM (New Zealand Police, 2008:47) show that 0.6% of arrestees self-reported dependence on ecstasy in the previous 12 months.

One could argue that this statistic relates to low prevalence in that part of New Zealand.[14] Similar data, however, are reflected on a national scale. For example, in the CADS treatment outputs for the period January to June 2008 ecstasy does not feature (CADS, 2008). Perhaps more significantly, however, Adamson et al. (2006) make no mention of ecstasy in their article comparing national alcohol and drug treatment populations for the years 1998 and 2004 (n=288 and n=383 respectively). Data reported on included main substance use problems. In a personal communication with the author of the present review, Dr Adamson confirmed that in the combined samples only one client presented with ecstasy as their principal drug of concern (in the 1998 survey). Moreover, Dr Adamson advised that in the yet-to-be-published 2008 data (n=350 approximately) no further treatment cases are reported with ecstasy as the primary drug (personal communication with Dr Simon Adamson, Senior Lecturer, National Addiction Centre, July 17 2009). Thus in combined samples totaling over 1000 individuals through a decade of treatment, ecstasy features only once (i.e. 0.1% of cases).

The above data receive some support from Wilkins et al.'s (2009) statistics indicating that 1% of frequent ecstasy users reported being in some form of drug treatment in 2008. This compares with 54% of IDU's and 21% of methamphetamine users. It would be useful to know what proportion of the ecstasy group was receiving treatment primarily for ecstasy. The same question could be asked where Wilkins et al. (2009) note that in 2008 seven percent of ecstasy users 'accessed medical and health services in relation to drug use' in the last six months. In a similar vein data reported for the Alcohol and Drug Help Line (2002-2008) do not mention ecstasy (Wilkins et al., 2009).

Overall, therefore, while Wilkins et al. (2009) conclude their drug harms chapter noting the 'high proportions' of ecstasy users being motivated to use due to 'boredom', that 19% had suffered from a mental illness, 4% were currently receiving treatment for a mental illness and that 9% had unsuccessfully sought help for their drug use in the past six month, even these comparatively modest figures require cautious interpretation. As research elsewhere has repeatedly shown, there are numerous confounders to eliminate—not the least being polydrug use, which is typically frequent among ecstasy users—before substantive comments can be made specifically about the effects of ecstasy (ACMD, 2009; Rogers et al., 2009).[15]

3.2.2 Youth, social deviance, criminality, enforcement and economics

3.2.2.1 Education

[14] Superficially, with some justification: the annual report of the Arrestee Drug Abuse Monitoring programme (New Zealand Police, 2008) notes that due to low 'through-put' in Dunedin for the year of that report only 101 individuals contributed their statistics to the entire sample of 820. See Hales, J. & Manser, J. (2008). *New Zealand Police: NZ-ADAM* (Annual Report). Kent Town: New Zealand Police, p. 9.

[15] Wilkins et al., (2009) reported a mean of 7 drugs used by frequent ecstasy users in the previous six months, and a lifetime mean of 11, the highest for all three groups.

Wilkins et al. (2009) provide some interesting data on the educational background and experiences of ecstasy users, as well as on socially deviant acts including crime and driving under the influence of drugs (DUID). A summary of these data shows that of Wilkins et al.'s (2009:183) sample of frequent ecstasy users:

i. twenty-three percent reported truancy from school 'often' or 'all the time';

ii. twenty-three percent had been suspended and 7% had been expelled from school;

iii. thirty-seven percent had committed a property crime, with 7% having done this in the previous month;

iv. fifty-two percent had sold drugs, with 27% having done this in the previous month;

v. eighteen percent had committed a violent crime, with 1% having done this in the previous month.

Regarding education, while substantial proportions of Wilkins et al.'s (2009) sample of frequent ecstasy users reported truancy (23%), suspension (23%) and expulsion (7%), only 4% of this group had no school qualifications. The difference between the ecstasy users and IDU's / methamphetamine users was statistically significant in both cases (p=0.0001). Additionally, Boden et al. (2006) note that while illegal drug use and dependence is commonly reported to be associated with a lack of formal education, in their cohort analysis association with education was mediated by a number of other factors. These included family and childhood factors (i.e. illegal drug-using parents; sexual abuse), peer factors (i.e. affiliation with other drug users) and personality factors (i.e. cigarette and alcohol consumption; novelty-seeking and conduct problems by age 14). Thus a model of cumulative risk becomes the most useful means of predicting illegal drug use (Ibid:161).

3.2.2.2 Driving

Driving and drug use (including alcohol) was also examined by Wilkins et al. (2009), with a substantial proportion of ecstasy users (43%) admitting they had driven under the influence of alcohol in the previous six months.[16] Ecstasy users were statistically more likely to have driven while alcohol-affected, between 2008 vs 2006 (p=0.15).

Additionally, the authors comment on the *extent* to which frequent ecstasy users drove alcohol-affected, again comparing 2008 vs 2006, and noting a trend to significance (p=0.0797). However, the utility of these latter data may be questioned, given the subjective categories employed, e.g. users drove alcohol-affected 'hardly ever', 'some', 'most' or 'all' of the time. The meanings of terms such as 'hardly ever' 'some' etc. vary between individuals, with evidence of considerable variation between individuals when respondents are asked also to estimate a percentage (Noller, 2008).

[16] In their table (16.1, p 185) and Chapter Summary (p 204) Wilkins et al. (2009) report 43% while in the text the figure of 34% is used.

Methodological issues aside, Wilkins et al. (2009) also report that in the previous six months while driving under the influence of alcohol, of their sample of ecstasy users: 8% had a car crash; 11% lost their licence; and 7% were charged with a driving offence (e.g. DIC). Almost 70% of ecstasy users driving under the influence of alcohol acknowledged some level of impairment, with over half (54%) perceiving it unlikely they would be stopped.

Similar questions were asked about driving and the use of drugs other than alcohol, with 62% of ecstasy users (n=108) reporting some driving under the influence of drugs (DUID) in the previous six months (Wilkins et al., 2009). As with areas of use and unlike IDU's and methamphetamine users, ecstasy users most commonly reported a drug *other than* ecstasy (i.e. cannabis [80%] vs ecstasy [42%]) as the most frequently used drug while driving. Of these, half (49%) reported 'hardly any' DUID and 43% reported 'some' in the last six months. With regard to DUID in the previous six months, Wilkins et al. (2009) note that 3% of ecstasy users 'had a car crash' and 2% lost their licence. Sixty percent acknowledged some level of drug-driving impairment.

The New Zealand Drug Foundation's recently completed internet survey (Hammond, 2009) provides a further set of New Zealand data examining DUID. Although not representative of the general population, the study surveyed 1164 respondents aged over 15, asking them about DUID patterns, as well as their opinions, perceptions and experiences of use in this context. The sample was 83% pakeha (vs general population 68% pakeha); 6.6% Maori (vs 14.6%); 2% Pacific Islander (vs 6.5%); 1.5% Asian (vs 9.2%). More generally the sample was over-represented by well-educated females from Auckland and Wellington.

Of respondent drivers, 41.7% reported some DUID in the last twelve months, while 12.3% reported using 'ecstasy'. Of those using ecstasy, 3.3% reported some driving while affected by ecstasy (i.e. almost a third of the sample's ecstasy users). Of the whole sample, DUID on cannabis (24.5%) and alcohol (21.4%) were most common. Of DUID drivers, males (31.5%) were more likely than females (21.5%) to drive drug-affected. The mean age of DUID ecstasy drivers was 29.1 years (Hammond, 2009).

The sample was also asked questions regarding perception of various risks (e.g. degree of impairment; likelihood of harm to self or others, likelihood of being caught). Regarding impairment, over 50% of ecstasy users saw either no change in their driving when DUID on ecstasy or an improvement. While some research (e.g. MacIntosh et al., 2008) would suggest this likely reflects drivers' greater concerns around being detected versus personal safety, in the present example this seems not to be the case, e.g. only 17% nominated detection as a reason not to drive drug-affected (see below). Nonetheless, ecstasy was rated by users as being moderately dangerous for driving under the influence of. In comparison, drugs perceived as more dangerous to drive on included alcohol, hallucinogens, ketamine, GHB and heroin. For DUID on ecstasy, risk perception in general was viewed as significantly greater ($p<0.01$) by non-DUID drivers vs DUID drivers.

This study (Hammond, 2009) also reports on respondents' knowledge of DUID, with 31.5% reporting they knew 'very little' about this and 25% claiming they knew 'nothing'. Over half (52.2%) did not know how long one would have to wait in order to drive safely once having taken ecstasy and having felt its effects. Even so, the study reports that in the previous twelve months 34.1% of ecstasy users had decided not to drive following consumption. The most common reason reported was having concerns about others (63.8%). Further reasons included feeling negatively affected (60%), worried about one's own safety (57.4%) and worried about getting caught (17%). Ecstasy users were also asked how likely it was that they would drive drug-affected during the next twelve months. Seventy percent replied 'not likely at all'.

As final evidence of the relatively common practice of DUID on ecstasy, NZ-ADAM (New Zealand Police, 2008) data indicate that 53% of arrestees claiming to have used ecstasy (n=110) had done at least 'some' of their driving while affected by it.

3.2.2.3 Criminality

Wilkins et al. (2009:172) provide a useful and succinct précis of criminogenic theories examining the linkages between drug use and acquisitive offending. A point emerging from their discussion is the difficulty in assigning causality as opposed to association. The lack of explanatory power of theories linking crime and drugs, therefore, challenges the viability of ascribing a set of characteristics to a given sample, e.g. to what extent is it meaningful to group individuals on the basis of their substance use or, more appositely for the present review, on the basis of their use of a specific substance?

Regarding criminality, Wilkins et al. (2009:176-83) examined frequent ecstasy users' associations with criminal offending, reporting lifetime prevalence for the following: property crime (37%), drug dealing (52%), fraud (12%) and violent crime (18%). They noted a median first offending age for property crime of 15 years for ecstasy users (n=135). While the proportion of this group who were ecstasy users at the age of 15 is not reported, prevalence data for this age from longitudinal (i.e. Boden et al., 2006 [1.8% at age 15]) and general population cross-sectional studies (i.e. Ministry of Health, 2007 [13.9% ages 13-17]) indicate it is likely to be relatively low.[17] Additionally, however, arrestee data (New Zealand Police, 2008) show that of those arrestees having used ecstasy (36% of the sample) 41% of them (i.e. 15% of the total sample) had tried ecstasy by age 18. Concerning property crime in the last month, a between-group comparison (Wilkins et al., 2009) reveals the following levels of involvement: IDU (25%), methamphetamine (25%) and ecstasy (7%) respectively.

[17] The comparison between these two studies (Boden et al., 2006 vs Ministry of Health, 2007) is problematic given the different ages and periods reported on. For example, at the time of the CHDS sample's interview at age 15 (in 1992), New Zealand prevalence of ecstasy was much lower than at present. There is also the issue of self-reporting drug use. The present author has previously discussed this with Prof. Ritchie Poulton (Director of the Dunedin longitudinal study [Dunedin Multidisciplinary Health and Development Study—DMHDS]) who advised that while reporting rates would likely be more accurate in the New Zealand longitudinal studies than general population surveys, there would potentially be an under-reporting factor of approximately 5% on illicit drugs. Hence the 1.8% use at age 15 noted by CHDS is conservative.

With reference to selling illegal drugs, ecstasy users' median age of first selling (19 years) was the same as that for IDU's and methamphetamine users. Wilkins et al. (2009) also report there was less difference between groups than for property crime, with respective figures for selling drugs in the previous month being IDU (32%), methamphetamine users (32%) vs ecstasy users (27%).

Although much smaller proportions of each group reported fraud during the previous month, again Wilkins et al. (2009) record there were clear differences between IDU's (7%) and methamphetamine users (5%) vs ecstasy users (1%).

While lifetime prevalence of violent crime also showed differences between IDU's (48%) and methamphetamine users (42%) vs ecstasy users (18%), the latter were clearly associated with this behaviour. As with fraud, however, there were substantive differences in reported violent offending for last month figures between IDU's (6%) and methamphetamine users (6%) vs ecstasy users (1%), with the difference trending towards significance (p=0.0864) (Wilkins et al., 2009).

The low last-month association of ecstasy users with violence reflects the comments made above regarding the difficulties in attributing causality concerning criminal activities and drug use, and also those relating to violence and ecstasy use reported elsewhere (i.e. Hendrickson & Gerstein, 2005; see section 2.4.7.2). The latter American study described Arrestee Drug Abuse Monitoring (ADAM) System data from 7794 men aged 16-25, and 9764 similarly aged men from the National Household Survey on Drug Abuse (NHSDA). While bivariate and regression analyses of these data yielded a positive association between ecstasy users and drug market participation, the association was negative for property and violence offences.

Neither do other New Zealand data indicate substantial associations of ecstasy with violent offending. For example, a New Zealand pilot of ADAM (NZ-ADAM; n=62) (Wilkins et al., 2004) reported that the majority of violent offences (57%) were proceeded either by the use of alcohol or alcohol in combination with other drugs. Ecstasy received only brief mention. While 27% of the sample reported lifetime use, 7% reported use last year with typical consumption being one pill per occasion. Two percent reported use in the last month, with an average of 3 pills per month consumed. There was no use reported in the 48 hours prior to arrest.

The most recent annual report for NZ-ADAM (New Zealand Police, 2008) offers similarly meager associations between ecstasy use and crime, and particularly violent offending, despite a larger sample (n=820) than the pilot. In this report, while 36% of arrestees acknowledged lifetime use of ecstasy and 6% (infrequent) use in the last month, only 0.2% tested positive by urinalysis (although 0.4% admitted use) and 0.6% self-reported dependence. Further, 92% of those reporting ecstasy use (n=110) claimed that it either reduced the likelihood of them becoming angry or made no difference.

This is not to suggest, however, that a history of using ecstasy precludes the consumer from acting violently. For example, the NZ-ADAM data indicate that 7% of those charged with a serious assault in the previous 12 months had used ecstasy, as had 11% charged for a minor assault. Use in the last 30 days dropped to 2.8% for serious

assaults. However, no use in the previous 48 hours was reported by those charged with either serious or minor assaults (New Zealand Police, 2008).

The above notwithstanding, when asked what proportion of their current criminal activity (i.e. the offence for which they were arrested) was caused by the drug/s they were using at the time, the sample's two ecstasy users claimed none of it (0%). By way of comparison, of those having consumed alcohol at the time of their arrest, 80% considered it contributed to all or most of their current offence (New Zealand Police, 2008).

The NZ-ADAM (New Zealand Police, 2008) report also examined arrestees' perception of risk and/or violence associated with their participation in illegal markets, by drug (i.e. risk from police when buying / selling, and risk from market violence generally). Thirty-nine percent and 46% of those having used ecstasy described police-associated risks as either fairly or very high for buying and selling respectively, while 34% considered risks from market violence either fairly or very prominent. Ecstasy consumers' perceptions, regarding the risk of market violence, is supported by police experts. In a discussion with the NDIB regarding the risks and harms of use, officials indicated that in their view a significant cause of ecstasy-related harm was that associated with market violence, where naïve users encountered financial problems with suppliers (personal communication with Les Maxwell, Strategic Analyst, NDIB).

Concluding this section on the associations between ecstasy and criminality is a brief consideration of New Zealand research examining the potential for ecstasy to be used as a 'date rape' drug, i.e. in Drug Facilitated Sexual Assault (DFSA). Studies reporting the incidence of DFSA were discussed previously (section 2.4.7.3). This phenomenon was also signaled as a concern by the authors of the U.K.'s recent report on ecstasy (ACMD, 2009), which noted a small number of cases implicating MDMA.

New Zealand research (Jansen et al., 2006) has critically assessed the issues surrounding DFSA. The authors concluded that the likelihood of ecstasy being used in this regard is low. Jansen et al. (2006) comment that MDMA can be portrayed as a date rape drug by skewed media reporting. As discussed above, they also note that where victims of DFSA receive toxicological screening, it is not unusual for MDMA to be detected. A simple explanation for this that victims may meet perpetrators in nightclubs or bars and that drug use, including MDMA, is not uncommon in these environments. For example, in profiling drug use trends in the Taiwanese club scene, researchers found 75.7% of a sample of clubbers to be positive for MDMA (Lua et al., 2003).

While drugs such as MDMA may be common in the club scene, for a substance to be a successful candidate for use in DFSA, Jansen et al. (2006) argue it must have a number of characteristics. It should physically disable a victim, sedating them to point of unconsciousness and memory loss. It should also markedly impair motor function (ability to move), be odorless, tasteless, dissolve readily in alcohol or other drinks, and be rapidly absorbed. In this context stimulants are an improbable choice. They tend also to have a 'vile' taste and therefore are not good for slipping into drinks. In countering this, the argument might be made that stimulants are an appropriate choice as it is not easy to drag an unconscious person from a venue. There is research,

however, suggesting much DFSA occurs not at clubs and bars, but when people are alone. In this context benzodiazepines and GHB (gamma hydroxybutyrate) are far more likely to be used (Welner, 2001).

Further mitigating against the use of MDMA in DFSA are its specific user-sought effects noted previously, i.e. it induces an increased sense of empathy and emotional closeness with others; it rarely causes ego disorganisation, with use leaving reality testing relatively intact, particularly in comparison with more familiar psychedelic drugs such as LSD. Thus MDMA is gentler, subtler, and more controllable; it invites rather than compels intensification of feelings and self-exploration. Despite making this argument Jansen has noted elsewhere (Jansen, 2001) that on rare occasions individuals can have strong negative reactions to MDMA including delirium, disorientation, hallucinations, amnesia. Nonetheless he and colleagues note (Jansen et al., 2006) that MDMA can also interfere with sexual function, i.e. it can mimic and stimulate stress functions. Thus it can affect blood supply, causing difficulties with erectile and ejaculatory function (Liester et al., 1992).

Taken collectively, therefore, evidence assembled by Jansen et al. (2006) argues against the likelihood of MDMA / 'ecstasy' being employed as a 'date rape' drug. As noted in the earlier discussion of DFSA (section 2.4.7.3), the drug with probably the greatest potential for facilitating sexual assault is alcohol.

3.2.2.4 Enforcement

One may also examine the intersection of crime and drug use from the perspective of enforcement. Wilkins et al.'s (2009) penultimate chapter considers frequent ecstasy users' contacts with the police and justice systems, and the implications of these. Wilkins et al. (2009) commence by noting the productive role enforcement may have in a harm reduction context, with different phases of drug problem development requiring different responses. Thus in a developing drug market situation police might attempt to prevent rapid uptake of a substance and development of the market through direct intervention, i.e. arrests and seizures. A later phase of intervention might alternatively involve enforcement initiatives emphasising institutional incentives whereby users are encouraged to enter treatment, i.e. to avoid arrests, incarceration and to embark on recovery. An example of the latter includes court-mandated entry into New Zealand therapeutic communities such as Odyssey House (Auckland and Christchurch) and Moana House (Dunedin).

Having noted the above, the extent to which this aspect of enforcement applies to ecstasy users is arguable (i.e. given lower rates of criminal offending, dependence etc.). Similarly, while ecstasy users do encounter law enforcement, aside from using, possession and dealing offences, this interaction appears to be less mediated by other criminal behaviours than is the case for those using other drugs. This is evident in Wilkins et al.'s (2009) survey, where they note statistically significant differences between methamphetamine and ecstasy users for lifetime arrest (66% vs 38%; $p=0.0001$), conviction (54% vs 12%; $p=0.0001$), imprisonment (30% vs 3%; $p=0.0007$) and twelve-month imprisonment rates (6% vs 1%; $p=0.0098$) respectively. Wilkins et al. (Ibid) comment that these differences are even more pronounced in comparing IDU's with ecstasy users.

3.2.2.5 Economics

As with enforcement, the economics of ecstasy use as reported by Wilkins et al. (2009) suggests differences relative to the use of other drugs. Whereas acquisitive crime over the last six months, as a proportion of income to pay for drugs, featured as the principal means for both IDU's (9%) and methamphetamine users (6%), this was not a feature of ecstasy users' (0%) payment for drugs. This proportionality is also reflected in the percentages of respective drug user groups deriving income from property crime in the previous month: IDU's (17%), methamphetamine users (13%) vs ecstasy users (1%). Having noted this, relatively similar proportions of each group derived previous month-income from drug dealing: IDU's (20%), methamphetamine users (24%) vs ecstasy users (17%).

Differences between IDU's and methamphetamine users versus ecstasy users are also noted by Wilkins et al. (2009) with the proportions of income used principally to pay for drugs derived from unemployment / social welfare benefits: IDU's (30%), methamphetamine users (23%) vs ecstasy users (6%). Contrarily ecstasy users (77%) were far more likely to principally use money from paid employment to purchase drugs than were IDU's (20%) or methamphetamine users (46%). It is interesting also to note the mean dollar amounts spent by each group in the previous week on the purchase of illegal drugs: IDU's ($227); methamphetamine users ($210) vs ecstasy users ($62).

3.2.3 Policy

As discussed in the introduction to this section, while policy aims to reduce harms associated with drug use, both internationally (e.g. MacCoun & Reuter, 2001) and in New Zealand (Heath Select Committee, 1998; 2003) evidence suggests it also has the potential to exacerbate harms. In this regard Wilkins and Scrimgeour (2000) have noted the propensity for analyses of drug policy efficacy to focus simplistically on numbers of drug users rather than on more sophisticated benefit-cost scenarios.

Concerning ecstasy, New Zealand policy has sought principally through enforcement to reduce availability and the numbers using, thereby limiting the harms users, their affiliates and wider society are exposed to. As the data discussed above indicate (i.e. very few deaths, small numbers of hospital admissions and seemingly low levels of abuse and dependence), in this regard policy appears to have been relatively successful.

This success notwithstanding, there remain questions over the extent to which present policy may also be implicated in the risks New Zealand ecstasy users are exposed to. In commenting on drug policy generally and on drug prohibition specifically, Wilkins and Scrimgeour (2000) invoke the notion of 'socially efficient' legislation. Thus policy's efficacy must be measured against a range of benefits and harms, not simply drug supply and numbers of users. As with others (e.g. MacCoun and Reuter, 2001) Wilkins and Scrimgeour (Ibid) catalog the harms attributable to prohibition, including: the harmful black market for drugs, which produces substances of poor

quality, leads to a market controlled by violent criminals and inflates drug prices, thereby exacerbating street crime to fund drug users' needs. These issues are considered below in the context of New Zealand ecstasy use data.

Discussion in earlier sections (2.4.4 and 2.4.5) centred on the international experience of pill purity and testing, with clear risks associated with pill content (Quin et al., 2004; Johnston et al., 2006). Moreover, while there was evidence of users actively seeking information about pill content through testing (White et al., 2005), concerns were also raised about the efficacy of testing and its potential for providing a false sense of safety for users (Winstock et al., 2001).

Regarding pill content, Wilkins et al. (2009) report that 32% of frequent drug users described the current purity of ecstasy as 'fluctuating' and 30% as 'medium'. This produced a mean score of 2.7, which the authors suggest indicates overall purity was 'fluctuating/medium'. Comparing these results with data for 2006 and 2007, the authors note no difference in purity for these years.

When considering the previous six months, 40% of frequent users believed purity to have been 'fluctuating' while 29% described it as 'stable'. Frequent users were more likely to consider ecstasy as decreasing in purity between 2008 and 2007, and even more likely (i.e. approaching statistical significance, p=0.0679) to see a decrease between 2008 and 2006 (Wilkins et al., 2009:75-76).

Though subjective, to some extent the likelihood of moderate and fluctuating purity noted by the above assessments is borne out by comparison with an earlier analysis of pill content commissioned by the Ministry of Health in 2000 (ESR, 2000), and more recent periodical analysis. In the first, the ESR analysed pills seized during the period July 1999-June 2000. Tables 6 and 7 (below) give an indication of pill content and purity respectively for that period. It shows that though of moderate purity, the majority of pills seized (76.8%) contained MDMA predominantly.

Table 6: Content analysis of 99 seizures of pills for the period July 1999 to June 2000

Major Drug(s) Detected *	Number of Seizures	**Percentage**
(Out Of 99)		
MDMA	76	76.8%
MDA	3	3.0%
Methamphetamine	10	10.2%
Amphetamine	3	3.0%
MDMA / MDA	3	3.0%
MDMA / Amphetamine	3	3.0%
MDEA / MDMA	1	1.0%

Source: ESR (2000:2)

Table 7: Strength and purity analysis of 92 seizures of pills for the period July 1999 to June 2000

Drug	No. of Seizures	Total Doses	Average Strength (mg/dose	Strength Range (mg/dose)	Average Purity (%)	Purity Range
MDMA	75	8604	91.8	30.2-172.4	36.3	12.7-97.3
Methamphetamine	9	514	18.5	0.8-42.7	9.0	3.1-16.2
Amphetamine	3	110	7.1	1.4-16.4	2.3	0.6-4.8
MDA	3	2440	48.2	37.7-57.1	35.4	12.9-76
MDEA	1	4	51.3	51.3	18.7	18.7

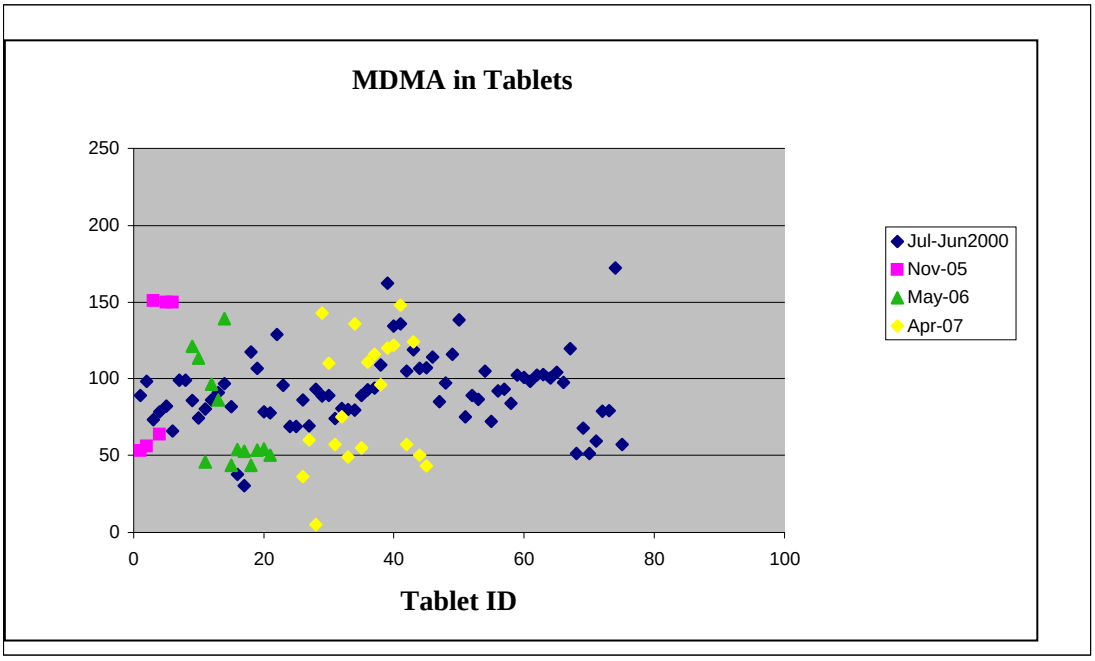
Source: ESR (2000:3)

Other substances found singly and in combination with the above included:

i. MDMA, amphetamine, caffeine;
ii. MDMA, cocaine;
iii. MDMA, caffeine;
iv. Methamphetamine
v. Methamphetamine, ketamine;
vi. Methamphetamine, ketamine, caffeine;
vii. Methamphetamine, procaine;
viii. Ketamine, caffeine.

The analysis comprising the above report (i.e. ESR, 2000) has not been repeated for the Ministry. However, the ESR completes quarterly analyses of seized pills, producing coloured sheets that include pill content, for identification. In Figure 4 (below) cumulative analyses of these reports (to 2007) are compared with the 2000 data.

Figure 4: Comparison of MDMA content of seized tablets for the years 2000, 2005, 2006, 2007



Source: Supplied by ESR, July 21 2009

It will be seen that as Wilkins et al.'s (2009) participants suggest, there is considerable variation in pill content, though an appreciable drop-off in overall quality is not evident over the three most recent years (i.e. 2005-2007). Hence, while Wilkins et al.'s (2009) data are of some interest they do not provide very specific information. It would be useful to know by what metric frequent users assessed the purity of their pills. For instance, what proportion of the sample actually tested their pills? Additionally, what level of knowledge or practice around pill testing exists in the New Zealand ecstasy user community (see Appendix V for an example of a New Zealand ecstasy user pill testing report)?

The ESR supplied the present review with more recent data yet to be plotted with previous years. It is interesting to compare this (ESR Group Drugs Report, December 2008) in terms of content with respect to the information above. Hence, the following substances were detected singly or in combination in the ESR's December 2008 report:

i. MDMA;
ii. MDMA, caffeine;
iii. BZP, TFMPP, di-BZP;
iv. MBDB, TFMPP, bk-MBDB;
v. BZP, TFMPP;
vi. Caffeine;
vii. MDMA, BZP, TFMPP;
viii. MBDB, Methylone;
ix. mCPP (metachlorophenylpiperazine);
x. 'unusual cases' (ESR's own description):
    a. BZP, TFMPP, diphynylprolinol;
    b. Amphetamine;
    c. BZP, TFMPP, prochlorperazine;
    d. Opium, eugenol (oil of cloves).

Immediately obvious in the above is the preponderance of BZP and related piperazines (i.e. TFMPP) found in the analysed pills, something that was not the case in earlier samples. It is not clear from the ESR's (December 2008) report what amounts of BZP or TFMPP are typically present in pills.[18] Neither is it known what kinds of synergistic reactions might obtain in the combining of the various constituents noted above or the extent of any risk associated with such combinations. Nonetheless, international research has proposed there might be dangerous drug-drug synergies resulting from the co-administration of piperazines at high dosages (EACD, 2004a; Baumann et al., 2005). Underscoring these concerns is the report of the death of a 23-year-old woman in North America who developed massive brain edema and subsequent tonsillar herniation (extreme intracranial pressure causing brain organs to be shifted in skull) after ingesting BZP and MDMA (Haroz & Greenberg, 2006).

Of issue here is the negative impact of policy on the illegal drug market. By criminalizing a substance, its use and users, an environment exacerbating harms has been created. In the case of ecstasy this has resulted in not only a low quality of pills being available (e.g. Table 7 indicates that even in 2000 the average purity of MDMA seized in New Zealand was only 36%), but also the adulteration of pills containing other psychoactive substances with the potential, through synergistic reactions, for even greater harms.

Ironically the latter substances (piperazines) were also recently criminalized (2008), along with their users, again with the aim of reducing harms. At that time psychologist James Green raised concerns about the impact, on substance use, of criminalizing BZP following a 2007 study of users at Otago University (Green, 2008). His participants (119 students aged 18-27 years) were questioned concerning their use of ecstasy and BZP, and how policy change involving BZP might impact on their drug taking. A sub-sample of the participants (n=41; 34.5%) reported they would consider taking BZP in the future, with almost half considering either stockpiling supplies or taking other illegal drugs, particularly ecstasy. Prior to the policy change Green submitted his unpublished results to the Health Committee deliberating on the proposed law change. He stated explicitly that his research indicated "current users of BZP-based party pills are intending to increase their illegal drug use, especially Ecstasy, if a ban of BZP is implemented" and that "some current users of BZP indicated that they were likely to stockpile BZP prior to the ban" (Green, 2007).

The issue of pill purity is of concern to users as well as to authorities. As discussed above there is evidence from Australia that users are proactive in seeking information about pill content, with one study reporting 84% of a sample of regular ecstasy users (n=810) making some attempt to determine their pills' quality (Johnston et al., 2006). Twenty-two percent of this sample reported personal use of testing kits. Also previously discussed (section 2.4.7.4) was the Dutch system of monitoring pill quality, initiated in the 1980's and subsequently embraced by their Ministry of Health (Uitermark & Cohen, 2005).

In New Zealand, however, the extent to which pill-testing is practiced by users is unclear. This is a neglected area of current research (e.g. Wilkins et al. [2009] make

[18] The EACD's advice to the Minister (EACD, 2004a) notes a standard single dose for BZP of 100 mg.

no mention of it in their discussion of quality) despite evidence that New Zealand users are aware of testing and do use the kits (see Appendix V for an example of a testing report). Furthermore, there is evidence that current policy creates barriers to testing. The issue of non-government and private testing of 'ecstasy' was raised with the ESR during the course of the present review. Their chief scientist advised that while the ESR had been approached to assay street 'ecstasy' their policy was to decline as to not do so would involve them in abetting illegal activities. However, Dr Bedford did note that the ESR had carried out analyses for Stargate International, at the behest of its founder, Matt Bowden (personal communication with Dr Keith Bedford, General Manager, ESR, 28 July 2009). In a conversation with Mr. Bowden, also spokesperson for the Social Tonics Association of New Zealand (STANZ), the present reviewer was given to understand that a number of samples of street 'ecstasy' had been supplied to the ESR for analysis under a standard commercial contract. The Police had also been advised that samples would be collected and tested (personal communication with Matt Bowden, Spokesperson, STANZ, 17 July 2009; see also Appendix VI). Both experts noted the difficulty posed by the lack of 'an official' position on testing for private / recreational purposes. Dr Bedford agreed than if an appropriate protocol should be negotiated, then the ESR could potentially engage in testing street ecstasy under the rubric of harm minimisation. Additionally, Mr. Bowden advised that given the expense of testing (approximately $350 per batch of samples) he had attempted to purchase the relevant equipment overseas. However, he had been denied purchase as the supplying company's policy forbade supply to non-government parties.[19]

Perhaps a final example of policy's culpability in the harms experienced by New Zealand ecstasy users concerns the potential for users to come into contact with organised criminals and violence in the market place. This has been discussed previously where ecstasy-using arrestees (36% of the 810-person sample) interviewed for the NZ-ADAM (2008) annual report were asked about violence associated with buying, selling and general participation in the market. Of this group, about one third (34%) considered risks from market violence to be very or fairly prominent. While Wilkins et al. (2009) did not ask their sample directly about risks from market violence, they did note that 10% of frequent ecstasy users 'purchased' their drugs on credit. The risk potential for this situation was also referenced by National Drug Intelligence personnel who identified, along with pill purity, the problem of indebtedness and subsequent violent retaliation as significant risks for ecstasy users (personal communication with Les Maxwell, Strategic Analyst, NDIB, June 2009).

In summing up the points made regarding policy's contribution to ecstasy-related harms in New Zealand, it is useful to conclude with comments by Wilkins and Scrimgeour (2000). They observe that in contrast to an illegal market, a legal market would allow authorities to regulate the sale and manufacture of drugs; to provide buyers and sellers with peaceful means to resolve contractual disputes; and to facilitate harm reduction activities (i.e. safe drug use education, reduction to barriers to treatment) (Ibid). The latter point echoes the recent U.K. review of ecstasy-related harms, the first four recommendations of which emphasised harm reduction initiatives and especially education around ecstasy harms and use (ACDM, 2009).

[19] A written précis of Mr. Bowden's related research, including his interactions with the ESR is included in Appendix VI.

3.3 Discussion

The preceding review of international and New Zealand literature has examined data on the effects of MDMA/ecstasy both in a general sense regarding chemical classification, history of use and research and effects, and in the context of harms to users and society. The subsequent section (section 4) places that literature in the context of New Zealand's Misuse of Drugs Act (1975), specifically in Section 4B(2). Prior to section 4 is a brief assessment of the New Zealand literature accompanied by relevant recommendations.

Hutton (submitted, 2009) makes the comment that much of the New Zealand research on drug use in general and club drugs / ecstasy in particular, is focused on surveys detailing prevalence. Thus there is a preponderance of quantitative and epidemiological data noting demographics, frequency and intensity of use, trends of use, supply, price etc. but little qualitative data. The present review generally supports her view. Of this type of research the gold standard is the work carried out by Massey University's SHORE institute (e.g. Wilkins et al., 2009). This is a source commonly referred to by other stakeholders in New Zealand's substance use and drug policy fields. This particular data stream is well organized, with standardised results consistently reported. There is a value in this consistency in that it allows comparison across studies, often an area of difficulty, as noted above (see footnote note 17).

Since 2005, with the deployment of the IDMS, SHORE has branched out from straightforward surveys to more ethnographically orientated research. This useful development has the advantage of gaining an insight into drug use from the users' perspective. While this is a welcome development, the opportunities afforded SHORE researchers to engage with the culture of use could be taken further. With the focus on harms, there is a tendency to concentrate on high-frequency, high-use individuals. While this affords insight into explicit risk and damage faced by drug users, at present it remains somewhat passively applied. As discussed previously, it would be useful to assess the level of users' knowledge about harm reduction techniques, an obvious example relevant to ecstasy use being that relating to pill testing. Participants could also be asked about their preferences for accessing information, a need Hutton (Ibid) has drawn attention to. A further problem with concentrating on 'high-end' users, particularly with ecstasy, is that data will very likely be confounded by polydrug use. While many recreational drug users also use other substances, this review has highlighted that polydrug use is a particular issue for ecstasy users and those researching their behaviour. As difficult as it may be, a well executed IDMS study of 'pure' ecstasy users *à la* Halpern's (2004) neurological work would be of great interest. Of similar value would be a study of ecstasy users drawn from a representative population, such as Reinarman et al.'s (2004) analysis of cannabis use in Amsterdam and San Francisco.

Reinarman et al.'s (2004) study signals a focus on the 'normative' use of drugs, i.e. that for some sectors of the population some drug use has become normal. This is a phenomenon David Fergusson, Director of the CHDS study, has also acknowledged (e.g. Boden et al., 2006). The trend has been discussed internationally as the 'normalisation hypothesis' (e.g. Parker et al., 1998). With the emphasis on harms associated with drug use—something very evident in New Zealand research—issues posed by the normalisation of drug use tend to be sidelined. Thus problematic users

are focused on while larger groups of non-problematic users are of less interest. It is this latter group that Hutton's (submitted, 2009) study of Wellington clubbers considers. She examines recreational club drug use, deploying cultural criminology as a means to explain the pleasurable side of something normally considered criminal. In moving away from strictly 'rational' explanations of drug use with an emphasis on pathology (i.e. principally negative consequences), the opportunity to understand drug use from the users' perspective also offers the chance of providing important harm reduction information. The lack of this important information is a significant gap on the landscape of New Zealand ecstasy use despite limited provision (e.g. the Sorted - party drug info guide produced by Waitemata DHB http://www.cads.org.nz/sorted). Again this is something noted by Hutton, this time in a report (Hutton, 2009) on alcohol harm reduction for students at Victoria University, where postcard information was developed. When asked to expand on the term 'drugs' focus group members noted ecstasy, commenting on a lack of information and that ecstasy was the substance this was most needed for.

A further significant gap in New Zealand data concerns the collection of information reporting adverse events, i.e. hospital presentations and admissions. While these data are available in combination with other stimulants they are not differentiated into specific ATS drugs, hence it is difficult to apportion precise levels of risk. At least two medical experts (Dr Paul Quigley [emergency medicine] and Dr John Fountain [New Zealand Poisons Information Centre]) commented on this problem. A factor compounding this matter seems to be differences among hospitals in their reporting protocols for short stay hospital ED visits (up three hours) as opposed to longer stays, which do not reach the threshold of formal admission. The general issue of undifferentiated ATS's was also noted in the previous EACD report to the Minister on MDMA (EACD, 2004). Clearly this remains a problem.

While Police and Customs seemed also to have some issues around specifically recording different ATS's, generally the data they provided was sound, if inconsistent between annual reports (see footnote note 11). Furthermore, while the NDIB notes the successes of ecstasy traffickers in evading border surveillance, as evidenced by increasing prevalence despite lower Customs interdiction, it seems possible that enforcement efforts may be a significant contributor to the relatively low levels of harmful use in New Zealand. Overall, while various data sources (UNODC, 2009; Wilkins et al., 2009) suggest use is relatively high in New Zealand, problems associated with use may be less so. This is likely due to several factors including New Zealand's geographical isolation and enforcement efforts, which keep prices relatively high. Thus for most users ecstasy remains a 'luxury pleasure', something Hutton (submitted, 2009) reported, with her participants noting that the high price acted as a barrier to frequent use.

3.4 Recommendations

1. As with recent international reports (e.g. ACMD, 2009) one of the most significant points to emerge from the present review is the need for accessible, accurate information aligned with the harm minimisation approach to drug use. This information should be targeted at users in a manner likely to be acceptable to them. There are

already some useful New Zealand (and international) internet sites offering this.

2. In accordance with the above, there is a need to develop alternative forms of information provision. An example might include an ecstasy version of the alcohol cards reported on by Hutton (2009).

3. Research engaging with the above issues of education and its appropriate development and deployment should be encouraged and funded.

4. In accordance with harm minimisation, it would be appropriate to consider pill-testing options. At present this aspect of reducing harm from ecstasy use is a hostage to the drug's illegal status. Given developments in the New Zealand market (i.e. adulteration of pills with piperazines and other substances) it seems likely that a major vector for harm is pill content. See also Appendix VI for examples and New Zealand options proposed by Stargate International.

5. Provision could be made for linkages between ESR research identifying pill content and the New Zealand dance community. Appropriate points of contact would be required to be developed, e.g. STANZ.

6. New Zealand data collection on acute adverse events associated with 'ecstasy' consumption (i.e. poisonings, hospital presentations), are at best underdeveloped. This was signaled in the previous report on MDMA (EACD, 2004). To gain a clearer picture of these types of harms an appropriate system of differentiating and reporting separate ATS drugs should be funded.

4.0 Information Concerning MDMA/Ecstasy Relevant to the Misuse of Drugs Act (1975) Section 4B(2)

4.1 General

The preceding review and discussion have canvassed the available international and New Zealand literature and research on MDMA / ecstasy. The sections below summarise this in the context of Section 4B(2) of the Misuse of Drugs Act (1975).

4.2 Detailed Criteria

4.2.1 Likelihood or evidence of abuse

Overall, the international experience of and literature concerning 'ecstasy' suggests that its use is broadly recreational rather than tending to be a drug of dependent or daily use (e.g. Measham, 2004). However, in experienced users there can be a tendency to increased dosage (Parrott, 2004), although adulterated pills with low MDMA content may also promote increased consumption (Forensic Science Service, 2008a & b), thereby giving the indication of preferred higher dosages and increased frequency of use.

Data on lifetime and last year prevalence indicate the use of 'ecstasy' is increasing with lifetime use in 2006 (8%) amongst the world's highest (ECMDDA, 2008; UNODC, 2009; Wilkins et al., 2009) despite a downward trend in enforcement seizures (NDIB, 2008). Use is particularly evident among males, those in their late teens to mid-twenties, and tertiary students.

In New Zealand Wilkins et al.'s (2009) frequent user study indicated that of combined drug user groups purchasing 'ecstasy' (i.e. IDU, methamphetamine, ecstasy users) 13% did so on a weekly basis, with 2% more than weekly. In the Christchurch longitudinal study (i.e. Boden et al, 2006; Appendix III), more representative of the general population, 4% of 25 year olds used at least monthly, with up to 1% reporting weekly or more frequent use. 'Ecstasy' users tend to be polydrug users, with this practice confounding data analysis and potentially increasing problematic substance use.

Although data on 'ecstasy'-impaired driving are equivocal (e.g. Kuypers et al., 2006; Kuypers & Ramaekers, 2008), there is strong evidence that in New Zealand 'ecstasy' users commonly drive while under its influence (e.g. 42% of the Wilkins et al., [2009] sample did so in the previous six months, with 3% reporting 'a crash'). By way of comparison, 80% of this same group (n=68) drove under the influence of cannabis. Forty percent of those driving under the influence of 'ecstasy' believed their driving to be either unimpaired or slightly improved (Wilkins et al., 2009).

New Zealand hospital data do not separate out 'ecstasy' use from other ATS's, hence cannot provide a definitive answer regarding its impact on ED presentations and hospitalisations. However, psychostimulant poisonings appear to be relatively stable (see Table 6). There were three MDMA-related deaths recorded by coroners between 1998 and 2003. Since that time there have not been any deaths specifically attributed to MDMA. However, ESR Forensic Toxicologist Dr Helen Poulsen, noted between 2005-2007 three 'sudden' deaths reported by coroners where MDMA was the principal drug, at around 1mg / ml of blood: i.e. one with no other drug than MDMA; one with MDMA and BZP; and one with MDMA and alcohol. At similar levels or greater, there was also one death by suicide and one involving a motor vehicle (this also involved alcohol). Dr Poulsen commented, however, than in none of the above was she aware that coroners had attributed death specifically to MDMA. She also noted problems with data collection due to its fractured nature. She suggested,

however, that a recently-implemented coronial reporting system might obviate some of these issues (personal communication with Dr Helen Poulsen, 28 July 2009).

Summary: Based on the above, it seems likely that MDMA / 'ecstasy's' abuse potential is moderate. There are not significant proportions of consumers using very frequently or daily. However, the context of use, i.e. driving, operating machinery, is an area for concern, as is polydrug use.

4.2.2 Specific effects

These have been covered in detail in section 2.3. Research has established that MDMA has an affinity for serotonin receptors and transport sites in the brain. The effects can be acute and chronic, positive and negative, with the latter being potentially fatal.

Positive effects may be noted within 60 minutes of ingestion and may include: euphoria; increased feelings of intimacy with others; a strong sense of inner peace and self-acceptance and intensification of sensory experience; There is a sense of contact with reality; increased concentration and a tendency to lack of aggression, (Ramaekers et al., 2006; Iverson, 2008).

Negative acute effects may include: panic attacks (Whitaker-Azmitia & Aronson, 1989) and hallucinations (not necessarily negative; Creighton et al., 1991), both rare; short-term memory loss; urinary retention (hyponatremia—see below); mydriasis (pupil dilation); increased heart rate, blood pressure, and body temperature—hyperthermia, see below); trisma (lockjaw); bruxia (involuntary teeth grinding); gurning (projecting lower jaw forward); nystagmus (rapid, uncontrollable eye movements).

Lingering self-reported side effects include: restlessness, fatigue, a period of general malaise, normally resolving within a few days.

On rare occasions acute effects can be fatal. There are a number of these. Dr John Fountain, Toxicologist, New Zealand Poison Centre (personal communication) suggested that a hierarchy of risk might take the following order:

i. Idiopathic (unknown cause) responses to ingesting MDMA / 'ecstasy'— these may a consequence of genetic risk and be unforeseeable, or be associated with hyponatremia, resulting in idiopathic kidney failure (Matthai et al., 1996). Cases are rare (e.g. Smith et al., 2005). A second issue perhaps relevant to this category of harms concerns serotonin syndrome, where ingested MDMA has reacted synergistically with other drugs. Of particular concern here are prescription antidepressants (see section 2.3 (5); Silins et al., 2007, for a detailed review and hierarchy of risk).

ii. hyperthermia— excessive and unusual elevation of set body temperature greater than or equal to 41.1 °C. Ingesting MDMA may precipitate the condition through a number of contextual, environmental factors including

iii. hyponatremia ('water intoxication')—Increasing blood volume reduces blood sodium concentrations, resulting in sodium leeching into the water-engorged gut. This produces a difference in osmotic pressure, causing body tissues, including the brain, to take on water and swell (Cherney et al., 2002). Being encased in the skull, this can crush the brain stem or result in cerebral hemorrhage. As with other 'ecstasy'-related deaths, this is relatively rare. For example, in the U.K. Rogers et al. (2009) reported nine published fatal cases, all in women aged 16-21, between 1997-2002;

iv. dehydration—principally contextual (i.e. relating to prolonged dancing / physical activity); profuse sweating, increased activity, tachypnea, and hyperthermia not uncommonly lead to significant body-fluid depletion. While those suffering dehydration require management, before managing patients it is important to exclude the possibility of hyponatremia as fluid administration may potentially be fatal in such cases;

v. aggravation of underlying health conditions— There is also the possibility that underlying health conditions, e.g. cardiovascular problems, such as heart disease may be exacerbated by some of the effects of MDMA. Thus on rare occasions use of MDMA can lead to intracerebral and subarachnoid haemorrhage (Gledhill et al., 1993; McEvoy et al., 2000).

Dr John Fountain's proposed hierarchy of events notwithstanding, according to the dance information site TheDea.org (2003) it is likely malignant hyperthermia and the associated risks of excessive rehydration, leading to hyponatremia, are the most common serious acute risks facing recreational 'ecstasy' users.

Chronic effects: Neurotoxicity

As noted above, probably the most prominent and yet also controversial long-term effect of concern regarding MDMA / 'ecstasy' is its association with neurotoxicity. Specific effects / concerns relate to axonal damage, psychopathology (i.e. depression), verbal memory, and cognitive function deficits. Evidence, however, is equivocal, with it being strongest among high-use populations. There are difficulties with the research due to arguable comparisons between high-dose animal studies and realistic doses likely to be consumed by recreational users, as well as confounders, i.e. polydrug use. Regarding the latter, memory deficits previously attributed to MDMA have been shown to be more likely associated with concomitant cannabis use (e.g. Gouzoulis-Mayfrank & Daumann, 2006). In summarising this aspect of MDMA research, Krebs et al., 2009:877) commented that in "over twenty years of repeated studies looking for brain damage in ecstasy users we see very few consistent findings and little consideration of pre-existing psychiatric factors that may influence young people to repeatedly risk criminal penalties in order to experience MDMA-mediated feelings of love and empathy".

Summary: There is a well-developed literature on the specific effects of MDMA / 'ecstasy'. These range from transient positive and negative psychotropic,

physiological and psychological effects to serious, occasionally fatal adverse events. These latter, however, are rare. There is also somewhat controversial evidence of long-term neurotoxicity, with a body of opinion suggesting a degree of reversability following abstinence. However, a small decline in a variety of domains e.g. verbal memory, even at a low cumulative dose, has also been noted, though its clinical relevance remains unclear (ACMD, 2009). Given the short history of New Zealand use (less than 20 years) long-term effects cannot be ruled out. Further research in this area is required.

4.2.3 Risks to public health

While this is a difficult task, there is a range of metrics by which public health risk can be assessed. These have been discussed above in detail in section 2.4.

One means is to look at fatal outcomes on a population basis. As noted above, fatality from use of MDMA is a rare outcome, with three cases being reported in New Zealand between 1998-2003. A recent U.K. assessment of 'ecstasy' harms (ACMD, 2009) considered data from the U.K. mortality register, numbers of U.K. users and amount of pills consumed per annum. These data suggested where ecstasy was mentioned at all, the risk of death per person per tablet was one in 39,000; where only 'ecstasy' was mentioned the risk was one in 1.8 million.

Seizure and prevalence data also offer an indication of public health risk exposure. As discussed above, while New Zealand seizure data suggest declining availability, it is generally agreed that prevalence is increasing (NDIB, 2004; 2008; Wilkins et al., 2009). Thus more people will be exposed to extant risks.

As the ESR (2000; 2008) analysis indicates, the level of pill purity is low and there are many adulterants, some with synergistic properties in terms of their reactions with MDMA. In Australia this has proved fatal, for instance regarding PMA content (Caldicott et al., 2003; Johnston et al., 2006). While pill testing has provided researchers and health authorities with an indication of the extent of this problem, the illegality of 'ecstasy' means that this means to obviate risk is generally not available to users, unless via potentially unreliable testing kits purchased privately (Winstock et al., 2001). This potentially exacerbates the risk posed by pill adulteration.

There are also concerns regarding the context of use, for example in association with driving and operating other machinery (Wilkins et al. 2009). Additionally, there have been concerns about the propensity for 'ecstasy' to be used in Drug Facilitated Sexual Assault (DFSA). However, as Jansen and Theron (2006) have argued, there are far more likely candidates for this phenomenon, including alcohol.

Overall, however, when compared with other substances, both legal and illegal, it is generally recognized that MDMA does not pose a significant public health risk (i.e. Gable, 2004; Nutt et al., 2007).

Summary: There is no doubt that MDMA / 'ecstasy' does pose risks to public health, in terms of potential fatal toxicity, and contextually inappropriate use. Regarding the former, MDMA fatalities are very rare, particularly when compared with other drugs,

for example alcohol. As the previous report to the EACD (Ministry of Health, 2003) noted, however, while there will always be those who disagree, a body of well-respected researchers, academics and practitioners suggest that the risk to public health of MDMA is relatively low.

4.2.4 Therapeutic value

This is an area where, since the previous examination of MDMA / 'ecstasy' (i.e. Ministry of Health, 2003), there has perhaps been a shift despite there still being no definitive empirical evidence of the therapeutic effectiveness of MDMA (i.e. in the sense of randomised, blinded clinical trials).

Although early investigations of the drug's therapeutic value are by now considered well-traveled territory (e.g. Greer & Tolbert, 1986; Holland, 2001; Pentney, 2001), there is increasing interest in the possibilities of the drug's potential in both psychotherapy and non-psychotherapeutic clinical practice. This has been discussed in section 2.5.1. Presently there is research being carried out in relation to MDMA's effectiveness in treating PTSD (Doblin, 2002; Bouso et al., 2008). Concerns about the lack of a neurobiological model for effective treatment (Parrott, 2007) have been countered by Johansen and Krebs (2009), while other researchers and clinicians have argued that the criminalisation of MDMA continues to undermine a potentially valuable treatment path (Sessa and Nutt, 2007). There is also emerging research suggesting MDMA may be a useful treatment for movement disorders such as Parkinson's (Sotkikova et al., 2008).

The revitalised interest in MDMA's therapeutic value has recently been reflected in New Zealand. Doug Sellman (Professor of Psychiatry and Addiction Medicine, Director, National Addiction Centre, Department of Psychological Medicine, University of Otago, Christchurch) has contributed a précis of proposed research into the therapeutic uses of a number of psychotropic drugs, including MDMA, to the present review (Appendix II).

Summary. While no conclusive empirical evidence exists regarding MDMA's therapeutic value, there is increasing interest in research exploring this area, both internationally and in New Zealand. Concerns have been expressed by respected researchers that the criminalisation of MDMA has created barriers to the development of this research.

4.2.5 Potential for use to cause death

This has been discussed in detail above (2.6). The particular risks concern idiopathic (unknown cause) and other acute reactions to MDMA / 'ecstasy' (i.e. hyperthermia, hyponatremia, dehydration, serotonin syndrome, combined with other drugs;

interaction with pre-existing health conditions), particularly where it is consumed in typically hot, crowded environments. While these risks are real, they are also rare, as noted by risks per population ratio analyses (e.g. ACMD, 2009). There is also the risk of fatal injury through contextual use, e.g. driving.

Summary. The evidence above, including the reporting of three MDMA-related deaths in New Zealand between 1998-2003 supports the previous report's (Ministry of Health, 2003) contention that the risk of death after using solely MDMA is low.

4.2.6 Ability for creation of physical or psychological dependence

As discussed above (section 2.7) there is a lack of clarity around MDMA's potential for causing physical and / or psychological dependence. The issues are complex, they rely on convoluted epidemiological data, are confounded by polydrug use, involve theoretical issues concerning diagnosis and, in New Zealand, claims of dependence are unsupported by a lack of general population treatment data.

Early studies (e.g. Peroutka et al. 1988; Solowij et al. 1992; Moore 1993; Beck and Rosenbaum 1994) suggested that MDMA was relatively benign and that dependence, if it existed at all, was rare. In part this was due to the rapid reduction of positive effects following repeated, frequent use, leaving the user to experience only negative side effects (something commented on more recently by Measham, [2004]).

In the late 1990's other studies (e.g. Topp et al., 1997; Cottler et al., 2001) began to look more closely at frequent-use, high-dose populations of 'ecstasy' users. For example, the former reported significant levels of tolerance, (83% of their sample of 185 regular users), and high rates of dependence (48%) and abuse (36%). Similarly for Cottler et al., (2001), who report 43% and 34% respectively for dependence and abuse.

There are, however, a number of concerns with these studies. There is the issue of pill purity (i.e. what exactly were the participants taking?). A major problem, which confounds so much research on MDMA, is the extent of polydrug use. This is very apparent with the study by Cottler et al., (2001). Their subjects (mean age 19.3 years) had, along with having taken 'ecstasy' >5 times, a lifetime prevalence of the following: alcohol (100%), cannabis (98%), tobacco (87%), hallucinogens (67%), stimulants (64%), cocaine (50%), opioids (50%), sedatives (40%) and nitrous oxide (39%). Teasing out the effects of 'ecstasy' from that cocktail of substances via the DSM-IV is problematic, particularly when the DSM-IV lacks a specific set of diagnostic criteria for MDMA. The latter is a point raised by Cottler and Grant (2006) who argue that it is diagnostically inappropriate to apply a generic set of criteria across all substances.

Further problems with diagnosing MDMA-induced dependence were highlighted by Von Sydow et al. (2002) who noted spontaneous cessation of symptoms in a prospective longitudinal study of self-reported symptoms of depression, where dependence at baseline had been diagnosed at 1%. They suggested that the existence of ecstasy use disorders might well be relatively transient and youth-specific, with only a small proportion of users going on to experience chronic problems. This is

supported by Measham (2004) in her study of the decline of ecstasy use in the 21st Century and the rise of binge drinking. She suggests substance use is mediated by cultural processes, and economic and social change.

The New Zealand treatment data reported above (section 3.2.1.1), e.g. Adamson et al. (2006; and personal communication with Dr Simon Adamson, National Addiction Centre, Christchurch) also mitigate against significant dependence associated with recreational 'ecstasy' use. These authors noted an almost complete absence of presentations for 'ecstasy' as the primary substance in drug treatment in a decade of data collection capturing over 1000 drug treatment clients.

It is clear, however, that some will experience problems with ecstasy. Using the Severity-of-dependence' scale Wilkins et al., (2009) assessed 7% of their sample of frequent 'ecstasy' users as dependent. Additionally, Boden et al. (2006) note that approximately 3.2% of their longitudinal cohort in the Christchurch Health and Development Study (CHDS) were diagnosed at 25 years as dependent on 'hallucinogens', though regrettably they do not specify exact numbers of 'ecstasy' users.

Summary. Data examined in the present review agree with the conclusions of the previous report to the EACD (Ministry of Health, 2003), specifically: there is a growing literature indicating that some users experience symptoms of dependence associated with their use of 'ecstasy'. However, given the confounders it is difficult to determine the extent that this may be attributed solely to MDMA. It is likely that in the future MDMA will be determined to be slightly to moderately dependence-inducing. It seems that where these disorders to occur, they are often transient, are mediated by other factors, including the cultural consumption of substances and that a small proportion of chronic 'ecstasy' users are likely to develop problems controlling their use.

4.2.7 International classification and experience of MDMA/Ecstasy in other jurisdictions

As discussed above (section 2.8.1), there is a generally uniform international response to the classification of MDMA / 'ecstasy'. It is a Schedule I substance under the 1971 United Nations Convention on Psychotropic Substances, along with its 'parent' compound MDA, and the chemically related substances DMA, DOB, DOM, PMA and TMA.

Most countries thus classify it in their first level schedule, i.e. either as 'I' (for example in the U.S., or as Class A (as in the U.K.). Two exceptions are the Netherlands and New Zealand. The former, in a typical flourish of Dutch pragmatism, classifies MDMA in Schedule I for trafficking and dealing purposes, and in Schedule II for the purposes of possession and use (Ministry of Health. 1995; Uitermark & Cohen, 2005).

New Zealand is another exception to the Schedule I rule, with it being classified as Class B(1).

4.2.8 Other issues that the Minister may see fit to consider

The present review has sought to examine all issues concerning MDMA / 'ecstasy' relevant to the Misuse of Drugs Act 1975 as specified in Section 4B(2), including matters not covered in previous reports to the EACD or the Minister (i.e. Ministry of Health, 2003; EACD, 2004). For example, the section considering risks to public health (2.4) was expanded from previous reports to embrace pill testing, the impact of skewed media, and societal harms such as drug facilitated sexual assault and the negative consequences of drug policy. Likewise, the inclusion of proposed research on the therapeutic potential of MDMA (Appendix II) signals a change in direction from previous reports and aims to draw attention to new developments that might subsequently impact on policy as it relates to MDMA. These efforts notwithstanding, the reviewer recognises that future developments may occur which have not been anticipated by the present report, and for which the Ministry and Minister will require additional information.

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Appendices

Appendix I Experts and other stakeholders contacted for comment on the literature review of MDMA / ecstasy

The following individuals and organisations were contacted and asked to comment on matters relevant to the present review. Specific contributions are noted, and greatly appreciated.

Dr Simon Adamson, Senior Lecturer, National Addiction Centre, Department of Psychological Medicine, University of Otago at Christchurch. Dr Adamson provided details of ecstasy prevalence in substance use treatment, from the National Treatment Survey (1998, 2004, 2008).

Dr Keith Bedford, General Manager Forensic Institute of Environmental Science and Research Limited (ESR), Mount Albert Science Centre. Dr Bedford provided literature on pill testing.

Mr. Matt Bowden, Founder of Stargate International (a private organisation promoting harm minimisation for drug users and within the New Zealand dance community), the initial developer of BZP-based party pills in New Zealand and spokesperson for the Social Tonics Association of New Zealand (STANZ), provided comment and a discussion document (see Appendix VI) on pill testing, involvement with the ESR and research on MDMA analogs in New Zealand.

Dr Gavin Cape, Medical Director, CADS (Dunedin), Senior Lecturer, Department of Psychological Medicine, Otago University Medical School, Consulting Psychiatrist. Dr Cape provided literature and comments on ecstasy in relation to dependence and abuse, and prevalence in treatment presentation.

Dr Phil Dalgarno, Research Lecturer, Department of Psychology, Glasgow Caledonian University. Dr Dalgarno commented on ecstasy in the U.K, regarding dependence, pill purity and price. See Appendix IV.

Assoc. Prof. John Fitzgerald, Executive Manager, Knowledge and Environments for Health, Victorian Health Promotion Foundation (VicHealth), Melbourne, Australia. Prof. Fitzgerald commented on the historical development of research on MDMA / ecstasy.

Dr John Fountain, Medical Toxicologist, National Poisons Centre, Department of Preventative and Social Medicine, University of Otago, Dunedin. Dr Fountain provided literature and commented on MDMA toxicity and hierarchies of risk.

Mr. John Horwood, Research Associate Professor, Christchurch Health and Development Study, Department of Psychological Medicine, University of Otago, Christchurch. Mr. Horwood provided literature and a substantive comment on the Christchurch study's cohort characteristics regarding use and prevalence of MDMA / ecstasy. See Appendix III.

Dr Fiona Hutton, Senior lecturer in Criminology, School of Social and Cultural Studies, Victoria University, Wellington. Dr Hutton provided literature (including pre-press original research) and comments on club drug use in New Zealand and the U.K.

National Drug Intelligence Bureau (Ms Laura Hayton and Mr Les Maxwell), Intelligence Analysts, NDIB, Wellington. Ms Hayton and Mr Maxwell discussed ecstasy prevalence, drug harm and provided enforcement information and documentation.

Dr Helen Poulsen, Forensic toxicologist, ESR, Wellington. Dr Poulsen provided comment and data on MDMA and 'ecstasy'-related deaths in New Zealand, and on extant data collection systems.

Dr Paul Quigley, Emergency Medicine Specialist, Wellington Hospital. Dr Quigley provided information on acute presentations and admissions relating to ecstasy, and on hospital data recording protocols.

Douglas Sellman, Professor of Psychiatry and Addiction Medicine, Director, National Addiction Centre, Department of Psychological Medicine, University of Otago, Christchurch. Prof. Sellman provided literature and commented on the significance of MDMA in a therapeutic context. He also provided an overview of impending New Zealand research in this area. See Appendix II.

Dr Chris Wilkins, Senior Researcher, Drugs Team Leader, Centre for Social and Health Outcomes Research and Evaluation (SHORE), Massey University, Auckland.

Appendix II Prof. Douglas Sellman: A brief overview of proposed entheogenic research

A brief overview of proposed entheogenic treatment research, provided by Douglas Sellman, Professor of Psychiatry and Addiction Medicine, Director, National Addiction Centre, Christchurch School of Medicine and Health Sciences.

National Addiction Centre

(Aotearoa New Zealand)

Entheogenic treatment research

Hallucinogenic substances, "entheogens", have been used by humans for thousands of years, although were traditionally confined to religious ceremonies as a way to facilitate communication with the 'spirit world'. Two key publications, a century ago, brought about a renaissance of interest in these substances as potential therapeutic agents: "The Varieties of Religious Experience" (1902) by psychologist William James, and "Phantastica" (1924) by toxicologist Lewis Lewin.

During the 1950s and 1960s, LSD was extensively utilized in Europe and the USA as a therapeutic agent for alcoholism. Randomized controlled studies indicated a positive effect in the first three months following treatment before this whole line of research was brought to an end with the "War on Drugs" initiative (Sellman in press).

In recent times, there have been calls for renewed interest into hallucinogens as therapeutic tools in psychiatry (Sessa 2005). Griffiths and colleagues have now built on research that had laid largely dormant for over 40 years finding in a US randomised controlled trial involving a group of healthy normals that psilocybin can bring about enduring positive spiritual change in contrast to methyphenidate, the control medication used in the study. In fact, a Russian research group had already completed a clinical trial of ketamine in patients with opioid dependence and found positive long term benefits for those who had an hallucinogenic dose of ketamine compared with those who only received a relaxant dose (Krupitsky et al 2002).

New Zealand Research

Initial steps for entheogenic treatment research in addiction have been taken with presentations at various fora over the past two years by Dr Gavin Cape (Dunedin) and Professor Doug Sellman (Christchurch). A strategic planning meeting is scheduled in December 2009, including Dr Fraser Todd (Christchurch) and Professor Paul Glue (Dunedin), as two further psychiatrists with a serious scientific interest in this area, to begin to plan more specifically for a controlled treatment trial here in New Zealand, possibly in alcohol dependence. At this stage it has not been decided which entheogenic agents ("addiction interrupters") will be used but the list being considered currently stands as: LSD, psilocybin, ibogaine, MDMA and ketamine, each of which has a scientific literature supporting potential therapeutic benefits for patients.

Doug Sellman
Professor of Psychiatry and Addiction Medicine
26/06/09

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Appendix III Mr. John Horwood: Overview of MDMA / ecstasy-related research by the Christchurch Health and Development longitudinal study (CHDS)

A brief overview of ecstasy-related research carried out by CHDS on 1265 children born in Christchurch in mid-1977. Includes a reference of a peer-reviewed article reporting drug use characteristics and risk of dependence for the cohort at age 25 years.

The Christchurch Health and Development Study (CHDS) is a longitudinal study of a birth cohort of 1265 children born in Christchurch in mid-1977. This cohort has now been followed from birth, through childhood, adolescence and young adulthood up to age 30 years. As part of the study detailed information has been gathered on illicit drug use and problems associated with drug use. This information includes measures of:

- Frequency of drug use for a range of different substances including MDMA/ecstasy, for each 12 month period from age 16 to age 30 years
- Standardised DSM-IV diagnostic criteria for substance abuse and substance dependence
- The experience of adverse events in the context of drug use (eg unpleasant side effects, violent behaviour, difficulty sleeping, collapsing/passing out, hospital attendance)

In addition, the study also has available comprehensive information on:

- Mental disorders and other adjustment difficulties (eg depression, anxiety disorders, suicidal behaviours, conduct disorders) that may be comorbid with illicit drug use
- Social, family, individual and related risk factors for substance use/misuse

Using these data the CHDS has the potential to address a wide range of issues relating to the prevalence, course, predictors, comorbidities and harms of MDMA and other illicit drug use.

To date the study has not conducted in depth analysis of MDMA use. However, brief examination of the CHDS data shows that around a third of the cohort had ever used MDMA by the age of 30. The peak age of use was in the early to mid 20s (22-25 years) with up to 20% of the cohort using MDMA in a given year. Most use was occasional, although a small minority (up to 4%) were regular (at least monthly) users and up to 1% reported weekly or more frequent use at any given age (DM Fergusson, personal communication). Around 3.6% of the cohort had met DSM-IV diagnostic criteria for illicit drug dependence (other than cannabis) by age 25. The majority of those meeting dependence criteria were users of MDMA or other hallucinogenic type substances (Boden, Fergusson & Horwood, 2006).

The study would be happy to consider producing a more detailed report on the use of MDMA and/or other illicit drugs in the CHDS cohort at the Ministry's request (DM Fergusson, personal communication).

Reference:

Boden, J.M., Fergusson, D.M., & Horwood, L.J. (2006). Illicit drug use and dependence in a New Zealand birth cohort. *Australian and New Zealand Journal of Psychiatry, 40*,156-163.

Appendix IV Comment by Dr Phil Dalgarno, Research Lecturer, Department of Psychology, Glasgow Caledonian University

Dr Dalgarno offered the following comments (excerpted) in response to a request for information regarding the review of literature on MDMA / ecstasy, on the 'ADDICT-L' e-group list, an international e-list subscribed to by lay and professionals having an interest in and working in the field of the addictions and drug research.

The author of the review had requested information in relation to MDMA / ecstasy's potential for abuse, dependence, neurotoxicity, price and purity.

Comments on MDMA / ecstasy

From: "Dalgarno, Phil" <P.Dalgarno@gcal.ac.uk>
To: "'Geoff Noller'" <geoff.noller@stonebow.otago.ac.nz>
Date: Fri, 10 Jul 2009 11:01:38 +0100
Subject: RE: Ecstasy

"Dependence:
As far as dependence goes, I don't really buy it; certainly not in any sense of "addictiveness".

Never heard of any cases of physical dependence to E, and I've interviewed a lot of people over the years. One does get told about a sort of dependence to the buzz of E (particularly the coming up part) but that's not really the same thing. And of course I've interviewed people who have taken it constantly for a number of days and have reached a stage where they're worried about stopping for fear of what the comedown *might be like*.

Pill price and purity:
I'm not too sure you should read too much into the price of Ecstasy in the UK. The quality is very much reflected in this. In "the old days" a pill or two would do most people (not the hardheads mind, but there are always people like that around) most of the night, whereas the same effect I'm told requires pills running into nearly double figures in terms of intake.

Hallucinogenic potential:
Maybe. I think there's a drug called "Ecstasy" that used to be MDMA, and this wasn't particularly hallucinogenic unless something else – acid, mushrooms or something like that - was piggybacked with it, in which case yes, it did become hallucinogenic. These days though, I think that "Ecstasy" is more a generic name for a pill containing any number of compounds, and not necessarily MDMA. There are a lot of hallucinogens to choose from and they'd all kind of fit the bill as an MDMA mimic, particularly if there's some sort of amphetamine in there as well.

Every so often a batch of pills turns up here containing a sort of non-MDMA psychedelic cocktail. Ketamine and ephedrine was one of these and while they were reportedly good for 'sitting in the house', they caused mayhem on the dance floor."

Email concludes.

Dr Dalgarno has authored or contributed to a number of articles on MDMA / ecstasy and related drug use issues, including:

Dalgano, P., & Shewan, D. (2005). Reducing the risks of drug use: The case for set and setting. *Addiction Research and Theory, 13*(3), 259-265.

Shewan, D., Dalgarno, P., & Reith, G. (2000). Perceived risk and risk reduction among ecstasy users: the role of drug, set, and setting. *International Journal of Drug Policy, 10*, 431-453.

Shewan, D., & Dalgarno, P. (1996). Ecstasy and neurodegeneration. …like ketamine. *British Medical Journal, 313*(7054), 424

Appendix V Pill testing protocols and New Zealand example from: www.pillreports.com

The following is an example of a recently submitted (June 22, 2009) pill report from an Auckland consumer. The site (pillreports.com) is international but with regional reporting capacity. New Zealand has its own section.

NZ testing and Pill Reports, from:

Source: http://www.pillreports.com/index.php?page=display_pill&id=17209#comments

Accessed: July 15th 2009

Pill Report template as proposed by New Zealand internet site user:

SHAPE/LOGO:
DIMENSIONS:
WEIGHT:
COLOUR:
EDGES:
TEXTURE:
SMELL:
TASTE:
SCORE:

~~~~~TEST~~~~~

MARQUIS:
MANDELIN:
SIMONS:
ROBADOPE:

Example of a user testing report:

Red Dots

Date Submitted:	June 22, 2009, 11:48 pm GMT
Last Updated:	June 24, 2009, 11:56 pm GMT
Submitted By:	thisdude101
Name:	Red Dots
State/Province:	Auckland
Logo:	Raised Dot
Colour:	Red/Pink
Shape:	Round
Texture:	Crumbly, Pink/red, Speckled
Edges:	Sharp, square.
Report Quality Rating:	(5 stars, 1 vote)
Description:	Round, flat slides, no score on the back. Logo is a raised dot.
Suspected Contents:	MDMA
Rating:	MDxx High
Warning:	no
Tested:	yes
Marquis Reagent:	Black
Consumed:	yes
User Report:	I took one last saterday went into town i noticed euphoria kicking in around 40 minutes after taking it, which steadily progressed into an intense euphoric buzz all and all had an awsome night, nice and love dovie. Tested em out with a marquis and as soon as I put it in purple patches appeared progressing into a black colour.
~~~~~

Appendix VI A discussion document provided by Matt Bowden, Stargate International founder, backgrounding pill testing.

The following document backgrounds pill testing, technical issues, Stargate's use of ESR testing for local street 'ecstasy' consumers and proposes a New Zealand protocol to facilitate testing as an important component of harm minimization.

Pill testing programmes and harm minimisation: discussion document

Aims

Illegal "Ecstasy" pills are known to often contain dangerous contaminants. This results in significant increases in potential harm to users. Pill testing programmes overseas have been shown to reduce this harm through several mechanisms, and so can be considered a valid public health initiative. We feel that this is equally applicable to New Zealand, and wish to build on the informal pill testing conducted to date in order to construct an organised system for testing black-market pills. Stakeholders who can be expected to gain benefit from such a programme would include hospitals, police, customs service, Ministry of Health and Expert Advisory Committee on Drugs, as well as Ecstasy consumers. This document aims to gather feedback from such stakeholders with the aim of developing a testing programme that gives the maximum benefit to all involved.

Introduction

Use of illegal drugs such as MDMA is made far more dangerous by the fact that pills sold on the black market as "Ecstasy" can have widely varying dosage, and indeed often contain mixtures of several drugs with unpredictable pharmacological interactions, which may sometimes not include any MDMA at all.[1] Even where pills do contain only MDMA, it can still be a dangerous drug in its own right; the highly variable strength of different batches, as well as the varying tolerance of individual users, can lead to hospitalisations resulting from people getting accustomed to a set dose of a relatively weak batch of pills, then inadvertently taking an overdose when they take the same number of pills from an unusually strong batch.

In recent years the unpredictable contents of street ecstasy pills has become a particular problem, with a wide range of different contaminants reported in seized pills from around the world, ranging from chemical contaminants left over from MDMA manufacture [2], to legal pharmaceuticals such as aspirin, paracetamol and diphenhydramine, to illegal drugs such as ketamine and amphetamines, and including some particularly dangerous compounds such as PMA, 4MTA and Fentanyl. [3, 4]

The presence of pharmacologically active contaminants in Ecstasy pills not only makes them more dangerous for users, but can also complicate emergency treatment of individuals who present at hospitals with "Ecstasy" overdoses; a system that allowed for quick and accurate analysis of the contents of a particular batch of pills could be life-saving. [5]

"Research chemicals" with little history of human use and no formal safety evaluation, such as 2CB, 2CT7 and 5MeODiPT have also appeared in pills, often sold legally in specialty stores (e.g. "smart" or "head" shops) and then re-sold on the illicit market as "ecstasy". [6, 7, 9] This could be particularly dangerous given the unknown properties of these drugs; 2CT7 for instance was recently found to be a potent monoamine oxidase inhibitor [8], which could make it potentially lethal to combine with amphetamines, and unfortunately this was not discovered until several such deaths had occurred. [9]

Testing of street pills to determine the active ingredients and any contaminants can be an important element of both harm reduction, and also demand reduction; users are generally reluctant to purchase or consume pills that have been reported as containing particularly dangerous ingredients. By identifying potentially harmful batches of drugs such as Ecstasy, risks to users of these illicit drugs can be minimised. Interviews with Ecstasy users suggest that they will avoid purchasing or using pills that are known to contain compounds which produce dangerous or unpleasant side effects such as PMA or 2CB. Interviews with users of home "testing kits" in Australia showed that over half of them would not take a pill if it was shown to contain ketamine, and over three quarters indicated they would not take a pill that contained "unknown" contents which the test could not identify. [1]

Inaccurate or misleading tests can however be dangerous and give a false sense of security to users of these potentially dangerous drugs. Although some “pill testing kits” are available, using colour-changing chemicals such as Marquis Reagent to determine the contents of pills, they can often be unreliable. While such testing kits are usually sensitive to the presence of amphetamines or MDMA, they may not reveal the presence of dangerous contaminants; neither PMA nor 4MTA react with Marquis Reagent [10], so a pill containing both MDMA and PMA would appear to only contain MDMA, and therefore be assumed to be relatively safe. Pill testing kits can also be fooled by unscrupulous manufacturers; several adulterants such as dextromethorphan and opiates are reported to cause a similar colour change to that produced by MDMA, so testing kits can sometimes give false positive results, indicating there is MDMA present when in fact there is not. [11]

Options for pill testing

As a result of this difficult situation, there is a need for services providing proper testing of illicit pills; either using laboratory based analytical testing equipment such as HPLC and GC-MS, or newer technologies such as portable Ion Mobility Scanners. Only this kind of testing using complex and expensive machines can be relied upon to determine accurately exactly what is in a pill, and in what quantity. [11] At present, HPLC/GC-MS testing is generally only carried out on pills that are intercepted at the border by Customs or seized in enforcement operations by the Police. This gives the authorities a reasonable overview of what kind of compounds are currently being imported or sold as Ecstasy at any one time, but is of little assistance to individual users who wish to test their own pills in order to minimise the risk of adverse drug reactions.

Highly accurate portable ion scanners are used to test travelers for traces of drugs at airports in Australia and the USA, but at present these devices are only available to government and law enforcement personnel, and because of their sensitivity they can sometimes test positive even though there are only tiny traces of drugs present, which could potentially make results difficult to interpret when a variety of different compounds are found in one pill. Also most laboratory tests give only qualitative results, saying what compounds are detected in a pill, but not what dose is present. As discussed above, a major part of the risk involved in using illicit Ecstasy is the wide variation in doses between different batches of pills, so quantitative testing which revealed the exact contents of a pill would be of considerably more benefit from a harm minimisation perspective. [1]

Summary

In the current environment in New Zealand there is marked inconsistency in the quality of street “Ecstasy” pills. Most pills tested contain a mixture of several compounds, the only common ingredient being MDMA. Poor manufacturing practice means that even within the same batch of pills there is often significant variation in dosage and the relative ratios of the various ingredients. Finally, the availability of legal “Party Pills” based on BZP and similar drugs has resulted in instances of these pills being misrepresented and sold as “Ecstasy”; more rarely psychoactive prescription drugs have been similarly misrepresented and sold on the black market.

Consequently there is a clear need for an anonymous, consistent and reliable pill testing programme, to be made available to the general public at a reasonable price. Obviously the actual cost of GC-MS testing is relatively expensive, but newer technologies such as portable ion scanners could reduce the costs involved significantly. If testing groups use IMS (Ion Mobility Scanner) systems in the field these are very accurate and so the system would require far less use of GC-MS analysis. Only pills that contain substances that the IMS has not been calibrated to detect would need further testing via GC-MS.

Lack of availability of such a formal testing process has resulted in the growth of internet sites such as Pillreports.com and colour-based “pill testing kits” such as Marquis reagent, which as discussed

above can give inaccurate or misleading results and hence be counterproductive and potentially dangerous. [3, 11]

Unfortunately these limited services are the best that is available for most users of street ecstasy, and their popularity clearly demonstrates the need for more accurate and reliable testing services. Stargate has offered some pill testing services in the past when particular batches of pills with unusual effects have elicited requests from users that someone have them analysed. One example was a batch of pills known as “yellow CS” which produced unpredictable and highly variable effects. These were analysed with GC-MS, and shown to contain a mixture of MDMA, methamphetamine and 2CB, a result which was consistent with the unusual effects reported. Testing services were provided by an approved laboratory and we felt that providing this information to the community was a useful service and may well have influenced ecstasy users not to purchase these particular pills.

However a more regular and formalised testing programme which aimed to give an up-to-date summary of what is currently on the market would be much more useful, especially to stakeholders such as the police and hospitals for who this information could be directly relevant. Also some kind of alert system to provide emergency notification to the public when a batch of pills was found to contain especially dangerous compounds such as PMA or 4MTA could well save lives by warning people not to buy these pills in the first place.

Examples of pill testing programmes overseas

The main barriers preventing individuals from having street ecstasy pills properly tested are the cost of the testing, lack of access to laboratories with proper testing equipment, and the desire of otherwise law-abiding citizens not to incriminate themselves by being associated with illicit drugs. Some European countries such as Austria and Holland view pill testing programmes as part of their harm minimisation strategy, and programmes in these countries are thus government funded and can operate with no concern of arrest among users.[12] One testing programme in Austria attended dance events in big cities with an HPLC machine set up in a tent, and provided free and accurate analysis of pill scrapings voluntarily submitted by individual users, with each test taking around 20 minutes. [13]

A similar service in Switzerland provided an integrated programme which also included a significant element of intervention and counselling services; during the 20 minutes that the test took to complete, the individuals submitting the pills were interviewed about their drug use and given advice about safe usage practices. Once the test was complete, the results were explained to the submitter and their relevance explained. This can be an important part of the harm reduction process, as while users may be familiar with the drugs found in their pill, they might not be aware of potential interactions or contraindications, and so providing additional education to ecstasy users can be useful. This programme also conducted follow-up interviews which measured the effectiveness of the education given by questioning users on their usage patterns, and a general trend towards safer usage practices was observed. Another important conclusion from this programme was that it had been a particularly useful way of engaging ecstasy users who would otherwise not present at drug treatment services, and so provided help to a segment of the community that is difficult to reach. This particular testing programme was supported by a grant from the Swiss government which allowed purchase of the $100,000 HPLC machine. [14]

Such projects are rare however; few research institutes have expensive analytical equipment sitting around unused that can be borrowed for the night, and the small amount of such work that has been done is all volunteer based, and often struggles to find funding. Legal difficulties with pill testing are also a common problem, with the inconsistencies in legislature between jurisdictions meaning an identical testing programme may be illegal in one country, yet both legal and government subsidised in another.

Legal status of pill testing

Stargate sought and received permission from the New Zealand Police to collect ecstasy pills anonymously from individuals, and deliver them to an approved laboratory for testing. Unlike in some overseas jurisdictions, the legal status of pill testing in New Zealand is fairly clear, at least where an intact pill is sent to an approved laboratory. Since the pill is destroyed in the testing process, as soon as it is destined for the laboratory rather than human consumption, the person in possession of the Ecstasy pill is no longer committing any crime so long as they can demonstrate that the pill is definitely going to be destroyed rather than consumed. [15]

Testing programmes involving pill scrapings, where the remainder of the pill is allowed to be kept by the user for possible consumption later on, are more legally suspect as this might be interpreted as allowing someone to commit an illegal act. This can be avoided with the use of ion scanners, as the high sensitivity of detection with these devices means that the client needs to merely wipe a piece of paper or wooden applicator stick across the surface of the pill, and then hand this in to be tested, so ensuring that the testing personnel need never come into actual physical contact with illegal drugs and are thus protected from any legal liability.

Conclusion

As with any harm minimisation strategy the objective should be to reach as wide a segment of the drug-using population as is achievable, so ideally this would involve a system whereby users could anonymously submit drug samples to an approved laboratory and have them tested for free, with the results reported in a publicly available forum such as an internet site. Automated systems have been developed whereby the user can go into a private booth, weigh and measure the pill and enter the name of the pill onto a computer, before swiping a piece of paper across it and submitting this for the ion scanner test. This kind of process allows fully automated pill testing with no requirement for staff to even be present.

Our proposed pill testing programme in New Zealand would be conducted in the following manner.

1) Advertising: internet-based promotion of the programme would be the primary means of contacting individuals who wanted pills tested, although other advertising such as posters at clubs or events might be used.
2) Collection: pills must be collected from users in an anonymous manner. Exactly how this should best be done so as to protect the identity of submitters and avoid any breaches of the law is the main unresolved issue, but should not be a particular problem. Some kind of drop-box might be the easiest solution.
3) Analysis: initially all pills would be analysed at ESR using HPLC and/or GC-MS. While the use of Ion Mobility Scanners would be quicker, easier and cheaper in the long term, the considerable cost of purchasing one of these devices means that they would not be used initially unless appropriate funding was available to buy one.
4) Publication: test results would be made available on a publicly accessible website so that users could conveniently view them. An automated notification process could also be used so that interested stakeholders would be notified by email once testing was complete.
5) Stakeholder benefits: main benefit would obviously be to ecstasy consumers who wished to minimise their risk of harm by knowing the contents of the pills they intend to take. Hospitals would also benefit as treatment of ecstasy overdose would be easier if the contents of the pill taken were available. Police would benefit as analysis of pills can be expected to clarify their legal status – active ingredients of street “ecstasy” could fall into class A, B or C, depending on what compounds are present, so accurately knowing the contents of pills could have considerable influence on court cases. The customs service, Ministry of Health and the Expert Advisory Committee on Drugs would also benefit as analysis of street pills may well be the first notification of the arrival of novel recreational drugs into New Zealand, and the earlier such new drugs can be identified, the better.

6) Alerts: particularly dangerous pills would be specifically advertised to warn users to avoid them. While this might promote such pills to a minority of individuals, most users could be expected to avoid pills which are known to contain highly dangerous content.

This is of course just a draft outline of the programme envisioned. All stakeholders are encouraged to give feedback on what aspects of this scheme they feel need to be improved or altered; and it should be quite possible to come up with a system which suits the specific needs of all participants.

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