



E.M.C.D.D.A.

European Monitoring Centre
for Drugs and Drug Addiction

Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs



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Foreword

It gives me particular pleasure to present with this publication the results of the risk assessment undertaken by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the substance ketamine. The risk assessment was carried out under the terms of a joint action adopted on 16 June 1997 by the Council of the European Union ⁽¹⁾ and is the third such exercise undertaken to date by the EMCDDA ⁽²⁾.

Ketamine is a substance with a large and well-established therapeutic use, particularly in veterinary medicine, but since the mid-1990s it has surfaced as a recreational drug. This presented a new challenge for the risk-assessment committee, that of how to assure a drug's continued availability for medical and veterinary use while taking appropriate measures against its diversion to the illegal drugs market for illicit use and the associated health risks.

Information on the patterns of use and implications for illegal drugs trafficking networks were collected through the EMCDDA's early warning system via the European network of national focal points and Europol's national units. On the basis of the findings, the Horizontal Working Party on Drugs of the EU Council requested a risk-assessment procedure to be carried out which reviewed the pharmacotoxicological data on ketamine and assessed the public health risks and the available sociological and criminological evidence. The resulting 'Report on the risk assessment of ketamine' was presented to the Council in March 2001. On the basis of the report, the Council requested the EMCDDA and Europol to continue monitoring ketamine — its manufacture,

⁽¹⁾ Joint action concerning the 'information exchange, risk assessment and the control of new synthetic drugs' (OJ L 167, 25.6.1997). A joint action is a decision adopted unanimously by the EU Member States within the framework of the third pillar of the Treaty on European Union (cooperation in the field of justice and home affairs). Synthetic drugs are psychoactive substances produced in laboratories and not derived from natural products. They include MDMA (ecstasy), other amphetamines and LSD.

⁽²⁾ The three previous risk-assessment exercises concerned the substances N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), 4-methylthioamphetamine (4-MTA) and gamma-hydroxybutyric acid (GHB).

trafficking, patterns of use and health consequences and particularly trends in recreational use — until the end of 2001. The Council will then consider whether control at EU level is appropriate.

I would like to thank all those who participated in the risk-assessment process for the high-quality work carried out. This makes a valuable scientific contribution, validated at European level, to the knowledge base on medicines diverted for illicit use.

Georges Estievenart
Executive Director, EMCDDA

Introduction

A risk assessment of any chemical is a unique scientific event in which a range of evidence is evaluated and discussed in depth. Risk assessments of new synthetic drugs under the aegis of the joint action of July 1997 are even more unique because not only the pharmacotoxicological effects on health must be considered but also the social effects and the possible consequences of prohibition. The risk assessments performed in September 2000 on ketamine and GHB (gamma-hydroxybutyric acid) were respectively the third and fourth such risk assessments performed by the extended Scientific Committee at the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). The unique feature of these substances is that they are both licensed medicines of value in human or veterinary medicine. The task faced by the risk assessment committee therefore involved not just an assessment of the scientific evidence but also an assessment of how best to safeguard public health while simultaneously ensuring that valuable medicines could still be available to practitioners and their human (and animal) patients. These assessments involved detailed and robust discussions among the multidisciplinary committee, which was drawn from each of the Member States. The ability of scientists from a range of laboratory and non-laboratory sciences to debate the issues surrounding new synthetic drugs is a key strength of the joint action process and my colleagues on the Scientific Committee are to be commended for their detailed and learned contributions to our overall understanding of these two substances. Their individual contributions, allied to those of the two experts, Dr Leon van Aerts (Ketamine) and Mr Simon Elliott (GHB), plus the invaluable inputs from the staff of the EMCDDA, provided the basis for the final recommendations made to Council about the two drugs. These recommendations do not only relate to the question of control of ketamine and GHB but also highlight the need for the Member States to consider other elements such as the need for research on the neurotoxicity of ketamine and on the role of GHB (and other drugs) in cases of drug-assisted sexual assault. Given that these subsidiary recommendations come from a committee composed of the leading experts on new synthetic drugs in the EU, their importance should not be underestimated by the Commission, the Council or the Member States.

As ever with these risk assessments, an enormous debt of gratitude is due to my colleagues on the Steering Committee for Risk Assessment who worked incredibly hard before, during and after the meetings to finalise the reports. The work of Salme Ahlström (Finland), Aldo Perissino (Belgium), Wolfgang Werdenich (Austria), Jean-Pol Tassin (France) and Christina Poethko-Müller (Germany) was more than matched by the efforts of the staff of the EMCDDA, including Alain Wallon, Lena Westberg and Deborah Olszewski.

My admiration for all of them has grown with each risk assessment because of their acumen, commitment and enthusiasm for a unique European activity.

Dr Desmond Corrigan
Chairperson, Scientific Committee of the EMCDDA

Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs

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On 17 April 2000, the Portuguese Presidency of the European Council formally notified ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) to the EMCDDA for risk assessment under Article 4 of the joint action on new synthetic drugs of 16 June 1997.

A meeting of the Scientific Committee of the EMCDDA, extended with experts nominated by the Member States and representatives of the European Commission, Europol and the EMEA (European Agency for the Evaluation of Medicinal Products), to assess the health and social risks as well as the possible consequences of prohibition of ketamine, was held on 25 and 26 September 2000.

The meeting considered the following documents:

- 'The pharmacotoxicological report on ketamine', report to the EMCDDA;
- 'Public health risks: epidemiological evidence', EMCDDA;
- 'Sociological/criminological evidence', EMCDDA;
- Europol's contribution to the risk assessment of ketamine;
- EMEA's contribution to the risk assessment of ketamine.

These documents, in conjunction with further information and comments from the expert participants, formed the basis of the risk assessment reported below.

1. Chemical description

The chemical name of ketamine is 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, an arylcycloalkylamine. It is structurally related to phencyclidine (PCP: 'angel dust') and cyclohexamine. It occurs in racemic form and also as the S-enantiomer.

Registered names (for human use) are: Ketalar, Ketamine Panpharma, Ketolar, Ketanest-S.

Registered names (for veterinary use) are: Ketalar, Ketaminol Vet., Clorketam, Imalgene, Anesketin, Ketamine Ceva, Vetalar Vet., Narketan, Ketaset.

Ketamine is known in Member States by the street names: K, special K, kit kat, tac et tic, cat valium, vitamin K, ket, super K and others.

2. Pharmaceutical description

Ketamine was first synthesised in 1962 and patented in Belgium in 1963. As an anaesthetic and analgesic, ketamine has a recognised unique therapeutic value in veterinary practice and, to a lesser extent, in human medicine. For therapeutic purposes, ketamine usually is administered intravenously or intramuscularly.

In recreational use, typical doses are: 75–125 mg intramuscularly or subcutaneously; 60–250 mg intranasally; 50–100 mg intravenously; and 200–300 mg orally.

Ketamine is manufactured by the chemical industry for use in the manufacture of pharmaceutical products which use as precursors cyclopentyl bromide, o-chlorobenzonitrile and methylamine. Due to the complicated multi-step synthesis, and the difficulty of purchasing the necessary precursors and numerous solvents and reagents, ketamine sold illicitly for recreational use appears to be mostly obtained by diversion of legitimate supplies of either the bulk drug or of pharmaceutical preparations containing it.

Pharmaceutical products may be injected or may be modified by evaporation, after which the resultant powder may be snorted in pure form or mixed with other drugs and/or inactive components. In powder form, combination with

cocaine has been observed. In the form of tablets, the concentration of ketamine and other substances is mostly unknown by users. These tablets are sold as 'ecstasy' in some Member States. Other substances reported to be present in tablets containing ketamine are pseudoephedrine, ephedrine, caffeine, amphetamine, methamphetamine and MDMA. As the effects of ketamine are dose-dependent, the fact that the amount of ketamine concentrated in the powder (and *a fortiori* in fake 'ecstasy' tablets) is unknown poses a risk in recreational use.

Preparations containing ketamine hydrochloride are used as an anaesthetic and analgesic agent in human and veterinary medicine, with important clinical applications in paediatric and ambulatory anaesthesia, treatment of burn-wound patients and for short anaesthetic procedures. However, the use of ketamine for humans in the EU is restricted to special indications, due to the occurrence of emergence reactions. Outside the EU, its ease of use gives ketamine a major advantage under difficult circumstances (developing countries and remote areas). Its use in veterinary anaesthesia, especially for small animals, is widespread and considered by several Member States and by the Federation of Veterinarians of Europe as indispensable in veterinary medicine.

3. Health risks

3.1. Individual health risks

(a) Acute effects: Ketamine is a dissociative anaesthetic. The term 'dissociative' has two meanings. Firstly, it refers to an effect on the brain, inducing a lack of responsive awareness, not only to pain but also to the general environment. Secondly, it refers to a feeling of dissociation of the mind from the body ('out-of-body experience'). Ketamine would be expected to block or interfere with sensory input to centres of the central nervous system (CNS); in a way, the drug selectively interrupts association pathways of the brain before producing somaesthetic (sensation of having a body) sensory blockade.

Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output and blood pressure. In recreational ketamine users presenting themselves to an emergency department, tachycardia was the most common finding. As a mild respiratory depressant, ketamine is unlikely to produce respiratory depression at recreational doses, even if this cannot be wholly excluded.

Cardiovascular effects usually do not pose a problem in patients without cardiovascular problems, but ketamine is contraindicated in patients with significant ischaemic heart disease and is to be avoided in those with a history of high blood pressure or cerebrovascular disorders.

The findings of neurotoxicity in the rat may indicate some cause for concern in recreational users of ketamine. These users may not take ketamine in combination with protective agents like benzodiazepines, as is usually the case in the clinical setting. Moreover, compounds increasing the neurotoxic potency of ketamine (like alcohol) might be co-administered. Recreational use also implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in chronic users of ketamine have been reported, though rarely, and these include persistent impairment of attention and recall and a subtle visual anomaly. The *Report on the risk assessment of 4-MTA* noted that ketamine increased the neurotoxicity of 4-MTA in mice. Neurotoxicity of repeated exposure to ketamine in primates including humans has not been studied.

(b) Clinical effects: Ketamine is considered to be an anaesthetic with a good safety profile, based on extensive clinical experience. The major drawback, which limits clinical use, is the occurrence of emergence reactions in patients awakening from ketamine anaesthesia. These reactions include hallucinations, vivid dreams, floating sensations and delirium. However, preclinical data on the effects of repeated ketamine administration may be of greater importance for recreational use, which, unlike clinical practice, may present cases of long-term use.

A total of 12 deaths in which ketamine was identified were noted between 1987 and 2000, including seven from the United States. Only three reported fatal cases involving ketamine alone were identified. Two reports concern mixed drugs fatalities. In one case, ketamine had only a minor role. For the remaining six cases, insufficient details were available to be evaluated properly. In the three cases involving only ketamine, the routes of administration were intramuscular or intravenous and the cause of death was mainly overdose (multiple intramuscular doses or accidental intravenous overdose), in line with preclinical findings. In the other cases involving ketamine mixed with other drugs, the observed lower ketamine concentrations indicate that drug interaction may have contributed to these deaths. Substances with CNS/respiratory depressant effects, like ethanol, opioids, barbiturates and benzodiazepines, or drugs with cardiostimulant effects, like cocaine or amphetamines, may increase ketamine acute toxicity.

Regarding non-fatal intoxications, potential dangerous interactions may also arise when different drugs are combined. Ketamine has sympathomimetic properties. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects. Serious side-effects such as hypertension and pulmonary oedema have been reported, but such adverse effects appear to be rare and may be related to the combination of ketamine with other drugs, such as amphetamine and its analogues, ephedrine and cocaine.

(c) Dependence: Tolerance, dependence and withdrawal signs have been observed in a number of animal studies. Tolerance to the desired effects of ketamine develops quickly and may result in an escalation of the dose, the toxicological implications of which are unknown. A risk associated with the recreational use of ketamine is the potential of the drug to cause psychological dependence in some individuals, based on case reports and information from users. The prevalence of long-term use is unknown. There is no evidence that ketamine causes an abstinence syndrome in humans.

(d) Psychological effects: The recreational user of ketamine may experience an altered, 'psychedelic' state of mind ('the K-hole') that allows the user to travel beyond the boundaries of ordinary existence. The intensity of 'psychedelic effects' is dose-related. Ketamine in subanaesthetic doses produces a clinical syndrome which both neurophysiologically and behaviourally resembles that of a schizophrenic psychosis. Ketamine acutely affects cognitive performance and profoundly affects perception of the body, time, surroundings and reality.

The main effects of ketamine are neurobehavioural: anxiety, agitation, changes of perception (e.g. loss of sense of danger, visual disturbances), impairment of motor function and the analgesic effects. In such a condition, the user may be at risk of injury to themselves (burns, falls) or to others (accidents).

3.2. Public health risks

(a) *Availability and quality*: Ketamine preparations have marketing authorisations in most countries of the EU, except in Greece where the marketing authorisation was recalled in 1998 ⁽³⁾. Seizure data suggest mostly low levels of availability of ketamine for illicit use within different Member States, with a decrease occurring in the United Kingdom and an increase in two other Member States. A large proportion of ketamine seizures are in tablet form and the tablets carry the same logo as is often used for ecstasy tablets. It may also be found in powder form and sold as a stimulant, such as amphetamine or cocaine. Forensic laboratories have found ketamine in variable doses mixed with manitol, caffeine, ephedrine and pseudoephedrine, MDMA, methamphetamines and amphetamines. In Belgium, 89 kg of pure ketamine powder was seized in September 1999 and a further 3 kg in January 2000. Four Member States (Belgium, Ireland, the Netherlands and the United Kingdom) seized significant amounts of ketamine. However, seizures of ketamine are small when compared to seizures of 'regular' types of synthetic drugs, such as amphetamine, MDMA and MDA.

(b) *Knowledge and perception of ketamine among users*: There appears to be low awareness of and experimentation with ketamine in Europe compared with drugs such as cannabis, MDMA, amphetamine and cocaine. Lack of information about the dose content of the ketamine on the market may be an important factor. Anecdotal reports from France and the United Kingdom indicate growing awareness among consumers about how to manage doses to achieve the desired effects and to avoid negative ones. A survey in a dance setting in Austria found that the respondents who regularly use MDMA and amphetamines considered the psychological risks attached to ketamine to be very high.

At low doses, ketamine is sometimes reported to have a stimulant effect. This could be the result of the stimulant effect of other drugs or active cutting agents (like caffeine), because ketamine is often snorted with amphetamines and/or cocaine or taken with other drugs in the illicit drug scene. There is some indication that ketamine has an upmarket image as an esoteric drug for experienced drug users.

(3) Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992. Article 12 of Directive 75/319/EEC of 20 May 1975 regulates, through the Committee for Proprietary Medicinal Products (CPMP), the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with pharmacovigilance.

(c) Prevalence and patterns of use: Surveys of selected groups of drug users in dance settings have shown that a significant number of people experiment with ketamine but that the level varies between sub-populations and geographical areas. A London club survey in 1997 found that up to 40 % of the 200 respondents had experimented with ketamine and were to use it that same evening. A large French survey conducted the same year found that 15 % of the 900 respondents in techno party settings had experimented with ketamine. Recently, a large school survey conducted in the north-east of England found that 1 % of 13/14-year-old children and 2 % of 15/16-year-olds had tried ketamine compared to 2 and 5 % respectively who had tried cocaine.

The most popular routes of administration are to snort ketamine as a powder and to inject liquid preparations. There have also been reports of it being swallowed, smoked or inserted rectally.

(d) Characteristics and behaviours of users: Although there is evidence of use by younger people, targeted surveys and anecdotal reports indicate that prevalence may be higher in older, highly educated, experienced MDMA users, particularly in the free party/new-age traveller scene, in the gay club scene and among small groups of self-exploratory individuals. Among 'closed' groups in Europe, initiation into ketamine use is often ritualised.

The most vulnerable group is those who take ketamine under the illusion that they are taking MDMA or some other stimulant drug. The volume of seizures of ketamine in tablet form with ecstasy-type logos reflects the scope for this scenario and the need for better information about drug contents and harm reduction. Ketamine does not react with commonly used field tests (e.g. Marquis reagent), although other drugs present in the tablet may produce a positive reaction.

(e) Indicators of health consequences: Four deaths in the EU in which ketamine was found by laboratory analysis have been reported to the EMCDDA since 1996, of which two occurred in 1996, in Ireland. In neither of the Irish cases was ketamine considered to be the main cause of death. The death of a 19-year-old male has been reported in France where ketamine, LSD and ecstasy were implicated. The fourth death, also reported from France, was a polydrug user.

There has been a notable lack of reporting about hospital emergencies in Europe. A recent report in France presents some data on 17 cases of intoxication associated with ketamine.

An important factor of health risk is the lack of reliable indications of dose accompanying sales of ketamine at street level. In the absence of advice, first-time users of ketamine tend to follow similar consumption patterns as those previously adopted for other drugs. This uninformed use of ketamine increases the risk of both physical and psychological problems. The existence of tolerance may increase a tendency to move from snorting to injecting ketamine, with the risks associated with injection.

(f) Context of use: The phenomenon of ketamine entering the recreational drug market in the guise of ecstasy or other stimulant drugs means that someone expecting to take MDMA, cocaine or amphetamine may find themselves inadvertently taking ketamine, without warning, knowledge or support.

Compared to the effects of stimulants, the rapid physical incapacity induced by ketamine consumption has serious implications for driving.

4. Social risks: sociological and criminological aspects

4.1. Sociological aspects

(a) Social consequences: The main social consequences for the user stem firstly from its anaesthetic properties and loss of physical control if too high a dose is taken, and secondly from reported psychological effects of either regular or heavy use, which include dependency. In addition to loss of physical control, it may cause tension due to the introspective quality of effects, other psychological symptoms and compulsive use by a small minority.

(b) Consequences for the social behaviour of the user: The main consequences for social behaviour stem directly from ketamine's specific effects and a tendency towards compulsive use by some users.

(c) Other social consequences: In dance settings, ketamine often appears in the form of well-made tablets which are visually similar to MDMA and are usually mixed with a stimulant such as caffeine or amphetamine. It is also found as liquid, powder and capsules. Ketamine has also been used as a cutting agent for drugs such as cocaine, amphetamine and heroin and may be taken

by problem opiate users. The chosen route of administration for a small minority is by injection, which raises a value conflict in a drug-using culture which is strongly against injecting.

A range of social factors increase the probability of use, such as the existence of a large market of long-term ecstasy users seeking new drug experiences, a rather intellectual trend-setting image and low price. However, other factors mitigate against widespread diffusion, such as the anaesthetic effects, marked discomfort with intranasal use, the short action, acute psychological reactions when taken without due knowledge about dose or effects, psychological dependence and negative effects on social relationships.

In view of its potential anaesthetic and numbing effects, psychological disturbances and compulsive use, there are implications for drug services, research institutes, hospital emergency departments and the press.

4.2. Criminological aspects

The seizure of considerable amounts of ketamine in Belgium, Ireland, the Netherlands and the United Kingdom could suggest the involvement of organised crime. In the United Kingdom, it is believed that ketamine raw material is imported in bulk from legitimate suppliers in Europe. A number of sources close to the user suggest that there may be diversion from licit sources or foreign purchase, particularly from Asia.

5. Possible consequences of prohibition

5.1. Legal status

Ketamine is subject to control in five Member States: Belgium, France, Greece, Ireland (to be scheduled in the Misuse of Drugs Act) and Luxembourg. It is controlled through general medicines legislation in all Member States. Due to the fact that ketamine preparations, as medical and veterinary products, have marketing authorisation in most Member States and have a recognised unique therapeutic value, the major concern appears to be diversion from legitimate supply to the black market.

The complex routes of synthesis for illegal manufacturing of ketamine reduce the potential impact on the illegal market for ketamine of targeted

measures to control ketamine precursors. Illegal production of ketamine is unlikely to develop, due to these conditions. However, the implication of organised crime in the production and supply of ketamine in tablet form, with the possible health risks associated with sale of ketamine tablets with ecstasy logos, represents a particular matter for concern.

5.2. Possible consequences of prohibition

The possible consequences of prohibition discussed at the meeting included the following.

- The EMEA highlighted the fact that changes in the conditions of marketing authorisations for ketamine containing medicinal products proposed by the meeting should be dealt with at national level or referred to the Committee for Proprietary Medicinal Products (CPMP) and the Committee on Veterinary Medicinal Products (CVMP).
- Introducing penalties for use would be unlikely to deter use in groups where illegal drugs are already well established.
- Concern was expressed about the effects of prohibition and control measures on informal information and harm-reduction networks.
- One opinion was that control measures might draw unnecessary attention to the drug, thus increasing its attractiveness to potential users.
- In discussions on possible mechanisms of control, differences between control of the bulk drug and of medicinal products containing ketamine were mentioned. In this regard, there was strong support for the suggestion that the chemical and pharmaceutical industry should be consulted about suitable control measures.
- The view that, as a common minimum approach, medicines legislation ⁽⁴⁾ should be used as a control measure received strong support.

(⁴) Legislation such as the EU regulation based upon Council Directive 65/65/EEC of 26 January 1965, as amended by Directives 83/570/EEC, 87/21/EEC, 89/341/EEC and 93/39/EEC, as well as decisions of the Court of Justice of the European Communities, especially Case C-112/89.

- Another opinion expressed at the meeting was that, in addition to existing medicines legislation, stronger control measures to deal with diversion, trafficking and inadvertent exposure (i.e. through fake 'ecstasy' tablets) were necessary. It was also felt that such measures are required to control the import and export of ketamine.
- The meeting noted the concern of the Federation of Veterinarians of Europe that placing ketamine under the same stringent restrictions as opioids could be detrimental to good veterinary medicine. It was noted that the same concern could apply to the use of ketamine in human medicine.

6. Conclusions

The Scientific Committee of the EMCDDA, enlarged with experts from the Member States and representatives of the Commission, Europol and EMEA, have considered the health and social risks as well as the possible consequences of prohibition of ketamine and, in accordance with Article 4 of the joint action, submit the following conclusions:

- 6.1. Ketamine is not a new synthetic drug. While it has a significant therapeutic use, it is also being used in recreational settings.
- 6.2. The meeting noted the main risks of the recreational use of the drug, such as psychological dependence, loss of self-control and the risk of acute intoxication. To date, the use of ketamine has been reported as associated with mortality or morbidity in a small number of cases.
- 6.3. An opinion which received strong support at the meeting was that, as a common minimum, ketamine should be subject to control under medicines legislation in Member States.
- 6.4. Another strong opinion expressed at the meeting was that, in addition to the medicines legislation, stronger control measures to deal with diversion, trafficking and inadvertent exposure to the drug were necessary.
- 6.5. The meeting recommends that both the EMCDDA and Europol should further monitor the manufacture, trafficking, distribution, patterns of use and health consequences of ketamine, particularly the fatalities and non-fatal emergencies.

- 6.6. The meeting recommends that a study on the possible neurotoxicity of ketamine in primates should be considered in the context of the fifth framework research programme of the European Commission.
- 6.7. The possible options for improving control of diversion should be discussed with the chemical and pharmaceutical industry in order to ensure the continued availability of ketamine for medical and veterinary use.
- 6.8. The meeting recommends that consideration should be given to how appropriate information can be disseminated to the most vulnerable risk groups.

Lisbon, 25 September 2000

Europol–EMCDDA progress report on ketamine in accordance with Article 3 of the joint action of 16 June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs

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Introduction

The Horizontal Working Party on Drugs, at its meeting of 22 September 1999, asked the EMCDDA and Europol for preliminary information on the substance ketamine under Article 3 of the joint action. Europol national units and Reitox national focal points were subsequently requested to provide information on ketamine. The EMCDDA and Europol also conducted enquiries. No reporting took place using the 'Europol–EMCDDA reporting form on new synthetic drugs'.

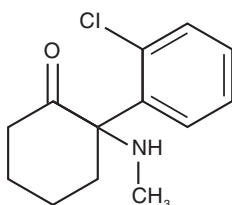
Ketamine is subject to control in five Member States: Belgium (Royal Decree 31.5.1976), Greece (Law 1729/87); France (Decree 8.8.1997); Ireland (to be scheduled under the Misuse of Drugs Act); and Luxembourg (Grand-Ducal Decree 4.3.1974). It is controlled through means of medicinal legislation in Germany, Spain, the Netherlands, Austria, Sweden and the United Kingdom. In the United Kingdom, the Advisory Council for the Misuse of Drugs recommended monitoring of ketamine.

Available information on ketamine

Chemical and physical description, including the name by which ketamine is known

The chemical name for ketamine is 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone.

Figure 1: Structural formula of ketamine



It is a dissociative anaesthetic drug used as a licensed product in veterinary medicine (i.e. Vetalar and Imalgene) and to a lesser extent by the medical profession, mainly for emergency care (i.e. Ketalar). Ketamine is freely soluble in water or alcohol and usually comes from the pharmaceutical industry in liquid form in ampoules for intramuscular or intravenous injections.

Ketamine is known in Member States by the street names: K, special K, vitamine K, ket, super K, liquid E and others ⁽⁵⁾.

In the United Kingdom, ketamine appears in the form of well-made tablets, visually similar to and often sold as 'ecstasy' tablets. It is rarely found alone in tablets but is usually mixed with a stimulant drug (e.g. amphetamine or MDMA, ephedrine and/or caffeine). Typical impressions on the tablets are the same as those found on 'ecstasy' tablets, such as a bird, clover/club, heart, etc.

Ketamine is also found on the 'illicit recreational' drug market as liquid, powder and capsules, where it is snorted or swallowed. It has also been used as a cutting agent for drugs such as cocaine, amphetamine and heroin.

Ketamine does not react with commonly used field-test kits (e.g. Marquis reagent) although other drugs present may produce a positive reaction.

The typical nasal dose is around 200 mg, thus one dose at this price is less than EUR 3. With ease of access, at relatively low prices, it is unlikely that

⁽⁵⁾ However, as occurs with logos, drug users and suppliers in different countries may apply the same synonym to different drugs, either mistakenly or deliberately. For example, in Australia, 'liquid ecstasy' has been reported to be a synonym for ketamine, whilst in the United Kingdom it is a synonym for GHB. In the absence of facilities for chemical analysis at user level, the significance of a logo or a synonym is uncertain with regard to drug content. 'K hole' is a term used by conscious consumers of ketamine to describe and locate the effects of the drug.

illicit tablet manufacturers would contemplate the synthesis of ketamine, which is probably too difficult for most clandestine chemists.

Information on the frequency, circumstances and/or quantities in which ketamine is encountered

In Austria, although there have been no reported seizures or hospital treatment episodes attributed to ketamine, there is some anecdotal evidence of use among very small, closed groups.

In Belgium, 89 kg of ketamine were seized in September 1999. In January 2000, another seizure of 3 kg took place. Both seizures contained pure ketamine in powder form. In addition, there have been a few seizures of ketamine in tablets, mixed with MDMA or amphetamine. Ketamine is not free for trade in Belgium.

In Finland, there were 14 seizures of ketamine in 1998, totalling 614 tablets. In 1999, five seizures occurred, totalling 49 tablets with the 'propeller' logo.

In France, two seizures of tablets with an ecstasy-type logo containing ketamine and amphetamine were reported in 1998 and 1999. A survey of young people who were regular attendees at techno party events found that 15 % reported that they had taken ketamine. Among a matched control group of young people who did not go to such events, consumption of ketamine was non-existent, indicating that use is not widespread.

In Germany, six people were arrested in May 1999 in relation to the seizure of an illicit synthetic drug laboratory. A large amount of laboratory equipment was seized, as were chemicals and end products. These included 182 g of ketamine hydrochloride in tablet form (700 tablets with blue colour) and 0.9 g of ketamine powder. Another 2 000 yellow tablets were seized containing methamphetamine hydrochloride and ketamine hydrochloride.

In Greece, treatment staff and helplines reported three instances of ketamine use in 1999 in the same recreational drug scene as ecstasy and cocaine. There are reports of ketamine liquid being boiled to obtain powder that is sniffed.

In Ireland, from 1 January 1998 to 15 October 1999, there have been 43 incidents of ketamine seizures. In 40 of these cases, ketamine and ephedrine were present

in tablet form (number of tablets 4 500); one case was of 27 000 tablets with ketamine only or ketamine with caffeine, one case of 26 tablets which contained only ketamine and one case of 0.23 g of ketamine powder. The vast majority of ketamine seized in Ireland emanates from the Netherlands. Organised crime groups or Irish nationals are responsible for the importation and distribution of ketamine. There are no indications that Ireland is a transit or export point.

In Spain, a combination of ketamine and cocaine is known as 'special CK' ⁽⁶⁾. Early seizures took place in 1995 in the Balearic Islands and in 1996 a submission of ketamine mixed with manitol was found in Barcelona. There have been a series of small seizures throughout 1996 to 1999. Between 1995 and 1996, a British police team visited the Balearic Islands to investigate the origin of ketamine tablets that had been seized in discotheques and bars and were suspected to have been manufactured in the United Kingdom. The seizures were mainly from foreign tourists and none have occurred in Madrid and other major cities. This, together with the absence of deaths, indicates a lack of widespread popularity in Spain.

In Sweden, ketamine is an integral ingredient in four different medicinal products and some years ago stolen ketamine products from the legal pharmaceutical trade appeared on the illegal market. Misuse is a minor concern at present. There have been occasional and minor seizures of ketamine on the domestic user market.

In the United Kingdom, seizures climbed rapidly in the early 1990s. In 1995, almost 100 000 tablets containing ketamine and ephedrine and carrying a logo commonly found on ecstasy tablets were seized. During 1995 and 1996, a number of hospitalisation cases were reported. Ketamine seizures peaked in 1997 and over the past two years have stabilised at around 200 submissions per year. There have been few significant customs seizures, suggesting that most, if not all, tablets consumed in the United Kingdom are produced there. It is believed that ketamine raw material is imported in bulk from legitimate suppliers in Europe. Ketamine appears to be distributed through illicit drug distribution networks. Small quantities can be obtained by mail order from chemical catalogues at around EUR 64 for 5 g. A number of ketamine tablet manufacturers have been successfully prosecuted for

⁽⁶⁾ Referring to Calvin Klein, the popular American designer.

conspiracy to supply, or attempt to supply, a controlled drug and some dealers have been prosecuted for conspiracy to defraud contrary to common law.

Recently, in the north-west of England and in London, it has been reported that, among some circles of 'early adopters' and 'media types', ketamine is being sought out as a drug experience in its own right. In a targeted survey of 200 regular techno dance clubbers in London in 1998, 40 % said that they had experimented with ketamine and 10 % were planning to use it that evening. The survey placed ketamine in fourth place after cannabis, amphetamine and ecstasy. More recently, some outreach workers have expressed scepticism about the existence of a significant trend in ketamine use. However, considering the perceived influence of the media on patterns of drug consumption, it is too early to dismiss the development of ketamine use as a new trend.

A first indication of the possible risks associated with ketamine

Ketamine is not strictly hallucinogenic, but in small doses users feel detached from their immediate environment. It also causes catalepsia (muscle rigidity) and reduces reaction to pain. Overdose is rare, but adverse effects include hypertension, tachycardia, headache, nausea, vomiting, slurring of speech, numbness and, in more severe reactions, temporary unconsciousness, respiratory collapse or heart failure. It can also provoke panic or acute anguish or anxiety, particularly when taken unknowingly or without prior knowledge of its possible effects. There is also some evidence that the effects of ketamine are considerably diminished in someone with tolerance. However, the sudden anaesthetic effects of ketamine create high risk for accidents and makes driving following consumption dangerous.

Two deaths linked with the use of ketamine were reported for 1996 in Ireland. Both persons who died had a history of ecstasy use. In one death, ketamine was found in combination with opiates. In the other it was found in combination with ephedrine and pseudoephedrine.

During 1995 and 1996, in the United Kingdom, a number of hospitalisation cases occurred of users suffering anxiety attacks who had taken large doses of ketamine believing it to be ecstasy. Since 1996, no deaths have been recorded but there is growing documentation showing similarity to phencyclidine, associated with foetal malformation (mainly cephalic size reduction) in pregnant women and effects on neonates.

A study of 346 young people attending raves in Vienna found that young people who were regularly taking ecstasy and amphetamine considered the psychological risks attached to taking drugs such as ketamine very high.

Information on chemical precursors

The precursors mainly used for illicit production of ketamine are cyclohexanone, methylamine and chlorobenzene.

Information on the mode and scope of established or expected use of ketamine as a psychotropic substance

Ketamine is often sold in a form which is indistinguishable from ecstasy, although there are also reports of ampoules, liquid, powder and capsules. The dose varies depending on the pattern of use and route of administration. For example, at low doses ketamine is a stimulant, especially if it is sniffed with amphetamine and/or cocaine or taken with drugs in the 'illicit recreational' drug scene. It may also be administered in intramuscular doses for a specific ketamine experience.

A study of 100 ketamine users conducted by the Australian National Drug and Alcohol Research Centre in the mid-1990s reported that there appeared to be four primary user groups:

- injecting heroin users;
- members of the gay scene;
- regular drug users in the 'dance' scene; and
- 'self-exploratory' people.

There have been no prevalence studies on ketamine use in Europe but there is little evidence that it is abused on a wide scale. The anaesthetic properties and unpredictable effects make it an unsuitable drug for widespread 'going out' recreational purposes. These effects distinguish ketamine from MDMA and are likely to prevent widespread dissemination of illicit ketamine use.

Numerous books and journal articles have been written concerning ketamine. Information about its effects, supply and health risks are provided on the Internet.

Information on other use of ketamine and the extent of such use

The role of ketamine in producing psychotherapeutic effects, particularly in relation to 'near-death experiences', is widely documented.

*Drafted by Europol and the EMCDDA
17 March 2000*

Use of ketamine in human medicine in the EU Member States (EMA)

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As part of the EMA's preparation for the risk assessment of ketamine, they asked for information on each national situation regarding the terms of authorisation and therapeutic value of the product.

Ketamine is authorised in most countries of the EU with similar indications, except for Greece, where the marketing authorisation was recalled in 1998. It is indicated for special situations in anaesthesia (alone or in combination) and for special situations in pain treatment. Its use generally seems to be limited and decreasing, with the exception of Belgium, where a steady increase in use has been observed in the last 10 years, and the United Kingdom, which reported an increase in hospital prescriptions between 1997 and 1999. Although most responses did not contain information as to whether action has been taken to list the products under the 1971 UN Convention on Psychotropic Substances, in many countries ketamine is subject to restricted prescription or regulated as a psychotropic substance.

London, 30 March 2001

Use of ketamine in veterinary medicine in the EU Member States (EMA)

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In September 2000, the EMA Veterinary Unit Secretariat was requested by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) to provide information in order that the health and social risks as to the possible consequences of prohibition of ketamine could be assessed. This was to be considered at a meeting to be held in Lisbon, Portugal, on 25 and 26 September 2000. As ketamine is not a centrally authorised product under the terms of Council Regulation (EEC) No 2309/93, the EMA undertook to consult with the competent authorities for veterinary medicinal products in the Member States as to the authorisation status of this product at national level and sought detailed information on its use and value as a veterinary medicinal product for veterinary practitioners in the European Union. As a result of that consultation, through the Veterinary Mutual Recognition Facilitation Group of the European Union and an in-depth review with the Federation of Veterinarians of Europe (FVE), the following points can be concluded about the use of ketamine in veterinary practice in Europe.

Ketamine constitutes an essential medicine for the veterinary profession in the EU today. It is widely used for anaesthesia and analgesia by the veterinary profession. Ketamine is an essential anaesthetic for veterinary use, because it is the only injectable anaesthetic that is safe, well established and well tolerated among the full range of species that the veterinarians are called upon to treat. These include both large and small domestic animals, children's pets and laboratory animals, large, wild and zoo animals, as well as birds and reptiles. It has been used safely by virtually every veterinary practice throughout Europe and on a global basis under prescription-only medicine conditions for many years.

Whilst the veterinary profession also uses pure μ -opioid analgesics, in most countries these are kept under very tightly controlled conditions, locked in a dedicated cupboard with only veterinary access, their use recorded very precisely. There is no doubt that pure μ -agonists are not used as often as good anaesthetic and analgesic practice would indicate, because they are controlled under such tight restrictions. It would therefore be very detrimental

to good veterinary practice if ketamine also had to be kept under such stringent restrictions. On welfare grounds alone, it is essential that the veterinary profession is able to use such an agent easily on a daily basis and in field situations where inhalation anaesthesia is not possible.

London, 28 May 2001

Review of the pharmacotoxicological data on ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) (7))

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This report was commissioned by the EMCDDA as part of a risk assessment on the drug ketamine in accordance with Article 4 of the joint action concerning the information exchange, risk assessment and control of new synthetic drugs adopted by the Council of the European Union on 16 June 1997. This report summarises the relevant data required by the Technical Annexes A and B of the guidelines for the risk assessment of new synthetic drugs, as adopted by the Scientific Committee of the EMCDDA.

Introduction

The anaesthetic ketamine was first synthesised by Calvin Stevens at Parke-Davis laboratories in 1962 (Jansen, 2000a) and patented in Belgium in 1963 and in the US in 1966 (Budavari et al., 1989). Ketamine was first marketed in the early 1970s (FDA, 1979) and promoted as a more acceptable alternative to its congener, PCP ('angel dust'; Dotson et al., 1995). PCP was abandoned, except for veterinary use, because of its adverse effects, such as hallucinations and delirium. Although ketamine is not devoid of similar side-effects, these are less persistent, and ketamine has now achieved a unique place in medical practice. PCP had become popular as a recreational drug in the 1960s and had caused considerable problems as such. Ketamine abuse was first noted on the west coast of the United States in 1971 (Siegel, 1978). In the early 1990s in the United Kingdom, several reports of more widespread recreational use of ketamine appeared (Hall and Cassidy, 1992; McDonald and Key, 1992; Jansen, 1993; Dalgarno and Shewan, 1996). An inquiry by the EMCDDA has shown that recreational use of ketamine is noted in other Member States as well (e.g. Arditti, 2000).

(7) This report was written by L.A.G.J.M. van Aerts and J.W. van der Laan of the Laboratory for Medicines and Medical Devices, National Institute of Public Health and Environment, the Netherlands. Valuable help and advice was contributed by Dr Peter Kasper of the Federal Institute for Drugs and Medical Devices, Berlin, Germany.

Since ketamine has existed for 37 years as a chemical entity, it is difficult to call it a *new* synthetic drug. Ketamine cannot be considered a drug with limited therapeutic value, as its pharmacological properties have given it a unique place in human and veterinary medical practice. Nevertheless, in light of its current use as a recreational drug in the EU, the Portuguese Presidency, on behalf of all Member States and in the framework of the Horizontal Working Party on Drugs of the Council of the European Union, formally referred the substance ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) to the EMCDDA for a risk assessment under Article 4 of the joint action concerning the information exchange, risk assessment and control of new synthetic drugs adopted by the Council of the European Union on 16 June 1997, on the basis of Article K3 of the Treaty on European Union. This report summarises the relevant data required by the Technical Annexes A and B of the principles for risk assessment of new synthetic drugs, as adopted by the Scientific Committee of the EMCDDA.

Pharmacotoxicological evidence

Chemical information

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone), an arylcycloalkylamine, is structurally related to phencyclidine (PCP) and cyclohexamine. Ketamine hydrochloride is a water-soluble white crystalline and has a pKa of 7.5 (Budavari et al., 1989). Its free base, ketamine, has a lipid solubility 10 times that of thiopentone. It contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomers exist, S-(+)-ketamine and R-(-)-ketamine. Ketamine is used in human and veterinary medicine as an anaesthetic and analgesic. The commercially available pharmaceutical form is an aqueous solution for injection of the racemic mixture of the hydrochloride salt. Clinically, ketamine usually is administered intravenously or intramuscularly. Recreationally, ketamine is taken intranasally, orally, intramuscularly, subcutaneously or intravenously. Typical recreational doses are 75–125 mg intramuscularly or subcutaneously, 60–250 mg intranasally, 50–100 mg intravenously and 200–300 mg orally. Doses may vary considerably, depending on the strength of the effect desired, differences in sensitivity and development of tolerance.

Ketamine contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomers exist: S-(+)-ketamine and R-(-)-ketamine.

The **CAS number** for ketamine is:

Free base 6740-88-1

Hydrochloride salt 1867-66-9 (current); 81771-21-3, 96448-41-8, 42551-62-2 (previous)

The **molecular weight** of ketamine is:

Free base 237.73

Hydrochloride salt 274.18

1.15 mg of the hydrochloride salt is equivalent to 1 mg of the free base.

The **melting point** of ketamine is:

Free base 92–93 °C

Hydrochloride salt 262–263 °C

The **proprietary names** used for ketamine are:

Ketalar, Ketolar, Ketaject, Ketanest, Ketaset, Ketavet, Ketavet 100, Ketalin, Vetalar, Kalipsol, Calipsol, Substantia, Ketamine Panpharma, Ketamine UVA, Chlorketam, Imalgene (Budavari et al., 1989; Reynolds et al., 1989; Arditti, 2000).

The most common **street names** for ketamine currently in use in the EU are ketamine, K, ket, vitamin K, special K and super K (Jansen, 1993; Europol/EMCDDA, 2000). Liquid E, a name more often used for GHB (gamma-hydroxybutyric acid), was mentioned as well (Europol/EMCDDA, 2000). Additionally, the French assessment report on ketamine (Arditti, 2000) mentions k eta K, kit kat, cat valium, flatliners (also in use for 4-MTA), kaddy, kate, tac et tic, liquid G and sp ecial la coke. Other names that were reported earlier in the United States are kay, jet, super acid, 1980 acid, special LA coke, super C, purple, mauve and green (FDA, 1979; Felser and Orban, 1982).

Synthesis, precursors, excipients and impurities of ketamine

Ketamine is manufactured by the pharmaceutical industry. The preparation is described by Stevens, Belgian patent 634208 (1963), which corresponds to the US patent 3254124 (1966 to Parke-Davis). The synthesis of the optical isomers is described by Hudyma et al., German patent 2062620 (1971 to Bristol-Myers) (Budavari et al., 1989).

Ketamine that is used recreationally is mostly diverted from the pharmaceutical supply to hospitals, veterinary clinics or the pharmaceutical distribution network. The precursors that are mainly used for its illicit production are cyclohexanone, methylamine and chlorobenzene (Europol/EMCDDA, 2000). Sources on the Internet rate the synthesis of ketamine as difficult. A specific route described on rhodium.lycaem.org involves the precursors cyclopentyl bromide, o-chlorobenzonitrile and methylamine. Several additional reagents and solvents are needed for the four-step synthesis described. The same site mentions that two ketamine analogues have been found on the black market: the compound missing the 2-chloro group on the phenyl ring, and its N-ethyl analogue. According to this Internet site, both of these compounds are considered to be more potent and longer lasting than ketamine. Using the same synthesis route as described for ketamine, the precursors benzonitrile and ethylamine would be involved instead of o-chlorobenzonitrile and methylamine.

Ketamine prepared by the pharmaceutical industry meets the standards of good manufacturing practice (GMP), which means that the quality and purity is guaranteed. Ketamine is sold as hydrochloride salt in an aqueous solution and is packaged in small sealed glass vials. A preservative may also be present.

When the drug is diverted for recreational use, the original pharmaceutical form is often abandoned. Most users dislike using needles, and the most popular medium for ketamine is powder form, which is snorted. The powder is prepared by evaporation of the original solution. This powder is usually sold in small plastic or paper bags. The ketamine in these bags may be mixed with other drugs or inactive components. As the effects of ketamine are dose-dependent, the uncertainty about the concentration of ketamine in the powder poses a risk for overdosing.

Ketamine can also be administered intranasally by transferring the ketamine solution to a vaporiser, or it may be presented in tablet form, to be taken orally. Again, the concentration and presence of adulterants are mostly unknown.

Tablets containing ketamine are often sold as 'ecstasy'. Other substances reported to be present in ketamine-containing tablets are pseudoephedrine, ephedrine, caffeine, amphetamine, methamphetamine and MDMA.

Legitimate uses of the product

Ketamine hydrochloride is used as an analgesic and anaesthetic in human and veterinary medicine, where it has acquired a unique place. Important clinical applications are brief procedures in paediatric and ambulatory anaesthesia, the treatment of burning-wound patients, use in obstetrics and for the induction and maintenance of anaesthesia in hypovolemic pericardial tamponade, constrictive pericarditis and cardiogenic shock patients (Reich and Silvay, 1989; Haas and Harper, 1992; Bergman, 1999).

According to the information provided by the EMEA on current use in the EU, it appears that, in general, medicinal use of ketamine for humans is limited. Its use is considered useful in special circumstances. Italy had no difficulty in finding alternatives to ketamine. In Germany, S-ketamine has been licensed as an anaesthetic in human medicine since 1997.

According to the information provided by the EMEA, the use of ketamine in veterinary anaesthesia, especially in small animals, as well as in exotic animals, is currently widespread in the EU. Several Member States (Denmark, Germany, Portugal, Sweden) indicate that ketamine is indispensable in veterinary medicine in those countries.

Outside the EU, the use of ketamine as an anaesthetic in human medicine may have a more prominent place in Third World countries, where facilities are much poorer. Its ease of use gives ketamine a major advantage under such difficult circumstances (Green et al., 1996).

Pharmaceutical form (powder, capsules, tablets, liquid, injectables, cigarettes)

Figure 3: Ketamine vials and bags containing ketamine powder



The pharmaceutical form of the preparations used in medicine is an injectable solution of the racemic mixture of ketamine hydrochloride in water (10, 50 or 100 mg/ml). The solution is packaged in small sealed glass vials.

On the street, ketamine has appeared in various forms. These may be the original vials containing the ketamine solution, or as a vaporiser, a powder (in bags or in ampoules) or in tablets.

In powder form, combination with cocaine has been observed (CK, or Calvin Klein). In tablet form, mixtures of ketamine and a range of other substances have been reported, including pseudoephedrine, ephedrine, caffeine, amphetamine, methamphetamine and MDMA. The ketamine content of three tablets in which ketamine was quantified by a Dutch drug supply monitor varied from 89 to 114 mg. In these tablets, methamphetamine (6 and 11 mg), caffeine (31 and 55 mg) and ephedrine were also found.

Routes of administration

Clinically, the drug is usually administered by intramuscular or intravenous injection. For analgesia, the intrathecal route is used as well. Administration by the oral and rectal routes has also been reported (Reich and Silvey, 1989).

When ketamine is used recreationally or experimentally, the most popular route of administration is the intranasal route (i.e. snorting the powder or inhaling a solution from a vaporiser). Some long-term users may use the

intramuscular, subcutaneous or intravenous route as well. All routes of administration that involve the use of needles bear the risk of transmitting diseases like HIV or hepatitis if the needle or syringe is not clean. In the rave scene, oral administration of ketamine-containing tablets occurs as well. These may be sold as ecstasy tablets, which poses a risk of inadvertent use of ketamine by someone expecting to use MDMA.

Dosages by all routes of administration

A dose equivalent to 2 mg of ketamine per kg of body weight given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds lasting for 5 to 10 minutes (the dose may range from 1 to 4.5 mg/kg). An intramuscular dose equivalent to 10 mg per kg of body weight (ranging from 6.5 to 13 mg/kg) usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes (Reynolds et al., 1989).

Intravenous administration of 0.2–0.75 mg/kg of ketamine produces analgesia (Reynolds et al., 1989). Using the oral or intramuscular route, a dosage of 0.5 mg/kg induces analgesia (Grant et al., 1981). Although the time differs, depending on the route, the similarity of the dosages to obtain analgesia using different routes might be explained by the analgesic properties of the primary metabolite norketamine (Reich and Silvay, 1989).

Subanaesthetic intravenous doses inducing psychotropic effects range from 0.1 to 1.0 mg/kg. In clinical studies, this dose may be divided into a bolus of 0.1–0.2 mg/kg and a maintenance infusion of 0.0025–0.02 mg/kg/min (Krystal et al., 1994; Malhotra et al., 1996; Engelhardt, 1997; Vollenweider et al., 1997; Oranje et al., 2000).

Intramuscular administration of ketamine in a dose ranging from 25 to 200 mg has been reported to produce psychotropic effects in humans (Hansen et al., 1988).

Recreational users who snort the powder describe the dose as a 'typical line', suggesting a quantity between 60 and 250 mg (Dalgarno and Shewan, 1996). Malinovsky et al. (1996) found that bioavailability of nasally administered ketamine in children was approximately 50 %, whereas bioavailability of intramuscularly administered ketamine is approximately 93 % (Grant et al., 1981). The dose range for intranasally administered ketamine is, therefore, probably higher than that for the intramuscular route.

Bioavailability is low when ketamine is administered orally (see the section 'Pharmacokinetics', page 42). The main active metabolite, norketamine, which has a potency one third of the parent compound, predominates after oral administration. Consequently, oral dosages are larger than those administered by other routes (typical doses may be expected to be around 200–300 mg).

Besides the route dependency of the dose needed to evoke psychotropic effects, the dose will vary among users, depending on the strength of the effect desired, differences in sensitivity and development of tolerance. Commonly, users titrate the quantity individually to achieve the desired effects.

Toxicology and pharmacology in animals and humans

Pharmacodynamics

A large body of literature exists on the neuropharmacological properties of ketamine. These studies were performed both *in vitro* and *in vivo*. The main characteristics of ketamine's action on the central nervous system will be summarised in this section.

Ketamine is a dissociative anaesthetic (Domino et al., 1966). Originally, the dissociation component referred to a functional and electrophysiological dissociation of thalamoneocortical and limbic systems (Reich and Silvey, 1989; Haas and Harper, 1992). More recently, the nature of the subanaesthetic ketamine experience has led to the use of the term 'dissociative' in a more psychological sense, referring to a feeling of dissociation of the mind from the body (Jansen, 1990, 2000a).

Ketamine binds to the so-called PCP-binding site, which is a separate site of the NMDA-receptor complex located within the ion channel, thereby blocking the transmembranous ion flux. This makes ketamine a non-competitive NMDA-receptor antagonist. NMDA-receptors are calcium-gated channel receptors. The endogenous agonists of the receptor are the excitatory amino acids glutamic acid, aspartic acid and glycine. Activation of the receptor results in opening of the ion channel and depolarisation of the neurone. The NMDA-receptor is involved in sensory input at the spinal, thalamic, limbic and cortical levels. Ketamine would be expected to block or interfere with sensory input to higher centres of the CNS, with the emotional response to these stimuli and with the process of learning and memory (Bergman, 1999).

Awakening from ketamine anaesthesia takes place at plasma concentrations of 0.064 to 1.12 $\mu\text{g/ml}$ (Reich and Silvy, 1989). Psychotropic effects have been described when plasma concentrations range from 0.05 to 0.3 $\mu\text{g/ml}$ and with regional brain concentrations higher than 0.5 $\mu\text{g/ml}$ (Hartvig et al., 1995; Bowdle et al., 1998; Oranje et al., 2000).

Several studies indicated that opioid receptors are also involved and that the analgesic effect of ketamine may largely be attributed to the activation of these central and spinal receptors. The plasma levels at which analgesia is achieved are 0.15 $\mu\text{g/ml}$ following intramuscular administration and 0.04 $\mu\text{g/ml}$ after oral administration. This difference may be explained by a higher norketamine concentration due to first-pass metabolism. This main metabolite apparently contributes to the antinociceptive effect (Shimoyama et al., 1999).

Some of the effects of ketamine may be due to its actions on catecholamine systems, notably an enhancement of dopamine activity (White and Ryan, 1996; Smith et al., 1998; Vollenweider et al., 2000). A series of experiments by Hancock and Stamford (1999) on the effects of ketamine on uptake and efflux of dopamine in the rat nucleus accumbens (NAc) led the authors to conclude that ketamine increases NAc dopamine efflux not by block of dopamine uptake, autoreceptors or NMDA receptors, but by mobilisation of the dopamine storage pool to releasable sites. In the rat, it has been shown that repeated ketamine administration diminished the initial five-fold increase in dopamine release in the prefrontal cortex, whereas the increase in extracellular 5-hydroxyindole acetic acid (5-HIAA, a serotonin metabolite) levels is enhanced. This suggests that the balance between dopamine and serotonin neurotransmission in the prefrontal cortex is altered after repeated exposure to ketamine (Lindfors et al., 1997). The dopaminergic effects may be of relevance for the euphorogenic, addictive and psychotomimetic properties of ketamine.

Other neuropharmacological actions are an agonistic effect on α - and β -adrenergic receptors, an antagonistic effect at muscarinic receptors of the CNS and an agonistic effect at the σ -receptor (Bergman, 1999).

The principal metabolite, norketamine, is pharmacologically active. Its binding affinity to the NMDA-receptor and its anaesthetic properties are approximately one third of the parent compound contributing significantly to the analgesic effect of ketamine (Shimoyama et al., 1999).

The commercially available ketamine is a racemic mixture of two enantiomers. The S-enantiomer is shown to be the more potent one, with an approximately three- to fourfold anaesthetic potency compared to R-ketamine. This correlates to the higher binding affinity for the PCP site of the NMDA-receptor. The psychotomimetic properties of ketamine are mainly caused by the S-enantiomer, although subanaesthetic doses of R-ketamine may induce a state of relaxation (Engelhardt, 1997; Vollenweider et al., 1997).

Secondary pharmacology

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output and blood pressure (Haas and Harper, 1992). The mechanism is not well understood, although elevated levels of circulating catecholamines due to reduced re-uptake may contribute to this phenomenon. On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion preventing any sympathomimetic effects of ketamine and unmasking a negative inotropic effect which is usually overshadowed by sympathetic stimulation (Reich and Silvey, 1989; White and Ryan, 1996). The cardiovascular effects of ketamine usually do not pose a problem, but its use is contraindicated in patients with significant ischaemic heart disease and should be avoided in those with a history of high blood pressure or cerebrovascular accidents (Haas and Harper, 1992). In recreational ketamine users, presenting to an emergency hospital department, tachycardia was the most common finding upon physical examination (Weiner et al., 2000).

EFFECTS ON THE RESPIRATORY SYSTEM

Ketamine is a mild respiratory depressant. Depending on dose, it causes a shift of the CO₂ dose-response curve to the right but does not change the slope of the curve. Respiratory drive to CO₂ may be depressed by as much as 15 to 22 %. This effect is similar to that of opioids but different to most sedative hypnotics and anaesthetics, suggesting that opioid receptors may play a role in the respiratory depressant effect. In clinical studies, these effects were observed only at high doses. Some case reports describe respiratory depression after rapid intravenous injection, but also after routine paediatric use of ketamine administered intramuscularly (Reich and Silvey, 1989; White and Ryan, 1996). It appears that respiratory depression is not likely to occur at recreational doses, but it cannot wholly be excluded.

Ketamine has a bronchodilatory effect, but pharyngeal and laryngeal reflexes are maintained (Reich and Silvy, 1989).

OTHER PHARMACOLOGICAL EFFECTS

Other pharmacological effects that have been noted are as follows:

- ketamine increases muscle tone (Reich and Silvy, 1989);
- blood glucose and plasma cortisol and prolactin are increased after ketamine administration (Reich and Silvy, 1989; Krystal et al., 1994); and
- ketamine may decrease intraocular pressure (Reich and Silvy, 1989).

Pharmacokinetics

The pharmacokinetics of ketamine have been studied in humans (e.g. Grant et al., 1981; Clements et al., 1982; Malinovsky et al., 1996). The reported volumes of distribution varied from 1.5 to 3.2 l/kg. The clearance was in the range 12–28 ml/kg/min. The volume of distribution and clearance for S-ketamine are 9 and 14 % greater than those for R-ketamine (Engelhardt, 1997).

ABSORPTION

Ketamine is rapidly absorbed when administered through the intramuscular (T_{max} 5–15 min.), nasal (T_{max} 20 min.) or oral route (as a solution; T_{max} 30 min.). The bioavailability is low when ketamine is given orally (17 %) or rectally (25 %). Extensive first-pass metabolism in the liver and intestine is largely responsible for this effect. Bioavailability after nasal administration is approximately 50 % (Malinovsky et al., 1996). The lower bioavailability with this route compared to the intramuscular route may partly be caused by swallowing significant amounts of the intranasal deposit.

DISTRIBUTION

Initially, ketamine is distributed to highly perfused tissues, including the brain, to achieve levels four to five times those in plasma (distribution half-life after i.v. 24 sec). CNS effects subside, following redistribution to less well-perfused tissues (redistribution half-life 2.7 min). Ketamine has a high lipid solubility and low plasma protein binding (12 %), which facilitates rapid transfer across the blood–brain barrier.

BIOTRANSFORMATION

Biotransformation primarily takes place in the liver. The most important pathway is N-demethylation to norketamine. When administered orally or rectally, initial plasma norketamine concentrations are higher than those of ketamine, but the plasma area under the curve (AUC) for norketamine is similar for all routes of administration. Norketamine has one third the anaesthetic potency of ketamine and has analgesic properties. Norketamine may be metabolised through multiple pathways, but the majority is hydroxylated and subsequently conjugated.

ELIMINATION

The predominant route of elimination is by liver metabolism. The high extraction rate (0.9) makes ketamine clearance susceptible to factors affecting blood flow. The conjugated hydroxy metabolites are mainly excreted renally. Reported terminal elimination half-lives were in the range of 100 to 200 minutes.

Toxicology

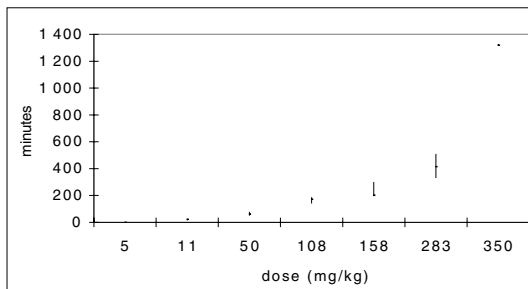
The clinical safety profile of ketamine is largely based on extensive clinical experience. The preclinical data may therefore be of less importance for clinical safety. However, unlike recreational use, long-term clinical use of ketamine is rare. Therefore, some preclinical data may be of greater importance for the recreational drug user than for clinical practice.

SINGLE-DOSE TOXICITY

Single-dose acute toxicity shows an LD₅₀ of between 140 (intraperitoneally in the neonatal rat) and 616 mg/kg bw orally in the mouse (EMEA, 1997). In adult mice and rats LD₅₀ values were 224 ± 4 mg/kg and 229 ± 5 mg/kg, respectively (route not indicated) (Budavari et al., 1989).

In squirrel monkeys (Greenstein, 1975), doses above 25 mg/kg administered intravenously caused anaesthesia. Return of righting reflex as a function of the dose administered is shown in the graph in Figure 4.

Figure 4: Return of the righting reflex in squirrel monkeys



At the highest concentration tested (350 mg/kg), four out of five monkeys died. In humans, the lowest recommended intravenous dose to induce anaesthesia is 1 mg/kg. Applying the same ratio of minimal anaesthetic dose to highest non-lethal dose to humans implies that doses above 11.3 mg/kg administered intravenously may be lethal in humans. For a person of 60 kg, this is equivalent to intravenous doses above 680 mg. This estimate is based on an experiment with a low number of animals and interindividual and interspecies differences may exist. For these reasons such estimates always hold some uncertainty and have to be regarded with caution. Yet, considering data from case reports of fatal ketamine intoxications in humans, this estimate seems to be a realistic one (see Table 1).

Several studies investigated the local tolerance of ketamine when administered intrathecally (e.g. Malinovsky et al., 1996; Errando et al., 1999). Ketamine, when injected without preservative, did not cause neurotoxicity in the spinal cord of swine or rabbits. However, when combined with the preservatives benzethonium chloride or chlorobutanol, it caused discrete histopathological changes in swine and rabbits.

NEUROTOXICITY

One issue that has been investigated in animals, but that has received little attention in the clinical literature and may be of importance for the recreational user of ketamine, is the neurotoxicity as observed in rats (Olney et al., 1989, 1991). When administered subcutaneously, ketamine (40 mg/kg) caused vacuolisation in posterior cingulate and retrosplenial cerebrocortical neurones in the rat. Lower doses (≤ 20 mg/kg) did not cause such pathological changes. These highly localised neurotoxic effects have also been shown for other NMDA-antagonists (PCP, tiletamine, MK-801; Olney et al., 1989, 1991; Auer, 1994; O'Callaghan, 1994).

It has been suggested that the mechanism for this neurotoxic response is based on an NMDA-antagonist-mediated hypofunction of the NMDA-receptor resulting in a combination of enhancement of excitatory neuronal pathways and inhibition of inhibitory neuronal pathways that lead to and from specific groups of neurones in the cingulate and retrosplenial cerebral cortices. Consistent with this hypothesis, it has been shown that several classes of drugs effectively inhibit the neurotoxic effects of the NMDA antagonists, including:

- muscarinic receptor antagonists;
- GABA_A-receptor agonists (benzodiazepines and barbiturates);
- σ -receptor antagonists;
- non-NMDA (kainic acid) receptor antagonists;
- α_2 -adrenergic receptor agonists;
- certain typical antipsychotic agents (haloperidol, thioridazine, loxapine); and
- atypical antipsychotic agents (clozapine, flupefiapine, olanzapine) (Bergman, 1999).

It may be anticipated that substances with opposite pharmacological actions to those classes of drugs mentioned here may enhance the neurotoxicity of ketamine (and related NMDA antagonists). In this context, the following substances from the recreational drug repertoire should be mentioned: *Amanita muscaria* mushrooms (muscarinic agonist), alcohol (NMDA- and partial GABA_A-antagonist), yohimbine (α_2 -adrenergic receptor antagonist) and other dissociative drugs (NMDA-antagonists) like PCP and tiletamine.

There may be several reasons why these findings in rats have not led to the clinical use of ketamine being abandoned. Firstly, ketamine is generally accepted as a safe anaesthetic without long-term adverse effects (Shorn and Whitwam, 1980; Reich and Silvay, 1989). Therefore, the preclinical data are considered to be of limited clinical relevance. Secondly, benzodiazepines are usually co-administered with ketamine to reduce the occurrence of emergence phenomena. Benzodiazepines have been shown to protect against the ketamine-induced neurotoxicity in rats.

On the other hand, there may be reasons why the findings on the neurotoxicity of ketamine in the rat may be of concern to recreational users of ketamine. Firstly, drug users do not take ketamine in combination with protective agents like benzodiazepines. Moreover, compounds increasing the neurotoxic potency of ketamine may be co-administered. Secondly, recreational use implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in long-term users of ketamine have been reported, however such data are scarce. Long-term effects that have been noted include persistent impairment of attention and recall and a subtle visual anomaly (Jansen, 1990). A review on the Internet (White, 1998) summarises reports from heavy users of 'dissociatives' (i.e. dextromethorphan, ketamine and PCP). Effects after frequent use that are mentioned include 'jolts' or 'shocks' when moving the eyes, sharply impaired visual tracking, impaired recognition of metaphor, impaired language skills and memory problems. The author relates these adverse effects (that fade with time) to malfunction of or damage to the cingulate and retrosplenial cortices. To date, there is insufficient evidence to prove such a relationship in humans. Also, such Internet reports are bound to be heavily confounded by self-selection bias, and it is impossible to narrow down the reported effects to a specific drug, as many subjects are polydrug users.

REPEATED-DOSE TOXICITY

In a toxicological repeated toxicity study carried out on dogs, three groups of four animals were given daily intramuscular doses of 4, 20 or 40 mg/kg of body weight over six weeks. At all dose levels there was some degree of weight loss and anorexia. Some blood parameters were also dose-related elevated. Histological changes in the liver were minor (EMEA, 1997).

In rats, daily intravenous doses of 2.5, 5 or 10 mg/kg of body weight over six weeks provoked a slight but not significant decrease in food intake and a moderate depression in weight gain (EMEA, 1997).

REPRODUCTION FUNCTION

Rats were injected during the pre-mating period (10 mg/kg of body weight intravenously on days 9, 10 and 11 prior to mating). No effect on litter size was observed (EMEA, 1997).

EMBRYO-FOETAL AND PERINATAL TOXICITY

Studies were conducted on the teratological effects of ketamine hydrochloride (25, 50 or 100 mg/kg/day) in rats (Kochhar et al., 1986). Ketamine treatment

had no significant effect on the number of animals per litter. The histological examination showed focal nuclear hypochromatosis and interfibrillary oedema of the heart, diffuse hemopoietic cell infiltration and parenchymal cell degeneration in the liver, and proximal convoluted tubule degeneration in the kidney. These degenerative effects were dependent upon the dose and the duration of treatment (days 1–15 or days 5–15 of gestation). The doses applied in this study are in the subanaesthetic range in rats (Hammer and Herkenham, 1983).

In another study in rats, doses (in mg/kg of body weight) 10 times the dose administered to humans for anaesthesia did not result in teratogenic effects (El-Karim and Benny, 1976).

When rats were treated on days 7 and 8 of gestation with a ketamine dose of up to 200 mg/kg, no disorders in the pregnancy course and the embryonic development were induced (Bandazhevskii and Shimanovich, 1991). At the administration of a dose of 40 mg/kg on days 11, 13 and 15 of pregnancy, ketamine was shown to exert a marked embryo-lethal action and administration of doses of 20 and 40 mg/kg on days 7, 9 and 11 of pregnancy increased the number of fetuses with haemorrhages in the internal organs.

Abdel-Rahman and Ismail (2000) studied the teratogenic potency of ketamine hydrochloride in CF-1 mice with and without cocaine. It was shown that ketamine (50 mg/kg/day) potentiated the teratogenic effects of cocaine (20 mg/kg/day) but was not teratogenic on its own. Considering the higher metabolic rate of mice, the authors stated that the doses applied were comparable to those used by addicted humans and should be toxic to first-time users. In the absence of toxicokinetic data expressing systemic exposure, such estimations should be considered rough approximations.

A reproduction study in nine female dogs injected with 25 mg/kg of body weight intramuscularly six times during one trimester of pregnancy (twice a week over a three-week period) did not appear to show adverse effects on the bitch or the pups (EMEA, 1997).

Rats and rabbits were injected during the three fundamental periods of the reproduction process:

- the pre-mating period (rats 10 mg/kg bw intravenously on days 9, 10 and 11 prior to mating);

- the period of organogenesis (rats and rabbits 20 mg/kg of body weight intramuscularly on days 6–10);
- day 11–perinatal period (rats 20 mg/kg of body weight intramuscularly on days 18–21 of gestation).

For all these groups, there were no significant differences in litter size and delivered pups (EMEA, 1997). These studies, cited from the CVMP (Committee on Veterinary Medicinal Products) summary report, have limited value, since the duration and level of exposure do not meet current standards of toxicity testing. Thus, possible effects may have gone undiscovered.

Olney and co-workers (2000) have suggested that ketamine has the potential to delete large numbers of neurones from the developing brain by a mechanism involving interference in the action of neurotransmitters (glutamate and gamma-amino butyric acid (GABA) at *N*-methyl-d-aspartate (NMDA)) and GABA_A receptors (see the section 'Neurotoxicity', page 44) during the synaptogenesis period, also known as the brain growth-spurt period. Transient interference (lasting ≥ 4 hr) in the activity of these transmitters during the synaptogenesis period (the last trimester of pregnancy and the first several years after birth in humans) causes millions of developing neurones to commit suicide (death by apoptosis). Further research will be required to fully ascertain the nature and degree of risk posed by exposure of the developing human brain to ketamine.

No data on human pregnancies exposed to ketamine exist (Friedman, 1988), with the exception of the obstetric use of ketamine during parturition, where it has been shown that ketamine may depress foetal functions when 2 mg/kg is administered intravenously to the mother.

In summary, at doses 10 times those used in humans for anaesthesia, histopathological changes in rat fetuses have been observed. These effects are dependent on the period of exposure. Based on these preclinical data, in the absence of sufficient toxicokinetic data in animals, and considering that rodents have a higher metabolic rate and doses administered were in the subanaesthetic range in these animals, it cannot be excluded that ketamine in (sub)anaesthetic doses may adversely affect pregnancy outcome in humans. However, no data on human pregnancies exposed to ketamine were found.

MUTAGENIC AND CARCINOGENIC POTENTIAL OF KETAMINE

Bacterial tests: Ketamine was tested in a limited Ames test using two salmonella strains (TA98 and TA100) and one high test concentration (10 mg/plate) only. The experiments were done in the presence and absence of rat liver S9 mix and showed a negative result (Waskell, 1978).

In another bacterial test, ketamine was tested for its ability to inhibit growth of three bacterial strains with decreased capacity to repair damaged DNA. No inhibition of growth of DNA-repair deficient strains relative to a strain with normal DNA-repair was observed, indicating that ketamine did not induce DNA damage under the test conditions used (Waskell, 1978).

Mammalian cell tests in vitro: Using an SCE test on CHO cells, ketamine at concentrations of 1.19, 2.38 and 3.66 mg/l was found to induce an increase in SCE/cell in a concentration-dependent manner (Adhvaryu et al., 1986). The highest effect (11.20 SCE/cell at 3.66 mg/l) was less than a doubling of the control value (7.28 SCE/cell).

No relevant *in vivo* studies with the racemic mixture of ketamine were performed.

In 1996, study reports of a mutagenicity testing programme with the S(+) enantiomer of ketamine were submitted to the German Federal Institute for Drugs and Medical Devices as part of an application for a marketing authorisation. Since the submission was processed as a new drug application and the applicant can still claim a period of exclusivity for the marketing authorisation, we are not authorised to provide any details of these studies. However, the following general assessment may be given. The mutagenic and clastogenic potential of the S(+) enantiomer of ketamine was tested both *in vitro* and *in vivo* in a battery of established and validated genotoxicity studies. The tests were conducted in compliance with GLP regulations and were in full compliance with recent EU and ICH guidelines regarding the scope of mutagenicity tests for new chemical entities. This means that the following test categories, at least, were considered:

- a test for gene mutation in bacteria;
- an *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay; and

- an *in vivo* test for chromosomal damage using rodent hematopoietic cells.

There was no evidence of genotoxicity seen in these studies and it is therefore concluded that the S(+) enantiomer of ketamine is devoid of genotoxic properties.

In conclusion, available published data from genotoxicity testing of racemic ketamine are insufficient and do not allow a reasonable assessment of the genotoxic potential of ketamine. Whereas negative findings were obtained in poorly conducted (compared to current standards) bacterial tests, a positive result was reported from an SCE test *in vitro*. However, the effects observed in the SCE study were only weak (i.e. less than a doubling of control values) and thus the relevance of this finding is questionable. Moreover, (unpublished) data from genotoxicity testing with the S(+) enantiomer of ketamine in a standard battery of validated *in vitro* and *in vivo* tests did not reveal any evidence of a genotoxic potential. Provided that the genotoxicity findings with the S(+) enantiomer of ketamine can be extrapolated to the racemate, it can be concluded that ketamine is highly unlikely to possess any relevant genotoxic properties.

No data on the **carcinogenic potential** of ketamine are available.

Behavioural studies in animals

SELF-ADMINISTRATION

Animal models of addiction are used to test the induction of drug-taking behaviour which might be similar to the recreational use of ketamine. To date there are no animal models that incorporate all the elements of addiction. The observation that animals readily self-administer drugs has led to the argument of face-validity, and psychologically this is based on the reinforcing properties of a compound. This animal model also has a high predictive validity, although there are some limitations (Willner, 1997; Koob et al., 1998).

Early assessments of the reinforcing properties of ketamine reported that rhesus monkeys that had been shown to self-administer intravenously methamphetamine or cocaine also self-administered ketamine (0.0032–1.6 mg/kg/inj) under limited access conditions at an intense schedule of reinforcement (fixed ratio 1; i.e. a reward is provided after pressing the lever a fixed number

of times). An inverted U-shaped dose-response curve was observed. A variation of the fixed ratio to about FR128 (implying that the animals have to make more effort to obtain their reward) produced an increase in the response rate with a factor 3 (Moreton et al., 1977). Increasing the fixed ratio in PCP administration, however, eliminated responding (Marquis and Moreton, 1987), suggesting a higher intrinsic power of reinforcement for ketamine, which might be more related to the depressant action of the drugs than to the psychotomimetic action. In baboons, however, self-administration was obtained at an FR160 schedule (Lukas et al., 1984) for both ketamine and PCP, suggesting that the observed difference between ketamine and PCP might be specific to rhesus monkeys. No obvious behavioural changes occurred during exposure to doses of 0.010–0.032 mg/kg. A dose of PCP 10 times higher was associated with sedation and ataxia. Food intake was unaffected by the lower doses.

From data on various species, it appears that drug intake tends to increase slightly with increases in the unit dose in each species. However, the increase does not generally occur with the self-administration of CNS depressants such as pentobarbital and morphine (Marquis and Moreton, 1987).

DRUG DISCRIMINATION

The drug-discrimination paradigm has been developed as a way of enabling animals to give an indication as to how a drug makes them 'feel'. This behavioural method offers the animal a choice, which is reinforced by pelleted food if they choose correctly, depending on the treatment (drug, saline or other drug). This drug-discrimination approach is a powerful means of differentiating between the subjective feelings (referred to as the stimulus) evoked by various drugs (e.g. between opiates and psychomotor stimulants). It is well established that such drug-response data can be handled as pharmacological data showing selectivity and sensitivity.

It is generally recognised that drug-discrimination paradigms can also be used for non-addictive drugs. However, when carefully designed, such studies will almost certainly be of value in the assessment of common subjective states produced by drugs (Schuster and Johanson, 1988).

Drug-discrimination data from a series of stereoisomers of compounds generalising to PCP or ketamine indicate that compounds exhibiting reinforcing properties comparable to PCP share similar stimulus properties with this pharmacological class (Shannon, 1981; Young et al., 1981).

A number of studies have demonstrated tolerance to the effects of ketamine (White and Ryan, 1996). This type of acute tolerance is related to changes at the site of action rather than any increase in the rate of metabolism, as it can be shown to be induced after one injection, without changing the plasma concentration.

Continuous intravenous infusion of PCP and ketamine at maximum tolerated dosages in rats was used to demonstrate whether dependence could be induced by these compounds. The animals were trained to lever press for their daily food rations under an FR30 schedule of reinforcement. Withdrawal of PCP as well as ketamine markedly reduced response rates, providing evidence of dependence. When the compounds were readministered, the rates increased rapidly to control rates, providing evidence of reversal of withdrawal. Cross-dependence from ketamine to PCP was described.

Observable withdrawal signs have been reported for rhesus monkeys with unlimited access to ketamine self-administration. Rats chronically exposed to ketamine exhibited subcortical withdrawal seizures without gross behavioural manifestations for up to five days after self-administration was discontinued (White and Ryan, 1996).

Clinical safety

Clinical experience

Ketamine is considered to be an anaesthetic with a good safety profile (Reich and Silvay, 1989). Its major drawback, limiting its clinical use, is the occurrence of emergence reactions. Emergence phenomena in patients awakening from a ketamine narcosis have been described following early clinical experience, and these include hallucinations, vivid dreams, floating sensations and delirium. These symptoms were found to be reduced by concurrent use of benzodiazepines (notably midazolam), putting the patient in a low stimulus environment, and by providing information preoperatively on the possibility of emergence reactions. These emergence phenomena appear to occur more frequently in adults (30–50 %) than in children (5–15 %) (White and Ryan, 1996; Bergman, 1999). Engelhardt (1997), reviewing eight randomised studies in volunteers and patients, addressed the impact of S-(+)-ketamine on recovery from anaesthesia compared with racemic ketamine. With only one exception,

the recovery phase was clearly shorter after administration of S-(+)-ketamine compared to racemic ketamine. However, the incidence of psychic emergence reactions was lower after S-(+)-ketamine in only a single study.

Both severe respiratory depression and cardiodepressant effects have been reported, but these adverse effects are rare with ketamine and can be managed within the clinical setting.

Studies on street users

REPORTED FATALITIES

Table 1 presents an overview of reported deaths involving recreational use of ketamine.

Table 1: Reported fatalities associated with ketamine

Case Number	Country	Sex	Age	Reference	Drugs involved
					Reported
1	Italy	M	18	Licata et al., 1994	Ketamine <i>Norketamine</i>
2	United States	F	31	Peyton et al., 1988	Ketamine <i>Norketamine</i>
3	United States	M	46	Peyton et al., 1988	Ketamine <i>Norketamine</i>
4	Italy	M	34	Centini et al., 1987	Ketamine <i>Norketamine</i>
5	United States	M	45	Cording et al., 1999	Ketamine Tiletamine Zolazepam
6	United States	M	32	Moore et al., 1997	Ketamine Ethanol Nalbuphine

NB: Metabolites are in italics.

Case Number	Drugs involved			Comments
	Blood (µg/ml)	Urine (µg/ml)	Other (µg/g)	
1	27.4 Present, not quantified	8.51	Bile 15.2 Brain 3.24 Liver 6.6 Kidney 3.38	Multiple intramuscular doses, with a probable total of 1 g
2	7 Present, not quantified		Liver 6.3 Kidney 3.2 Lung 1.6 Heart 2.4	Accidental intravenous overdose (probably 900 mg)
3	3 Not present		Liver 0.8 Kidney 0.6 Spleen 0.8 Brain 4.0 Lung 2.2 Heart 3.5	Gunshot victim who was given ketamine during surgery (case included for comparison with Case 2)
4			Liver 12.2 Brain 3.7 Lung 16.4 Kidney 15.5 Spleen 14.1 Liver 0.15 Lung 0.17 Kidney 0.7 Spleen 0.12	
5	0.037 0.295 1.71	0.381 0.682 1.33	Liver 0.196 Liver 15.5	Mixed-drug intoxication
6	1.8 170 < 0.020	2	Brain 4.3 Spleen 6.1 Liver 4.9 Kidney 3.6	Mixed-drug fatality due to ethanol and ketamine

Case Number	Country	Sex	Age	Reference	Drugs involved
					Reported
7	France	F		Gaillard and Pepin, 1998	Ketamine <i>Norketamine</i> Chloroform Cocaine <i>Benzoylecgonine</i> <i>Methylecgonine ester</i> <i>Anhydroecgonine ester</i> Codeine <i>6-acetylmorphine</i> <i>Morphine</i> Thiopental <i>Pentobarbital</i> Diazepam <i>Nordiazepam</i> Oxazepam
8	France	M	19	Arditti, 2000	Ketamine LSD Ecstasy
9	Ireland			Europol/EMCDDA, 2000	Ketamine Opioids
10	Ireland			Europol/EMCDDA, 2000	Ketamine Ephedrine Pseudoephedrine
11, 12, 13	United States			NIDA, 2000	

NB: Metabolites are in italics.

The circumstances of the death of Case 1 indicated that the victim probably received around 1 g of ketamine intramuscularly, divided over several doses. A long period of time may have elapsed between the first dose and the victim's death. The last dose was probably administered shortly before death.

Case 2 is another case of ketamine overdose, without the involvement of other drugs. Case 3, a gunshot victim who was administered ketamine for anaesthesia during surgery but died as a result of his injuries, was included only for comparison of ketamine tissue values with Case 2. Blood ketamine concentrations in Case 2 were only two to three times higher than those in

Case Number	Drugs involved			Comments
	Blood (µg/ml)	Urine (µg/ml)	Other (µg/g)	
7	1.4 30.7 0.576 0.78 0.12 0.013 0.420 1.97 2.64 0.070 0.2	Present Present Present Present Present Present Present Present Present	Hair 11.3 Hair 1.0 Hair 5.5 Hair 1.5 Hair 1.0 Hair 4.4 Hair 3.4 Hair 5.3 Hair 10.0 Hair 1.2 Hair 0.1	Polydrug addict
8				Notification by l'OCRITIS. No details available
9				No details available
10				No details available
11,12,13				Three ketamine deaths were reported in New Orleans in 1998. No details available.

the gunshot victim. However, tissue concentrations showed that distribution throughout the body had taken place in the overdose victim and that the administered dose may have been much higher than an anaesthetic dose. Based on these data and on circumstantial evidence, the case was ruled to be caused by an accidental intravenous overdose of ketamine, possibly 900 mg. Comparison of the data from Case 2 and Case 3 indicates that the presence of the metabolite norketamine and the tissue distribution are important for establishing whether a short or a long period of time elapsed between the administration of the drug and death.

The presence of a number of empty Ketalar bottles and numerous punctures in the elbow fold indicated that the deceased in Case 4, found dead with a syringe in his arm, was a repeated intravenous user of ketamine. Tissue levels indicated that the victim died due to an overdose. Blood, urine and bile concentrations were not obtainable due to the advanced state of decomposition of the victim. Pathology showed diffused lung oedema.

In Case 5, ketamine concentrations were low and may not have contributed to the cause of death. In this case, apart from ketamine, a pharmaceutical preparation for veterinary use was administered in which tiletamine, which is another dissociative anaesthetic, is combined with zolazepam, a benzodiazepine.

In Case 6, the victim had been drinking with friends during the evening. He died early in the morning. Ethanol, a CNS and respiratory depressant, may have added to the respiratory depressant effect of ketamine and thus have contributed to this (mixed-drug) fatality.

Case 7 concerns a polydrug addict who was abusing heroin, codeine, ketamine, cocaine, benzodiazepine and barbiturates. The ketamine blood concentration was in the anaesthetic range and this may have contributed to the cause of death. However, the multitude of drugs used by this victim makes it impossible to determine which drugs were major contributors. Both the respiratory depressant effects of other substances, notably opioids, barbiturate and benzodiazepine, and the cardiostimulant effects of cocaine may have exacerbated the potentially deleterious side-effects of ketamine.

Case 8 was mentioned by Arditti (2000) and Cases 9 and 10 were referred to in the Europol and EMCDDA joint progress report. However, no details were provided, so the importance of the role of ketamine in these three deaths cannot be evaluated. Finally, an Internet site for NIDA mentions three fatal ketamine cases (Cases 11, 12 and 13 in Table 1), but, again, no details were provided.

The following conclusions can be drawn from this survey.

- Only three reported fatal ketamine intoxications involving ketamine were identified. In these cases the intramuscular or intravenous route was used. Two reports concern mixed-drug fatalities. In one case, ketamine played only a minor role. For the remaining six cases, insufficient details were available for a proper evaluation.

- From the cases listed in Table 1, it can be learned that the ketamine blood concentrations were usually in the anaesthetic range or above. Tissue distribution data and norketamine concentrations give insight into the total amount administered and the period of time that elapsed between the first dose and death. Where clues (usually empty ketamine vials) about the quantity administered were available, such indicators suggested amounts of approximately 1 g administered intravenously or intramuscularly in the absence of other substances. Based on a body weight of 60 kg, such a dose is 4–17 times the recommended intravenous dose for anaesthesia or 1.3–2.5 times the recommended intramuscular dose for anaesthesia. The intravenous data are in line with preclinical findings. In squirrel monkeys, death occurred when ketamine was administered intravenously at a dosage more than 10 times the dose that produces anaesthesia (Greenstein, 1975). The relatively small margin of safety for the acute toxicity that applies to the intramuscular route is unexplained. Based on clinical experience and pharmacokinetic considerations, the acute toxicity is lower using the intramuscular route than the intravenous route. It is possible that the greater prevalence of this route of administration led to the emergence of fatalities in individuals with increased susceptibility due to premonitory conditions or deviant pharmacokinetics.
- The reported ketamine concentrations found in multiple drug users are lower than those found in the few cases involving ketamine only. This indicates that drug interactions may have contributed to these deaths. In this respect, substances with CNS/respiratory depressant effects, like ethanol, opioids, barbiturates and benzodiazepine, or substances with cardiostimulant effects, like cocaine and amphetamine, are indicated as drugs that may increase ketamine toxicity.

NON-FATAL INTOXICATION

The pharmacological action of ketamine may produce side-effects, many of which have been reported by recreational users (Siegel, 1978; Dalgarno and Shewan, 1996; Weiner et al., 2000). Ataxia, disorientation and anxiety are the most frequent complaints, especially in first-time users. Other side-effects were slurred speech, dizziness, blurred vision, palpitations, chest pain, vomiting and insomnia. The most frequent finding in users that were given a physical examination at an emergency department was tachycardia (Weiner et al., 2000). Nystagmus was, unlike with PCP, rather infrequent in this group of ketamine users. Complications such as hyperthermia, seizure or dysrhythmia

were not encountered in Weiner's study group, but two cases of rhabdomyolysis were noted (Weiner et al., 2000).

In an overview presented by a French report on ketamine (Arditti, 2000), 19 cases of non-fatal intoxication were mentioned that were registered by the CEIP between 1991 and 2000. The majority were recorded during the last four years. The most frequently observed adverse effects were neurobehavioural: agitation, delirium, consciousness disturbances (e.g. loss of sense of danger, sensation of floating, attempts to jump out of a window, amnesia, obsession) and motor function impairment. Less frequently mentioned adverse effects were anxiety, neuropathy of the Guillain-Barré type and physical effects such as general stiffness, raised body temperature (38°C), rhabdomyolysis, hepatic crisis, myalgia and mydriasis.

Felser and Orban (1982) have described a case of dystonic reaction after self-administration of ketamine.

A case of hypertension and pulmonary oedema was triggered by ketamine anaesthesia in an obstetric patient with a history of abusing multiple drugs (Murphy, 1993). The role of ketamine in this case is not as a drug of abuse but as an anaesthetic. This case shows that potentially dangerous interactions may exist when different drugs of abuse are combined. The hypertension was largely attributed to barbiturate withdrawal, and the use of cocaine may have predisposed the patient to developing increased pulmonary capillary hydrostatic pressure, thus causing pulmonary oedema. However, ketamine, being a sympathomimetic agent, may have triggered the hypertension and pulmonary oedema.

The following conclusions can be drawn.

- The main effects of non-fatal ketamine intoxication are neurobehavioural: anxiety (especially in first-time users), agitation, changes of perception (e.g. loss of sense of danger, visual disturbances) and impairment of motor function. In such a condition the user will have severely impaired self-control, which poses a risk of injury of him- or herself or others (e.g. when driving in traffic).
- Common side-effects reported by users were slurred speech, dizziness, blurred vision, palpitations, chest pain, vomiting and insomnia. The predominant symptom found on physical examination of users that went to

an emergency department was tachycardia. Rhabdomyolysis was noted in several cases. Other physical side-effects appear to be rare.

- Serious side-effects like hypertension and lung oedema have been reported. Such adverse effects appear to be rare and may be related to the combination of ketamine with other drugs of abuse.

EMERGENCY TREATMENT

In this section, the treatment of patients presenting to an emergency department is considered.

The following advice is taken from Weiner et al. (2000):

'Based on our experience, we offer the following treatment recommendations for evaluating Emergency Department patients who present after having abused ketamine. This diagnosis should be suspected in patients (especially young patients) who present with agitation, tachycardia, and either visual hallucinations or nystagmus. However, the absence of the latter two findings does not rule out the possibility of ketamine abuse. When laboratory confirmation of the diagnosis of ketamine abuse is critical to the patient's management (which is hardly ever the case), one of the aforementioned tests can be used (GC/MS or HPLC).'

'Symptomatic patients are best managed with standard supportive care, as the effects of the drug are usually short-lived. Keeping the patient in a quiet environment, with a minimum of external stimuli, may prevent excessive agitation. Benzodiazepines should be used for sedation in agitated patients who are at risk for self-injury, hyperthermia, and rhabdomyolysis. Intravenous fluids should be given to agitated patients at a generous rate until laboratory testing has ruled out rhabdomyolysis. Activated charcoal is not necessary after ketamine abuse unless there is evidence that an oral coingestant may be contributing to the patient's symptoms. All patients must be observed until their vital signs and mental status have normalised. Symptoms not improving within 2 h of presentation should prompt a search for other drugs of abuse or another disease process. The differential diagnosis of drug- or toxin-induced hallucinations should include LSD, hallucinogenic mushrooms, amphetamine, PCP, ketamine, cocaine, anticholinergic drugs, and a variety of plants, especially morning glory, jimson weed, and nutmeg.'

The advice given above is comprehensive, although the list of drugs mentioned at the end for differential diagnosis may vary in time and from region to region. Amphetamine analogues (e.g. MDMA, DOB) should be included. Additionally, special attention should be paid to observation of respiratory and cardiovascular functions. Respiratory depression and cardiovascular pathology are ketamine-induced side-effects that are rarely serious when ketamine is used solely, but which may be more serious when other drugs are used as well. The phenomenon of multiple drug-taking is very prevalent in patients presenting to emergency departments (Spaans et al., 1999).

DRUG INTERACTIONS

There are no known studies specifically addressing the problems of recreational use of ketamine and concomitant abuse of other drugs. However, preclinical data, data from fatal intoxication discussed above, clinical experience with ketamine as an anaesthetic and general pharmacodynamic and pharmacokinetic considerations do give some clues about possible interactions between ketamine and other recreational substances. These will be discussed below according to type of interaction.

CNS and/or respiratory depression: An early case report mentions severe respiratory depression in a seven-year-old patient given a subanaesthetic dose of ketamine (approximately 3.3 mg/kg i.m.) after premedication with secobarbital (Kopman, 1972).

Opioids have a known respiratory depressant effect (Buck and Blumer, 1991) and may therefore have an additive effect on the respiratory depression induced by ketamine.

Ethanol, another respiratory depressant, has been implicated in a mixed-drug fatality involving ethanol and ketamine (Moore et al., 1997).

Benzodiazepine is known to potentiate respiratory depressant agents. Flunitrazepam (Rohypnol) is known to induce respiratory depression in patients with chronic airway obstruction. Fatal cases associated solely with flunitrazepam have been described. Therefore, it may be anticipated that the combined use of flunitrazepam and ketamine may also increase the risk of severe respiratory depression.

These examples show that respiratory depressants like ethanol, opioids, barbiturates and benzodiazepine (flunitrazepam) may add to the respiratory

depression induced by ketamine and thus may provoke a dangerous interaction between these substances. Furthermore, these substances are CNS depressants as well and so may deepen or lengthen the ketamine-induced anaesthetic state.

Sympathomimetic effects: Ketamine has sympathomimetic properties. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects. This implies that ketamine may add to the sympathomimetic effects of other drugs such as amphetamine and its analogues, ephedrine and cocaine. Hypertension, tachycardia and lung oedema have been reported in a patient receiving ketamine who appeared also to be abusing cocaine (amongst other substances) (Murphy, 1993). However, barbiturate withdrawal may have played a major role in this case (see the section, 'Non-fatal intoxication', page 59).

On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion inhibiting the sympathomimetic effects of ketamine and unmasking a negative inotropic effect which is usually overshadowed by sympathetic stimulation (Reich and Silvey, 1989; White and Ryan, 1996). It may be hypothesised that drug users bingeing on stimulatory drugs may provoke a degree of catecholamine depletion. Therefore, the possibility of ketamine producing a cardiodepressant effect cannot be excluded under such extreme conditions.

Mixed CNS effects: Benzodiazepines clinically are used to reduce the occurrence of emergence phenomena (hallucinations, vivid dreams, etc.) associated with ketamine anaesthesia (Haas and Harper, 1992). Krystal et al. (1998) studied the interactive effects of subhypnotic doses of lorazepam and subanaesthetic doses of ketamine. Lorazepam reduced ketamine-associated emotional distress and there was also a non-significant tendency for it to decrease any perceptual alterations induced by ketamine. However, it failed to reduce many of the cognitive and behavioural effects of ketamine, including psychosis. Furthermore, lorazepam exacerbated the sedative, attention-impairing, and amnesiac effects of ketamine.

Potential neurotoxicity: Olney and co-workers (1989, 1991) described how neurotoxicity was induced in rats by the administration of ketamine (see the section 'Neurotoxicity', page 44). If the postulated mechanism for such a ketamine-induced neurotoxicity is applicable to the human recreational use

of ketamine, it may be anticipated that several substances from the recreational drug repertoire might enhance such neurotoxicity: *Amanita muscaria* mushrooms (muscarinic agonist), alcohol (NMDA- and (partial) GABA_A-antagonist), yohimbine (α₂-adrenergic receptor antagonist), and other dissociative drugs (NMDA-antagonists) like PCP and tiletamine.

Pharmacokinetic interactions: Ketamine and its primary metabolite, norketamine, are metabolised by enzymes from the cytochrome P450 (CYP) family. However, in the absence of more detailed information on which CYPs are involved and whether ketamine may induce or inhibit specific CYPs, it is not yet possible to evaluate interactions at this level. This point demands further attention in the future, especially since the possibility of involvement of CYP3A4, an isozyme that is susceptible to this kind of interaction and that is involved in the metabolism of medicines (e.g. protease inhibitors used in HIV therapy), cannot be excluded.

Psychological risk assessment (cognition, mood and mental functioning)

Acute effects

Studies investigating the pathophysiology of schizophrenia, using ketamine as a model substance, and studies investigating the psychotropic effects of ketamine in their own right have provided a good characterisation of the psychotomimetic action of ketamine (e.g. Krystal et al., 1994; Hartvig et al., 1995; Malhotra et al., 1996; Vollenweider et al., 1997, 2000; Bowdle et al., 1998; Adler et al., 1999; Oranje et al., 2000). It appears that ketamine in subanaesthetic doses induces a state of mind that both neurophysiologically and behaviourally resembles that of schizophrenic psychosis. This may be experienced by the experimental or recreational drug user as an altered, 'psychedelic', state of mind that allows him to travel beyond the boundaries of ordinary existence.

Effects on cognitive functioning (neuropsychological assessment)

Ketamine acutely affects cognitive performance, including attention, working memory and semantic memory.

In a double-blind randomised crossover study with five healthy volunteers, Hartvig et al. (1995) showed, by means of a word recall test, that short-term

memory could be impaired dose-dependently by intravenous administration of 0.1 and 0.2 mg/kg. Ketamine binding in the brain correlated well with the regional distribution of NMDA-receptors.

Ketamine hydrochloride (0.1 or 0.5 mg/kg i.v. during 40 minutes) did not have a significant effect on the mini-mental state examination (a brief bedside evaluation of cognition) in healthy subjects ($n = 18$). However, tests of vigilance, verbal fluency and the Wisconsin Card sorting test showed a dose-dependent impairment (Krystal et al., 1994). Delayed word recall was reduced, but immediate and post-distraction recall were spared.

Malhotra et al. (1996) assessed the effects of ketamine (total dose 0.77 mg/kg i.v. during 1 hour) on attention, free recall of category-related words and recognition memory of category-related words. All three cognitive functions showed significant decrements. Memory impairments were not accounted for by the changes in the subjects' attention and did not correlate to psychosis ratings. In further studies, Adler et al. (1998) found that ketamine-induced thought disorder significantly correlated with decrements in working memory but did not correlate with ketamine-induced impairments in semantic memory.

Effects on emotional status, behavioural patterns and personality (psychological instruments, rating scales)

Ketamine profoundly affects perception of body, time, surroundings and reality. A study on 10 psychiatrically healthy volunteers was performed by Bowdle et al. (1998). The subjects were intravenously administered an escalating dose of ketamine by infusion with plasma target concentration of 0.050, 0.100, 0.150 and 0.200 $\mu\text{g/ml}$. Each step was maintained for 20 minutes and the subjects were asked to rate various aspects of their consciousness on a visual analogue scale (VAS). A good correlation between the plasma ketamine concentrations and the VAS ratings was obtained. The following VAS scores were increased by ketamine, compared with a saline control.

Body: Body or body parts seemed to change their position or shape.

Surroundings: Surroundings seemed to change size, depth or shape.

Time: The passing of time was altered.

Reality: There were feelings of unreality.

Thoughts: There was difficulty controlling thoughts.

Colours: The intensity of colours changed.

Sound: The intensity of sound changed.

Voices: Unreal voices or sounds were heard.

Meaning: Subjects believed that events, objects or other people had particular meaning that was specific to them.

High: They felt high.

Drowsy: They felt drowsy.

Anxious: They felt anxious.

The intensity of the effects was greatest for High, Reality, Time, Surroundings, Thought and Sound. They were lowest for Anxiety and Meaning. There was not a significant difference for Suspicious (subject felt suspicious).

This study clearly shows that there is a dose–effect relationship between ketamine dose and intensity of ‘psychedelic’ effects. The quality and type of effects were exemplified in the following ways: ‘tingling sensation in the limbs, followed by numbness’; ‘floating, very carefree feelings throughout entire body’; ‘felt so different. Wasn’t able to describe the way I was feeling’; ‘floating in space’; ‘almost complete annihilation of physical self, shrunken’; ‘dizzy, shaky, light-headed’. One subject wrote the following: ‘The experience seems to be a mystical experience, an incomprehensible comprehension of the universe. There seemed to be no past, present or future, no time, just existence. Life and death at the same time.’ All but one participant spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion; one of these persons also reported these symptoms during the placebo infusion. Three participants became moderately dysphoric during the ketamine infusion, but none of them experienced dysphoria during the placebo infusion. One participant developed a mildly paranoid state characterised by multiple questions about the procedure and an intense affect. Another volunteer, who had experienced emotional stress in the recent past, experienced tearfulness, a sad mood and moderately intense ruminations about recent stressful events.

Krystal et al. (1994) also included a VAS of mood states in their study of 18 healthy volunteers after intravenous administration of 0.1 or 0.5 mg/kg ketamine hydrochloride for 40 minutes. They observed a biphasic effect on Anxiety, the low dose decreasing anxiety and the high dose increasing anxiety. The VAS rating for High was increased dose-dependently.

Hartvig et al. (1995) studied the psychotomimetic effect of low intravenous doses (0.1 and 0.2 mg/kg) of ketamine in a double-blind randomised

crossover study in five healthy volunteers. All subjects having peak plasma ketamine concentrations of 0.07 µg/ml or above or estimated peak regional brain ketamine concentrations of 0.5 µg/ml or above experienced psychotomimetic effects. These consisted of pronounced feelings of unreality, altered perception of body image, sensations of impaired recognition of the limbs, detachment from the body, and modulation in hearing, characterised by preoccupation with unimportant sounds. The intensity of the effects showed a dose–response relation with the degree of regional brain binding of ketamine.

Vollenweider and co-workers (1997) investigated the differential effects of S- and R-ketamine and found that S-ketamine is responsible for the psychotomimetic effects, whereas R-ketamine induced a state of relaxation. Results of a mood rating scale for S-ketamine showed increased scores for ‘deactivation’, ‘introversion’, negative and dysphoric feelings and anxiety. All subjects reported distortion of body image, loosening of ego-boundaries and alterations of sense of time and space, variously associated with emotional changes such as euphoria (30 %), indifference (30 %) or heightened anxiety (40 %).

In an open uncontrolled study (Hansen et al., 1988), seven individuals working in health care (two psychiatrists, one psychiatrist in training, one anaesthetist, one body therapist, one general practitioner and one medical student) explored the psychotropic effects of ketamine for its use as a possible adjunct in psychotherapy by intravenous, intramuscular and oral self-administration of various subanaesthetic doses. They recorded that their inner experiences were extremely intense and possessed of a subjective quality which made it difficult to put them into writing. To a certain extent, their experiences varied from subject to subject and, even for the same subject, from one session to another. Nevertheless, all the subjects experienced most of the following phenomena:

- a sensation of light throughout the body;
- novel experiences concerning ‘body consistency’ (e.g. being described as made up of dry wood, foam rubber or plastic);
- grotesquely distorted shape or unreal size of body parts (e.g. extremely large or small);
- a sensation of floating or hovering in a weightless condition in space;

- radiantly colourful visions (e.g. a sense of moving between rooms that are filled with moving, glowing geometrical patterns and figures);
- complete absence of a sense of time (i.e. an experience of virtual timelessness or eternity);
- periodic, sudden insight into the riddles of existence or of the self; occasionally, an experience of compelling emotional consanguinity, at times extending to sensations of melting together with someone or something in the environment; and
- an experience of leaving the body (i.e. an out-of-body experience).

In nearly every instance, subjects retained the sense of a sober, witnessing 'I' that could both observe and consider as well as be amazed, overjoyed or perhaps anxious, and that could, to a certain extent, later remember the unusual phenomena. Music played an important role in their experiences (synaesthesia), as exemplified by the following remarks:

'... the music has substance, the music itself made up the very walls in these endless rooms, it directed both upward and downward flight.'

'... the music was very nearly material; it could be touched and felt, as if it had been a sculpture.'

Other examples show that people under the influence of ketamine may have experiences related to death or expanding consciousness:

'... I am completely and irrevocably removed from my body and have this experience: this is death, you will never return. All such reflection ends, and I am floating out in space. I am in a timeless world filled with a profusion of light, colour, warmth and joy.'

'... it was clear that what I was experiencing was from beyond death — I bounded from insight to insight.'

'... it felt as if I rolled backward and upward out of my body. My consciousness rose up in an amazing way, crested upward and spread out into another dimension, which was 'I'-less. I was there for only a short time and went back to the normal dimension in the same way I had

come. The area in which I had been was hazy and lacked structure, but I noticed that I could return again and learn to understand it and to spread light into it.'

Effects on psychopathological status — psychiatric comorbidity

Studies in healthy volunteers given ketamine and schizophrenic patients have shown that ketamine produces a clinical syndrome with aspects that resemble key symptoms of schizophrenia.

Krystal et al. (1994) assessed four key positive and three key negative symptoms of schizophrenia in healthy subjects after intravenous administration of 0.1 or 0.5 mg/kg ketamine hydrochloride for 40 minutes. The positive symptoms were conceptual disorganisation, hallucinatory behaviour, suspiciousness and unusual thought content. The negative symptoms were blunted affect, emotional withdrawal and motor retardation. Ketamine produced a dose-dependent increase in scores for both positive and negative symptoms.

Similarly, scores for key symptoms of schizophrenia (conceptual disorganisation and disorganised speech, unusual thought content, emotional withdrawal, psychomotor retardation and blunted affect) were increased by ketamine (Malhotra et al., 1996).

Adler and co-workers (1998, 1999) studied the effects of ketamine on thought disorder and compared these effects with thought disorder in patients with schizophrenia. They found similar scores for 19 of 20 items on the 'Scale for the assessment of thought, language and communication'. Only the score for 'perseveration' was lower in schizophrenic patients. However, after Bonferoni correction, this difference was no longer statistically significant. A total dose of 0.56 mg/kg of ketamine over 125 minutes was infused in healthy volunteers ($n = 19$) to obtain a pseudo steady state plasma ketamine concentration of 0.134 $\mu\text{g/ml}$. Reduced processing negativity and P300 amplitude, psychophysiological anomalies commonly observed in schizophrenic patients, were recorded. However, no drug effect on mismatch negativity, another parameter that is commonly reduced in schizophrenic subjects, was found (Oranje et al., 2000).

Vollenweider and co-workers (2000) observed a negative correlation between raclopride binding potency in the ventral striatum and S-ketamine-induced euphoria and mania-like symptoms, suggesting a role for elevated striatal dopamine levels in these positive symptoms.

Chronic effects

Effects on cognition, mood and mental functioning

Short-term exposure to ketamine appears not to induce any long-term adverse effects on cognition, mood or personality. Long-term heavy use of ketamine may be associated with persistent deficits in attention and recall. However, such a condition has been documented only once in the literature.

CLINICAL STUDIES IN VOLUNTEERS

In a follow-up interview in a study by Krystal et al. (1994) of healthy volunteers given ketamine hydrochloride (0.1 or 0.5 mg/kg), no subject had lingering or recurrent physiological or psychological effects, such as nightmares, flashbacks or perceptual alterations, following a test day.

The subjects in the study conducted by Hansen et al. (1988) did not report long-term side-effects of any kind for up to three years following the ketamine sessions.

Corsen et al. (1971) studied 30 volunteers from a prison population who were given either ketamine or thiopentone or served as a control. Psychological assessment was performed before and at one week, four weeks and six months after drug administration. The study could not identify a difference between the three groups.

STUDIES IN PATIENTS

Psychological changes were compared in 221 patients following ketamine anaesthesia and patients receiving other anaesthetics. Psychometric tests were applied repeatedly for more than one year (Albin et al., 1970). There were no significant differences between groups in terms of mental performance, hallucinations and behavioural factors.

Seven case reports of prolonged (from several weeks up to one year) psychic phenomena after a single (or, in one case, dual) exposure were reviewed by Steen and Michenfelder (1979). In one patient, serious effects persisted for five days and in three others there were only minor disturbances for three weeks. Severe congenital brain abnormalities were present in two patients. One patient complained of hallucinations, 'passing out spells' and feelings of unreality and hesitation. These symptoms could have been linked to a single-dose exposure to ketamine one year earlier, but this seems unlikely.

Siegel (1978) stated that subjects who reported long-term use of ketamine sometimes complained of 'flashbacks', attention dysfunction and decreased sociability. Positive effects on mood were mentioned as well, which reinforced the drug use. However, standard psychometric tests did not reveal personality changes. The subjects described were mostly polydrug users, those snorting ketamine also using cocaine. Unlike the PCP group described in the same paper, a tendency to transient psychosis was not noted.

Amongst 20 recreational drug users studied by Dalgarno and Shewan (1996), lasting psychological effects were not reported. Eleven of them used ketamine less than 10 times, eight used it between 10 and 20 times and only one reported use on approximately 100 occasions. The last subject, who was an experienced polydrug user, reported 'a total loss of reality' during a month-long ketamine binge, after which he stopped using it completely without major difficulties. He reported subsequently having very lucid dreams similar in nature to the ketamine-induced state. These dreams lessened in intensity and ceased completely within 7 to 10 days of the final ketamine episode.

Jansen (1990) describes one case in which a subject had persistent impaired recall and attention and a subtle visual anomaly after cessation of long-term, high-dose ketamine use.

Psychological effects of drug-using careers

Dependence potential in humans

TOLERANCE

Tolerance to ketamine develops rapidly and can be high. The subject of one case report related the history of his ketamine use. During the first two years, his consumption developed from an occasional oral dose of 50 mg to 500 mg four to five times a day. Switching to intramuscular injection, he was injecting 300–750 mg five to six times a day within a month. The tolerance dissipated on stopping the habit, but redeveloped at the same rate (within a month) after restarting intramuscular injections (Kamaya and Krishna, 1987).

ABSTINENCE SYMPTOMS

There is no evidence that ketamine causes an abstinence syndrome in humans. The subject described in the case report by Kamaya and Krishna

(1987) found stopping the habit extremely difficult but never experienced a withdrawal syndrome.

Of 20 recreational ketamine users described by Dalgarno and Shewan (1996), 11 never experienced mental after-effects and eight never experienced physical after-effects following a ketamine episode. Of those that did experience mental after-effects, three reported a general feeling of well-being, two had a desire for physical contact, two felt mildly depressed and 'flat' and two said they felt 'dopey' (like being under the influence of cannabis). Of those that experienced physical after-effects, three reported a general feeling of contentment and happiness, four said they felt mildly 'hung over' or drained, three experienced vomiting, one said he felt physically and positively changed and one felt nauseous.

Jansen (2000b) states that an elevated mood after a ketamine binge is a common experience, whereas a cocaine-like swing into depression is rare. He suggests that high levels of norketamine can take days to subside, thereby providing a 'deflating cushion'. However, no evidence is provided for such a theory. In rats, norketamine-induced anaesthesia and locomotor activity are of shorter duration than when these effects are induced by ketamine. Both ketamine and norketamine are rapidly cleared from blood and brain (Leung and Baillie, 1986).

DRUG-SEEKING BEHAVIOUR AND ADDICTION

A distinction may be drawn between experimental (Ahmed and Petchkovsky, 1980) and dependent ketamine use (Kamaya and Krishna, 1987; Hurt and Ritchie, 1994). In dependent users, use of the drug continues despite increasingly apparent effects on their work or on their health. Of the 20 users described by Dalgarno and Shewan (1996), 7 had used ketamine once or twice and only 3 had used it 15 times or more. One user in this group reported that he had believed the experience was 'never going to end' and another experienced extreme dissociation. These two never repeated their first-time use. It appears that this dissociative experience discourages some experimental users. Another reason for limited use mentioned in this study was the scarcity of the drug. On the other side of the spectrum, one user in this study group said he believed he had been addicted to using ketamine during his heaviest period of its use.

According to Jansen (2000b), tolerance to the effects of ketamine soon develops and, with higher doses, the ability to remember the experience is sharply

reduced. Where many stop at this point, others carry on with compulsive binges which result in cocaine-like stimulation, opiate-like calming, cannabis-like imagery (which also disappears), alcohol-like intoxication, and relief from anxiety, depression and mental craving (Jansen, 2000b). Jansen states that repeated users of ketamine may rapidly become addicted. This addictive side of ketamine (in the sense of psychological dependence) may be more pronounced for those who persist in compulsive binges. No reliable data on the prevalence of long-term use are available.

Three well-known ketamine histories are those of John Lilly (1978), Marcia Moore (1978) and D.M. Turner (1994). The first was still using ketamine at the age of 83, even though at some point in his life he had elected to be hospitalised for ketamine withdrawal. The second, according to her husband, Howard Altounian, became addicted and committed suicide. The third slipped below the waterline in his bathtub, with a half-empty bottle of ketamine at his side.

Psychological factors that increase the probability of harm

No systematic studies were found on personality traits or other psychological factors which could lead to ketamine use or affect the probability of harm.

Jansen (2000b) describes several conditions that may motivate ketamine use. Amongst these is a characteristic of the ketamine experience which may be described as **escape from reality**. Few drugs offer such a powerful experience of entering a different reality, which is experienced as no less real than reality without the drug. This possibility for escape and discovery may appeal to some individuals, especially those who are discontented with their ordinary existence and are looking for meaning in their life. In this way, the ketamine experience offers a psychological reward, which contributes to the development of addiction.

For those interested in taking as much and as many drugs as possible, the sensation-seeking factor will certainly be important (Laviola et al., 1999). Ketamine, advertised as **the ultimate psychedelic journey** (Turner, 1994), will appeal to drug users looking for extreme experiences.

Conclusions

- Ketamine has existed for 37 years and is a registered medicine in EU Member States. It cannot be regarded as a **new synthetic drug**.
- Ketamine is in use in human and veterinary medicine as an anaesthetic and analgesic agent.
- Ketamine is a dissociative anaesthetic. It binds to the PCP-site of the NMDA-receptor, thus acting as a non-competitive NMDA-antagonist. Ketamine enhances striatal dopaminergic activity.
- Therapeutic use of ketamine in humans is limited due to the occurrence of emergence reactions (patients experiencing vivid dreams, hallucinations, and disorientation when emerging from anaesthesia). Veterinary use of ketamine is widespread in the EU and it would be difficult to replace it with another drug.
- Administration of ketamine for recreational use is predominantly by the nasal route, but it is also taken orally and by injection (usually intramuscular).
- Taken orally, the bioavailability of ketamine is low. However, the primary metabolite, norketamine, still has one third of the pharmacological activity of the parent compound.
- The main psychological effects are as follows:
 - ketamine acutely affects cognitive performance, including attention, working memory and semantic memory;
 - it profoundly affects perception of body, time, surroundings and reality; and
 - it produces a clinical syndrome with effects that resemble key symptoms of schizophrenia.
- The main risks associated with the recreational use of ketamine are as follows.
 - Ketamine has the potential to cause **psychological dependence** in some individuals. Self-administration and generalisation to other compounds of the PCP class in drug-discrimination tests have been

demonstrated in animals. There is evidence of physical dependence in animals, but this is not severe. Cases of psychological dependence in humans have been described. The prevalence is unknown.

- The acute psychological effects of ketamine may lead to **loss of self control** and subsequently increase the risk of self-injury and accidents.
- **Acute ketamine intoxication** presents itself clinically with tachycardia, agitation, hallucinations, anxiety, changes in perception of reality, impaired motor function, rhabdomyolysis, slurred speech, dizziness, blurred vision, palpitations, chest pain, vomiting and insomnia. Not all of these symptoms need to be present. In serious cases, hypertension and lung oedema have been observed. Several cases have been described in which death was attributed to the recreational use of ketamine, either alone or in combination with other substances.
- Preclinical data that may be relevant for the recreational ketamine user are findings concerning **neurotoxicity and reproductive toxicity**. However, to date there are no clinical data to support these findings.
- The following conditions, which increase the risks associated with the use of ketamine, should be regarded as contraindications:
 - psychiatric disorders;
 - history of substance abuse; and
 - cardiovascular pathology.
- Substances that result in pharmacological interactions with ketamine and therefore increase the risks associated with the use of ketamine are:
 - CNS and respiratory depressants; notably, ethanol, opioids, barbiturates and benzodiazepines (flunitrazepam);
 - sympathomimetic agents; notably, cocaine, amphetamine and its congeners, and other substances causing inhibition of central catecholamine re-uptake or increasing levels of circulating catecholamines.

Sociological and criminological (Europol) evidence

Introduction

Non-medical use of ketamine was not noted in Europe until the 1990s. In 1995 and 1996, concern in the United Kingdom about the prevalence of misuse and health risks associated with ketamine escalated and the Advisory Council for the Misuse of Drugs recommended continued monitoring of the drug. This report summarises the relevant data required by the Technical Annex C of the *Guidelines for the risk assessment of new synthetic drugs*. In the absence of systematic studies of non-medical use of ketamine, the sociological and criminological evidence is based on information collected from:

- the Reitox national focal points in the 15 EU Member States (1);
- Europol's contribution to the risk assessment of ketamine (2);
- the EMEA contribution to the risk assessment of ketamine (3);
- the Qualitative European Drugs Network (QED) (4);
- the literature (5);
- key European forensic scientists (6);
- key toxicologists in the United Kingdom (7);
- telephone interviews with international experts in the field of recreational drugs (8);
- the Internet (English-language searches) (9); and
- youth and mass media (English-language searches) (10).

Table 2 presents the topics covered by this annex by briefly indicating the extent and type of evidence that is available. The numbers in the list above

are used in the table to code the sources of information. Where information is available, it is presented and examined under the main category headings. In general, there is insufficient information, or too much overlap, to address each of the subheadings in the text.

Table 2: Sociological and criminological evidence for ketamine

Topics	Recorded evidence (see text for details)
Social consequences for the user	Social consequences stem firstly from its anaesthetic properties and from possible loss of physical control if too high a dose is taken and secondly from reported psychological effects of regular, or heavy, use which include dependency and paranoia (4, 5, 7, 8, 9, 10)
Primary relations and/or family problems	In addition to the loss of physical control, it may cause tension due to the introspective quality of its effects, other psychological symptoms and compulsive use by a small minority (5, 8, 9)
Education and employment problems	No evidence, but legal sanctions in Greece, France, Ireland and Luxembourg may result in users being dismissed from work or education (8, 9)
Marginalisation	No evidence, but related to legal controls and sanctions, particularly in Greece, France, Ireland and Luxembourg; however, this may vary depending on the sanctions applied (1, 4, 5, 8, 9)
Consequences for the social behaviour of the user	Main consequences for social behaviour stem directly from ketamine effects and a tendency towards compulsive use by some users (5, 7, 8, 9, 10)
Drug-related disorderly conduct	No formal evidence beyond loss of physical control related to its anaesthetic properties (10)
Drug-related acquisitive crime	No evidence of crime to finance ketamine use, but there is one report of diversion from medical and veterinary profession in France; market sales have increased in France and the UK and doubled in Belgium since 1995 (1, 3)

<p>Topics</p> <p>Drug-related violence</p> <p>Drug-related traffic offences</p> <p>Other social consequences</p> <p>Presence or absence of major value conflicts</p> <p>Implications for social institutions (school, labour, recreational, etc.) and community services</p> <p>Wholesale production and distribution</p> <p>Violence in connection with wholesale production and distribution</p> <p>Money laundering</p> <p>Involvement of organised crime</p> <p>The retail market</p> <p>Non-commercial 'private' consumption market among users</p>	<p>Recorded evidence (see text for details)</p> <p>No evidence</p> <p>High potential for road traffic accidents (6, 7, 8, 9)</p> <p>The chosen route of administration for a small minority is by injection, which raises a value conflict in a drug-using culture which is strongly against injecting (5, 8)</p> <p>In view of potential anaesthetic and numbing effects, psychological disturbances and compulsive use, there are implications for drug services, research institutes, hospital emergency departments and the press (4, 5, 6, 8, 9, 10)</p> <p>Wholesale production, diversion distribution and/or transiting of ketamine has been identified in four Member States</p> <p>Lack of sufficient data</p> <p>Lack of sufficient data</p> <p>In Belgium, Ireland, the Netherlands and the UK, there appears to be involvement of organised crime in the production and/or trafficking of ketamine, in addition to production and/or trafficking by these criminal groups of amphetamine and amphetamine-type stimulants (2)</p> <p>Ketamine has marketing authorisation in most Member States, except Greece; it is generally indicated for special anaesthetic and pain treatment (3)</p> <p>A private consumption market appears to exist for people seeking self-exploration and a 'near-death' experience, but there is no evidence about sources of supply (5, 8, 9, 10)</p>
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Topics	Recorded evidence (see text for details)
Semi-public subculture consumption market (discos, etc.)	In dance settings, ketamine often appears in the form of well-made tablets which are visually similar to MDMA and are usually mixed with a stimulant ranging from caffeine to amphetamine; it is also found as liquid, powder and capsules; it is usually snorted intranasally but may be swallowed, 'chased' or taken rectally (1, 6, 8, 9, 10)
Existence and characteristics of street markets	Ketamine has been used as a cutting agent for drugs such as cocaine, amphetamine and heroin and may be taken by problem opiate users (6)
Violence, public order and nuisance implications	No evidence
Entrepreneurial criminal suppliers	In Belgium, Ireland, the Netherlands and the UK, there appears to be involvement of organised crime in the production and/or trafficking of ketamine (2)
Social factors that increase the probability of harm	A range of factors, such as the existence of a large market of long-term ecstasy users seeking new drug experiences, a rather intellectual trend-setting image and low price, all increase the probability of use; other factors, such as its anaesthetic effects, marked discomfort with intranasal use, the short action, acute psychological reactions when taken without knowledge about dose or effects, psychological dependence and negative effects on social relationships, all mitigate against widespread diffusion (5, 8, 9, 10)

Social consequences for the user

Social consequences stem firstly from poly-recreational drug users taking ketamine in the same way and in the same quantities as they take stimulant drugs. Some of the commonly described effects of ketamine range from (at low doses) mild inebriation, dreamy thinking, stumbling, slurred speech and numbness to (at higher levels) extreme difficulty moving, nausea, complete dissociation, near-death experiences, compelling visions, blackouts, etc. These effects depend on the dose, route of administration and the setting.

The anaesthetic effects of ketamine reduce users' ability to deal with social situations and render them more liable to physical accidents. Cases of severe cuts, burns and bruising (particularly to the user's feet from dancing without shoes) going unnoticed are not uncommon. The psychological effects of ketamine use may include acute distress if taken without knowledge of its effects and, in the context of regular or heavy use, dependence, paranoia and egocentricity have been recorded (Kent, 1996). A general overview of the effects is illustrated in the music press by a quotation from a celebrity who admitted to using ketamine frequently for a couple of years:

'Get the quantity right and it's incredible. Get it wrong and you feel like you're dying.' (Muzik magazine)

Under current laws in the European Union, the social consequences of taking ketamine or supplying friends is significantly greater in countries such as Greece, Ireland, Luxembourg and Norway, which have placed, or are planning to place, ketamine under special drug controls (EMEA, 2000).

Primary relations and/or family problems

Reports of compulsive patterns of ketamine use and paranoia and egocentricity linked to ketamine use reveal its potential to damage relationships. Compulsive use of ketamine at least once a day is not uncommon. A paper written by a regular user of ketamine in 1996 which addresses the social consequences of ketamine use stated that:

'Ketamine has a very cold, unemotional vibe to it [...] People have taken ketamine chronically for a long time without suffering any substantial physical side-effects (effects on relationships, however, can be quite substantial).' (Kent, 1996)

In addition, novice users can encounter problems through lack of knowledge. The intense dissociative effects of ketamine may be particularly problematic if it has been taken by mistake because of its similar appearance to another drug. For example, a drug worker in the Netherlands reported two cases of people who thought they were buying cocaine and found the unexpected effects of ketamine particularly distressing.

Marginalisation

Marginalisation is more likely to be a consequence of lifestyle in general than of ketamine use in particular. For example, ketamine may be used within the new-age traveller community or among problem drug users or other already marginalised groups.

A small proportion of ketamine users inject the drug intramuscularly or intravenously. These are usually self-exploratory ketamine users who seek to experience a fully emergent/dissociative effect or those who have developed tolerance and have become psychologically dependent. Injecting ketamine, in a drug culture which is predominately anti-injecting, can lead to marginalisation within that culture. An illustration of marginalisation from within a culture was given by an outreach worker in London who reported that a woman who was found injecting ketamine in the ladies lavatories of a club was beaten up. It was not clear who the perpetrators of the violence were, but the reason was clearly the injecting rather than the use of ketamine itself.

There are indications that the sub-populations who inject ketamine generally do so very discreetly and often belong to trend-setting, elite professional groups who are least likely to suffer marginalisation (Dillon et al., 2000).

With regard to marginalisation as a result of legal sanctions, in most Member States the social consequences of using ketamine are considerably less than those resulting from use of other more tightly controlled drugs. In general, the prescribed medicines laws that relate to ketamine mean that sanctions usually apply to unauthorised suppliers rather than users.

Consequences for the social behaviour of the user

The main consequences for social behaviour stem directly from the physical and psychological effects of ketamine and the tendency towards compulsive use by some users. The sudden anaesthetic effects of ketamine create high risk for accidents and make driving following consumption particularly dangerous. This is illustrated in the August 2000 issue of an English-language lifestyle magazine that reported on 'out-of-control' recreational drug use. A 22-year-old recruitment consultant who was interviewed said:

'I've had three-day sessions (with ketamine) [...] I've sat on the floor in the middle of a club not knowing who I am.' (The Face, August 2000)

There is no evidence that acquisitive crime is committed in order to finance ketamine use. However, theft from medical and veterinary premises has been recorded in France. There have been a number of anecdotal reports of diversion from legitimate sources and this is supported by reports of a substantial increase in market sales in Belgium, France and the United Kingdom over the past few years. In Belgium, market sales have doubled since 1995 (EMEA, 2000).

A value conflict is located in the fact that the chosen route of administration for a small minority of ketamine users is by injection, which is anathema in the context of a recreational drug-using culture that is strongly against injecting. This mostly applies to those users who have a psychological dependence on ketamine or who are seeking self-exploration or a near-death experience, where the preferred route of administration is by injection (Kent, 1996).

There are implications for a number of social institutions in relation to the importance of doses, the anaesthetic and numbing effects of ketamine and the potential for psychological disturbance or dependence. Responses by some institutions are already evident in a number of Member States.

Information for drug services and outreach workers

Drug workers are key agents in prevention, harm reduction and providing reliable information for users (Dalgarno and Shewan, 1996). In addition to general information about contraindications and combinations, nausea and dissociative effects, appropriate information about ketamine can vary from one target group to another (Jansen, 2000a). For ketamine users in the dance club scene, practical advice is now being provided by outreach workers in dance club settings about the importance of titrating doses and about the body-numbing effects of ketamine and consequent risk of cigarette burns and bruised or cut feet. An outreach worker in France noted that there has been a considerable decrease in the numbers of users falling asleep now compared to a year ago, which she attributed to an increase in harm reduction advice about suitable recreational doses. In order to prevent ketamine being mistaken for a stimulant drug, an outreach worker in the United Kingdom reported that one dealer added pink food colouring to the

ketamine to ensure that his customers knew that this signified that it was ‘his’ ketamine. The fact that ketamine does not react with commonly used field-test kits (e.g. Marquis reagent), even though other drugs present may produce a positive reaction, has also been made known to drug outreach workers.

For those seeking profound dissociative effects, warnings are given about dependence, psychological distress and safe injecting.

Hospital emergency staff

Pharmacotoxicological information for staff about treatment for illicit users of ketamine may ensure more efficient and effective treatment responses.

Research institutes

Social research on illicit use of ketamine is being initiated in some countries and questions about ketamine have been added to European surveys targeted at clubbers and to at least one large school survey and two magazine surveys in the United Kingdom.

Press and mainstream media

With media coverage of all drugs, there is a danger of inadvertently promoting their use by giving them publicity or of increasing harm by promoting inaccurate information or encouraging stereotypes. It is well established among a small number of specialist media outlets in some countries that media can play an important role in providing evidence-based information with emphasis on harm reduction to users and potential users. Interest among editors of mainstream media papers appears to be growing.

Wholesale production and distribution ⁽⁸⁾

Violence in connection with wholesale production and distribution

Member States did not provide data on violence in connection with the production, trafficking and distribution of ketamine.

⁽⁸⁾ Europol's contribution to the risk assessment of ketamine.

Money laundering

No reliable data are available on the volume of money laundering in relation to the production, trafficking and distribution of ketamine.

Involvement of organised crime

Contributions of Member States' law enforcement agencies

Denmark, Greece, Spain, Italy, Luxembourg, Austria and Portugal have reported that, until now, there have been no seizures of ketamine, nor is there any information on production, trafficking and distribution of ketamine or on the role of organised crime in these activities.

In Belgium, 89 kg of pure ketamine powder were seized in September 1999 and, in January 2000, a seizure of 3 kg took place. There have also been a few seizures of ketamine in tablet form, mixed with MDMA or amphetamine.

In Finland, there were 14 seizures of ketamine in 1998, totalling 614 tablets. In 1999, 5 seizures occurred, totalling 49 tablets bearing the 'propeller' logo.

In France, two seizures of tablets with ecstasy-type logos containing ketamine and amphetamines were reported in 1998 and 1999. In September 1999, 36 bottles of ketamine were reported stolen from a veterinary clinic in Valence.

In Germany, six people were arrested in May 1999 in relation to the seizure of an illicit synthetic drug laboratory. A large amount of laboratory equipment was seized, as were chemicals and end products. These included 182 g of ketamine hydrochloride in tablet form (700 blue tablets) and 0.9 g of ketamine powder. Another 2 000 yellow tablets were seized containing methamphetamine hydrochloride and ketamine hydrochloride.

In Ireland, from 1 January 1998 to 15 October 1999, there have been 43 incidents of ketamine seizures. There were 40 cases in which ketamine and ephedrine were present in tablet form (totalling 4 500 tablets); one case of 27 000 tablets with ketamine only or ketamine with caffeine; one case of 26 tablets which contained only ketamine and one case of 0.23 g of ketamine powder. From 1 January to 1 June 2000, 24 individual tablet seizures and 4 powder seizures involving ketamine occurred. Although the seizures in Ireland could emanate from the Netherlands, it seems more likely that the

seized drugs originated from transit transport, since no illegal laboratories have been discovered in the Netherlands. Organised crime groups or Irish nationals are responsible for the importation and distribution of ketamine. There are no indications that Ireland is a transit or export point.

In the Netherlands, a single seizure of 4 barrels, containing 70 kg of ketamine, occurred in 1999. In Sweden, there have been occasional small seizures of ketamine.

In the United Kingdom, seizures climbed rapidly in the early 1990s. In 1995, almost 100 000 tablets containing ketamine and ephedrine were seized. These carried a logo commonly found on ecstasy tablets. Ketamine seizures peaked in 1997 and over the past two years have stabilised at around 200 per year. There have been few significant customs seizures, suggesting that most, if not all, ketamine tablets consumed in the United Kingdom are produced there. It is believed that ketamine raw material is imported in bulk from legitimate suppliers in Europe and distributed through illicit drug distribution networks.

Conclusions

The following conclusions can be made about the production and distribution of ketamine:

- Large-scale production, trafficking and distribution of ketamine are unknown to the law enforcement authorities of 10 Member States. Four Member States — Belgium, Ireland, the Netherlands and the United Kingdom — have seized considerable amounts of ketamine. However, seizures of ketamine in the European Union are small when compared to seizures of 'regular' types of synthetic drugs such as amphetamine, MDMA and MDA.
- Two Member States, Germany and the United Kingdom, have reported illicit production of ketamine. Production in Germany seems to be incidental. As the ketamine seized in Ireland was imported from the Netherlands, this would suggest that ketamine could have been produced in the latter country.
- Two Member States, Ireland and the United Kingdom, have reported on the role of organised crime in the production, trafficking and/or distribution of ketamine. The seizures of considerable amounts in Belgium and the

Netherlands suggest the involvement of organised crime in the production and/or trafficking of ketamine. With respect to the Netherlands, this is supported by information from Ireland, according to which Irish criminal groups import ketamine almost exclusively from the Netherlands.

The retail market

The retail market appears to consist of licit ketamine diverted from legitimate medical and veterinary establishments and illicit ketamine in various forms prepared specifically for the recreational drug market.

Ketamine has marketing authority in most countries, except Greece, where the marketing authorisation was recalled in 1998 ⁽⁹⁾. It is indicated for special situations in anaesthesia and for pain treatment. According to the European Agency for the Evaluation of Medicinal Products, its use appears to be generally decreasing, with the exception of Belgium, where its use doubled between 1990 and 1999. The United Kingdom and France also show an increase in market sales between 1997 and 1999 (EMEA, 2000). In Germany, the use of ketamine remained at a consistently moderate level. Ketamine from the pharmaceutical industry usually comes in vial/ampoules in liquid form for intramuscular or intravenous injection and small quantities can be obtained by mail order from chemical catalogues and the Internet at around EUR 64 for 5 g.

Forensic science services report that illicit ketamine often appears in the form of well-made tablets which are visually similar to MDMA and other tablets sold as ecstasy. Typical impressions on these tablets are the same as those found on ecstasy tablets, such as a bird, clover/club, heart, 'Mitsubishi', etc. These tablets have been widely distributed, usually mixed with a stimulant such as ephedrine and/or caffeine. Ketamine is also found on the 'illicit recreational' drug market as liquid, powder and capsules, in which case it is snorted, swallowed or occasionally 'chased'. Some synonyms for ketamine are 'K', 'ket' and 'special K', although, as with logos, these may

⁽⁹⁾ Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992. Article 12 of Directive 75/319/EEC of 20 May 1975 regulates, through the Committee for Proprietary Medicinal Products (CPMP), the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with pharmacovigilance.

change over time. In one recreational market for homosexual men in the United Kingdom, ketamine was coloured pink and sold in plastic wraps sealed with a pink fairy, to distinguish the product from others. This sold for approximately EUR 80.

Ketamine has also been used as a cutting agent for drugs such as cocaine, amphetamine and heroin. It can be bought over the counter in some Asian countries and one outreach worker in the United Kingdom reported that financially solvent users travel to countries such as Goa to purchase supplies, mainly for personal use and for their friends.

Easy availability of ketamine at relatively low prices renders it unlikely that illicit tablet manufacturers would contemplate the synthesis of ketamine, which is probably too difficult for most clandestine chemists. This is likely to limit the potential for a lucrative market.

Social factors that increase the probability of harm

The existence of a large market of long-term ecstasy users who are seeking new drug experiences and the upmarket, trend-setting image associated with ketamine increase the probability of its use. These factors, together with a lack of information about doses and effects, increase the probability of harm.

Attitudes to drugs play an important part in the diffusion of drug trends and there is an obvious link between an individual's willingness to try a drug and his/her perceptions about the health risks involved. This has been shown to be linked to whether or not the individual has been exposed to, or has experienced, the drug in question. This complex relationship is demonstrated by different attitudes in Europe to ketamine use and beliefs about the health risks. For example, a survey of 346 young people attending raves in Vienna, found that young people (who were regularly taking ecstasy and amphetamine) considered that the psychological risks attached to taking ketamine were very high. Use of ketamine among this Austrian survey population was low. However, a different attitude was found in a survey of London clubbers in which 40 % of respondents said they had tried ketamine and a substantial number planned to use it again (Release, 1997).

Some specific ketamine facts may mitigate against widespread diffusion and subsequent harm. The relatively low availability, short action of effects and unpredictable doses with subsequent unwanted physical effects are all factors that are likely to retard diffusion. Discomfort with intranasal use of ketamine is another factor which has been reported by users to be far more marked with ketamine than with stimulant drugs taken in this way. One regular ketamine user reported:

'I personally can't handle the stinging, burning, watering eyes, and awful metallic-anaesthetic taste in the back of my throat.' (Kent, 1996)

The acute psychological reactions when ketamine is taken without prior knowledge about dosage or effects, the danger of dependency and negative effects on social relationships are also factors which may give the drug a negative image among potential users.

It has been suggested that the growth in ketamine use may be linked to the poor quality of ecstasy between 1997 and 1998. The factors which mitigate against the diffusion of ketamine use highlight some important aspects in which ketamine is different to MDMA. One further perceived difference between ketamine and MDMA relates to the fact that ketamine cannot compete with MDMA's effect of enhancing the sound of music and its role in the music industry. A music magazine claimed that research into ketamine demonstrates that ketamine narrows the auditory band width, cutting out some frequencies, which reduces the capacity of ketamine to link with music, although ketamine may enhance very specific types of music or sound (*Muzik*, 2000). MDMA's association with a wide range of music has been an important and widely recognised factor in its diffusion (Shapiro, 1999).

In summary, an answer to a music media question posed in the headline of an article about ketamine — 'Everything started with an E. Will it end with a K?' — is that the sociological evidence suggests that it is unlikely that ketamine will compete with ecstasy as a drug of widespread diffusion.

Public health risks — epidemiological evidence

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Introduction

Non-medical use of ketamine was recognised over 20 years ago in the United States when the Food and Drinks Administration (FDA) expressed concerns about it in 1979. However, it did not come to public notice in Europe until the 1990s. In 1995 and 1996, concern in the United Kingdom about the prevalence of misuse and the health risks associated with ketamine escalated following a seizure of almost 100 000 ketamine tablets. These carried a logo commonly found on ecstasy tablets and some users suffering anxiety attacks were hospitalised after taking large doses of ketamine believing it to be ecstasy.

This report summarises the relevant data required by Technical Annex D of the guidelines for the risk assessment of new synthetic drugs. In the absence of systematic studies of non-medical use of ketamine, the epidemiological evidence is based on information collected from:

- the Reitox national focal points in the 15 EU Member States (1);
- Europol's contribution to the risk assessment of ketamine (2);
- the EMEA contribution to the risk assessment of ketamine (3);
- the Qualitative European Drugs Network (QED) (4);
- the literature (5);
- key European forensic scientists (6);
- key toxicologists in the United Kingdom (7);
- telephone interviews with international experts in the field of recreational drugs (8);

- the Internet (English-language searches) (9); and
- youth and mass media (English-language searches) (10).

Table 3 presents the topics covered by this annex by briefly indicating the extent and type of evidence that is available. The numbers in the list above are used in the table to code the sources of information. Where information is available, it is presented and examined under the main category headings. In general, there is insufficient information, or too much overlap, to address each of the subheadings in the text.

Table 3: Topics for public health risks: epidemiological evidence

Topics	Recorded evidence (see text for details)
Availability and quality of product on the market	
Availability at consumer level (extent/quantities)	Seizures and limited targeted survey data indicate relatively low availability and use outside of specific settings (1, 2, 4, 6, 8)
Sources (at consumer level)	Diversion from licit supply, illicit production of ‘ecstasy’ type tablets and foreign purchases, particularly from Asia (1, 2, 6, 8, 9)
Trends in availability	Appears to be decreasing in the UK and increasing in some other Member States (1, 2, 6)
Average dose and degree of variability	Depending on the concentration, form and method of administration, recreational doses range from 30 to 300 mg (1, 5, 6, 8, 9, 10)
Purity levels and presence of adulterants	No systematic evidence
Other active ingredients	Forensic laboratory analyses in the EU have found ketamine mixed with manitol, caffeine, ephedrine, MDMA, amphetamine and methamphetamine (1, 2, 6)
Typical prices and range	Ranges from EUR 15 to 80 per g (6, 8, 9)
Knowledge, perceptions and availability of information	

Topics	Recorded evidence (see text for details)
Availability of scientific information on product	See the review of the pharmacotoxicological data on ketamine
Availability of information on effects of product	Ranges from mild inebriation to visions and blackouts (8, 9, 10)
Level of awareness of product amongst drug consumers in general	Relatively low awareness and experimentation in Europe, but one targeted survey of clubbers in the UK found that up to 40 % have experimented with ketamine (4, 8)
Level of knowledge about product, effects and perceptions among consumers of product	Lack of chemical information about doses, but anecdotal reports from France and the UK indicate growing awareness among consumers about better management of doses and negative effects (8, 9, 10)
General population	No evidence, but appears low
Prevalence and patterns of use	
Extent of use of product	Targeted surveys and anecdotal reports indicate limited prevalence outside specific settings (8, 10)
Frequency of use	No evidence, but regular/heavy users report a tendency to psychological dependence (5, 8, 9, 10)
Route(s) of administration	Mostly intranasal, but also 'chased', swallowed, administered rectally or injected (5, 8, 9, 10)
Other drugs used in combination with product	Frequently used with, or cut with, a range of stimulants (5, 6, 8, 10)
Geographical distribution of use	In France and the UK, use is mainly in the free-party/new-age traveller scene and among experienced MDMA users and drug trendsetters (8)
Trends in prevalence and patterns of use	Some evidence of declining use in the UK, whilst increasing in Belgium and France (1, 2, 3)
Characteristics and behaviour of users	
Age and gender of users	Anecdotal reports of use among older, experienced drug users (8)

Topics	Recorded evidence (see text for details)
Social groups where product available/used	Experienced MDMA users, free-party/new-age traveller scene, homosexual populations, small groups of self-exploratory individuals and as a secondary drug by some opiate dependents (5, 8, 9, 10)
Risk behaviours associated with use	Physical accidents and psychological dependence or distress (7, 8, 9, 10)
Special concerns about vulnerable groups	The most vulnerable groups are those people who take ketamine under the illusion they are taking MDMA or another stimulant drug (2, 6, 8, 9, 10)
Trends in characteristics/behaviours of users	Among outreach workers in party settings there are some reports of marked improvements in users managing their doses to avoid blackouts and other physical risks; concern exists regarding tolerance and psychological dependence (8, 9, 10)
Indicators of health consequences	
Hospital emergencies	17 intoxications are confined to one French report; there are some references to harm in EMEA pharmacovigilance reports (1, 3, 5)
Deaths (direct and indirect)	One death associated with ketamine in France and two deaths in Ireland in 1996 in which ketamine was found (1, 5)
Traffic accidents	No evidence
Requests for treatment/counselling	No evidence, but anecdotal reports from drug outreach workers of users needing support and information (8)
Other health indicators	Concerns expressed by drug outreach workers and music media journalists about its anaesthetic effects in dance settings (8, 9, 10)

Topics	Recorded evidence (see text for details)
<p>Context of use</p> <p>Risk factors linked to circumstances and rituals of consumption</p>	<p>Insufficient knowledge about doses and adoption of the same consumption patterns for ketamine as those used for other stimulant drugs increase the health risks; tolerance and psychological dependence resulting from regular use may produce a tendency to gravitate to injecting ketamine (5, 7, 8, 9, 10)</p>
<p>Implications for the non-using population</p>	<p>Ketamine entering the recreational drug market in the guise of ecstasy or other stimulant drugs means that it may be taken inadvertently (1, 2, 6, 8)</p>

Following an EMCDDA request to all 15 Reitox national focal points for information about ketamine, five responded stating that they were unable to provide any official evidence of non-medical ketamine use in their countries (Denmark, Italy, Luxembourg, Austria and Portugal). Austria provided some anecdotal reports of its use.

Forensic laboratory analysis of samples of ketamine were reported by eight countries, either by the focal points or by Europol. The number of seizures and quantities of ketamine identified by laboratory analysis range from 89 kg in 1999 in Belgium to occasional small seizures in France and Sweden.

Three deaths have been reported in the European Union in which ketamine was identified by laboratory analysis: two in Ireland in 1996 and one in France. Ketamine was not considered to be the cause of death in the Irish cases and few details are available about the French death. Non-fatal hospital admissions associated with ketamine are difficult to assess in the absence of routine screening for ketamine by hospital toxicology laboratories. Medical staff may not distinguish symptoms of ketamine overdose from other drug overdoses or general psychiatric symptoms, which are mainly psychological or related to loss of physical control.

The main epidemiological indicators for ketamine use are summarised in Table 4.

Availability and quality of product on the market

Ketamine has marketing authorisation in most countries in the EU, except Greece, where the authorisation was recalled in 1998 ⁽¹⁰⁾. In human medicine, ketamine is indicated for special situations in anaesthesia and for pain treatment. In Ireland, ketamine is not used in human medicine and the government plans to add it to the list under the Misuse of Drugs Act. Elsewhere in the EU, licit use of ketamine is generally limited and is decreasing, with the exception of Belgium, Germany, France and the United Kingdom. In Belgium, its use has doubled in the past 10 years, although it has been controlled by royal decree since 1976. In many countries, ketamine is subject to restricted prescription or is regulated as a psychotropic substance so that unauthorised supply is illegal (EMEA, 2000).

Seizures

Seizure data suggest different levels of availability of ketamine within different Member States, with a decrease occurring in the United Kingdom and an increase in some other Member States (Europol, 2000). A large proportion of ketamine seizures are in tablet form and the tablets carry the same logos as those often found on ecstasy tablets. Synonyms such as 'K' and 'special K' are used. Forensic laboratory analysis has found ketamine, in variable doses, mixed with manitol, caffeine, ephedrine, MDMA, amphetamine and methamphetamine.

In Belgium, 89 kg of pure ketamine in powder form was seized in September 1999 and a further 3 kg in January 2000. Some tablets seized in Belgium also contained MDMA or amphetamine. In Denmark, no seizures have been reported. In Greece, three seizures have been reported, the most recent of which was from two British men on a Greek island in June 2000. They had in their possession 56 tablets containing ketamine and caffeine and bearing the 'Mitsubishi' logo. In Ireland, most seizures of ketamine took place in 1998, including a seizure of 27 000 tablets, some of which contained a mixture of ketamine and caffeine. One seizure was of ketamine in powder form. Since April 1999, only four cases have been recorded and ephedrine was present

⁽¹⁰⁾ Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992. Article 12 of Directive 75/319/EEC of 20 May 1975 regulates, through the Committee for Proprietary Medicinal Products (CPMP), the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with pharmacovigilance.

in all of these. It is believed that the vast majority of tablets seized in Ireland originated in the Netherlands. In Spain, early seizures took place in 1995 in the Balearic Islands and, in 1996, ketamine seized in Barcelona was found to be mixed with manitol. Between 1995 and 1996, an English police team visited the Balearic Islands to investigate the origin of ketamine tablets that had been seized in discotheques and bars and were suspected to have been manufactured in the United Kingdom. The seizures in Spain have been mainly from foreign tourists and none have occurred in Madrid and other major cities. In Sweden, there have been occasional small seizures of ketamine. Ketamine is an integral part of four different medicinal products and some years ago stolen ketamine products from the legal pharmaceutical trade appeared on the illegal market.

In the United Kingdom, seizures climbed rapidly in the early 1990s and then levelled out. A definite decline has occurred over the past year. In the January to March period of 1999, ketamine constituted 10 % of all illicit drug seizures. In the same period for 2000, ketamine dropped to 1.4 % of all illicit drug seizures. This decrease is believed to be due to a number of police investigations, particularly in the north-west of England. There have been few significant customs seizures, suggesting that most, if not all, of the tablets consumed in the United Kingdom are produced there. It is believed that ketamine raw material is imported in bulk from legitimate suppliers in Europe. A number of ketamine tablet manufacturers in the United Kingdom have been successfully prosecuted for conspiracy to supply, or attempt to supply, a controlled drug. Some dealers have been prosecuted for conspiracy to defraud contrary to common law.

Other information sources close to ketamine users in the United Kingdom and France suggest that there may be diversion from licit medical and veterinary suppliers and from foreign purchases, particularly from Asia.

Dose and price

Depending on the concentration, form and method of administration, recreational doses range from 30 to 300 mg and timing varies in both onset and duration. For example, an average intramuscular dose is 25–50 mg with an onset of 1–5 minutes and a duration time of 45–90 minutes. An average oral dose is 75–300 mg with an onset of 5–20 minutes and duration of 90 minutes. The effects of nasal doses have been described as quite different from other administration routes at low doses. An average nasal dose is 30–75 mg with an onset of 2–25 minutes and a duration time of only 10–30 minutes.

Prices range from EUR 15 to EUR 80 per gram and anecdotal reports suggest that, at such low prices, the illicit trade in ketamine is unlikely to be a lucrative one. A combination of ketamine and cocaine has also been reported and this is called 'special CK', with reference to Calvin Klein, the popular American designer.

Knowledge, perceptions and availability of information

There appears to be relatively low awareness and experimentation with ketamine in Europe compared with drugs such as cannabis, MDMA, amphetamine and cocaine. Lack of information about the dose content of the ketamine on the market is an important factor, according to outreach workers. Anecdotal reports from France and the United Kingdom indicate a growing awareness among consumers about how to manage doses to achieve sought-after effects and avoid negative ones. At low doses, ketamine is reported to have some stimulant effect. This could be the result of the stimulant effect of active cutting agents or because ketamine is often sniffed with amphetamine and/or cocaine or taken with other drugs in the 'illicit recreational' drug scene. Ketamine may also be administered in a series of intravenous or intramuscular doses for a specific ketamine experience. Numerous books and journal articles have been written concerning ketamine. Information about the effects, supply and health risks is provided on Internet web sites and newsgroups such as www.erowid.org and alt.drugs. Terms such as 'K hole' are used by conscious consumers of ketamine to describe and locate the effects of the drug.

Perceptions

Anecdotal reports suggest that ketamine has an upmarket image as an esoteric drug for experienced recreational drug users. The major advantages of ketamine from the user's perspective are: fast onset and recovery and minimal effect on cough and gag reflexes, thus reducing the risk of choking on saliva or vomit (Jansen, 2000). Internet newsgroups have made comparisons between ketamine and DXM (dextromethorphan), advising that DXM has a considerably longer half life and worse side-effects than ketamine for most people. Forensic scientists and toxicologists, however, have drawn attention to close similarities to phencyclidine (a Class A controlled drug in a number of countries) and to the (non-controlled) veterinary anaesthetic tiletamine.

Prevalence and patterns of use

The trend in non-medical use of ketamine appears to be decreasing in the United Kingdom and increasing in France and possibly Belgium and some other Member States. Targeted surveys of clubbers and a limited number of school surveys are the major source of information about prevalence and patterns of ketamine use. These have shown that a significant number of people experiment with ketamine but that the level varies between sub-populations and geographical areas. A London club survey in 1997 found that up to 40 % of the 200 respondents had experimented with ketamine and many were planning to use it that evening (Release, 1997). This survey placed ketamine in fourth place after cannabis, amphetamine and ecstasy. A large French survey conducted in 1997 found that 15 % of 900 respondents in techno party settings had experimented with ketamine (Médecins du Monde, 1999), whereas, among a matched control group of young people who did not go to techno events, consumption of ketamine was non-existent. Another survey targeted at a dance setting in Austria found that respondents who were regularly taking MDMA and amphetamine considered that the psychological risks attached to taking ketamine were very high.

Recently a large (over 1 500 respondents) school survey conducted in the north-east of England found that 1 % of 13/14-year-old children and 2 % of 15/16-year-olds had tried ketamine compared with 2 and 5 %, respectively, who had tried cocaine (Centre for Social Marketing, 2000). In Greece, during 1999, treatment services and telephone helplines reported some ketamine use in the same recreational scenes as ecstasy and cocaine.

Ketamine in its pharmacological presentation is usually sniffed as a powder or injected, but there have been reports of it being swallowed, inhaled by 'chasing' and inserted rectally. There are no reports of demand for treatment of ketamine-related problems from drug treatment services in Member States, but there appears to be a consensus among drug outreach workers, and users themselves, that regular ketamine use may lead to psychological dependence.

Characteristics and behaviour of users

Targeted surveys and anecdotal reports indicate that prevalence may be higher in older, experienced MDMA users, particularly in the free-party/new-age traveller scene, among homosexual populations and among small

groups of self-exploratory individuals. A study of 100 ketamine users conducted by the Australian National Drug and Alcohol Research Centre reported that there appeared to be four primary user groups (Dillon et al., 2000): injecting heroin users, members of the gay scene, regular drug users in the dance scene, and 'self-exploratory' users who like to take the drug in isolation and 'astro travel'. Among 'closed' groups in Europe, initiation into ketamine use is often ritualised. On such occasions, ketamine is given gratis.

It has been suggested by a number of different sources that the physical clumsiness, falling asleep and blackouts that are commonly reported by ketamine users are not tolerated in high-street and music-club settings. One outreach worker in the United Kingdom free-party scene observed that:

'... it's more popular at free parties because you can lie/fall down wherever you like and not get grief for spilling your drink all over someone's Pradas.' (Telephone interview)

Among outreach workers in party settings in both London and Paris there are reports of marked improvements among ketamine users in their ability to manage their doses in order to avoid blackouts and other physical risks (Dalgarno and Shewan, 1996). There are also reports of people with chronic opiate problems using ketamine for its anaesthetic and analgesic effects.

The most vulnerable group of users are those who take ketamine under the illusion that they are taking MDMA or some other stimulant drug. The volume of seizures of ketamine in tablet form with ecstasy-type logos reflects the scope for this scenario and the need for better information about drug contents and harm reduction. Compared with the effect of stimulants, the rapid physical incapacity rendered by ketamine consumption has serious implications for driving.

Indicators of health consequences

In the European Union, there have been three deaths reported to the EMCDDA in which ketamine was found by laboratory analysis. Two of these occurred in 1996 in Ireland. In one, there was a history of ecstasy use and ketamine and opiates were found. In the other case, ketamine, ephedrine and pseudoephedrine were found. In neither of the Irish cases was ketamine considered to be the main cause of death. One death of a 19-year-old male

has been reported in France in which ketamine, LSD and ecstasy were implicated. Further details regarding this case were not available at the time of writing (Arditti, 2000).

There has been a notable lack of reporting about hospital emergencies associated with ketamine. A recent report prepared in France presents some data on 17 cases of intoxication associated with ketamine. The report describes conditions such as difficulties in walking, agitation, fever and psychological disturbances (Arditti, 2000).

Health concerns have been expressed by drug outreach workers and music media journalists about the anaesthetic effects of ketamine in dance settings and sudden, unexpected, effects. Lack of information about doses and the adoption of the same consumption patterns for ketamine as for other stimulant drugs increase the potential for undesirable effects. In clubs, security staff are sometimes quick to remove a person who has fallen asleep and leave them in the street. According to outreach workers, risks such as these could be overcome with adequate information and appropriate warnings. A further health risk concerns the risk of tolerance and psychological dependence resulting from regular use (Jansen, 2000a). Where there is dependence, there may be a tendency to gravitate towards injecting ketamine.

Context of use

An important factor with regard to context of use is the lack of reliable dosage information accompanying sales of ketamine at street level. In the absence of advice or previous experience, first-time users of ketamine tend to follow similar consumption patterns as for other drugs. Such uninformed use of ketamine increases the risk of both physical and psychological problems. Outreach workers report that ritualised care is often given to first-time users by others to avoid such risks. Individuals who take ketamine mistakenly for MDMA or another stimulant may have no prior knowledge or ameliorative support.

Short-duration effects are not generally viewed as value for money by recreational drug users. However, in the context of ketamine's less sought-after

anaesthetic effects, the short duration may be viewed as an advantage. One music magazine refers to this particular ‘advantage’ of ketamine:

‘The great thing is it wears off pretty quick. If you see a girl you like, you can give it a rest for half an hour and chat her up without making an idiot of yourself.’ (Muzik)

Implications for the non-using population

The main implication for the non-ketamine-using population appears to be the phenomenon of ketamine entering the recreational drug market in the guise of ecstasy or other stimulant drugs. This means that someone expecting to take MDMA, cocaine or amphetamine may find themselves inadvertently taking ketamine, without warning, knowledge or support.

Table 4: Summary of key data on ketamine

	Date	Place	Comment
Illicit use first identified	1970s	United States	Indications of illicit use
	1990	United Kingdom	First indications of illicit use
	1995	Spain — Balearic Islands	
Legal controls	1976	Belgium	Control by decree
	1987	Greece	Control under law, List A
	1996	United Kingdom	Control under Medicines Act; ACMD recommend monitoring but not control
	1997 Aug.	France	Derivatives (excluding injectables) controlled under Narcotic Act entered into force
	1999 Aug.	United States	Classified as controlled Schedule 3 substance
2000	Ireland	Plans to control under the Misuse of Drugs Act	
	Luxembourg	Special legal status with narcotic drug-type restrictions	
Large seizures	1995	United Kingdom	Almost 100 000 tablets in one seizure
	1998	Ireland	27 000 tablets in one seizure
	1999	Netherlands	4 barrels containing 70 kg
	1999 Sep.	Belgium	89 kg pure ketamine powder

	Date	Place	Comment
Small seizures/ market studies	1995–99	Spain — Balearic Islands and Barcelona	6 seizures of 409 tablets and series of small seizures
	1998–99 2000 Jan.–June	Ireland	42 seizures of 4 500 tablets 24 individual tablet seizures and 4 powder seizures involving ketamine
	1998–99	Finland	19 seizures totalling 660 tablets with ecstasy logo
	1998–99	United Kingdom	Seizures stabilised at approx. 200 a year and recently decreased from ketamine accounting for 10 % of all illicit seizures to 1.4 %
	1999–2000	Greece	3 seizures, 2 in powder and 1 in tablet form
	1998–99	France — d’Aquitaine, Rhone-Alpes	2 seizures of tablets with ecstasy-type logo
	1999 Sep.	France — Valence	36 bottles of ketamine reported stolen from a veterinary clinic
	2000 Jan.	Belgium	3 kg of powder seized
Laboratory/ other supply investigations	During 1990s	United Kingdom	A number of ketamine tablet manufacturers prosecuted
	1999 May	Germany	Equipment and 700 blue tablets and 2 000 yellow tablets and 0.9 g powder
Deaths associated with ketamine	1996	Ireland	Two deaths, but ketamine was not recorded as the main cause
	?	France — Paris	19-year-old male — LSD and ecstasy
Non-fatal intoxication	1991–2000	France — six different cities	17 recorded intoxications
Source notes — It is notable that there is an absence of recorded deaths — in which ketamine was recorded as the main cause — and intoxications, particularly in relation to seizures. Also there are few data on seizures, because in most EU Member States ketamine it is not usually controlled by drug laws.			
Pattern and effects — There is a large body of literature on both positive and negative effects. It appears to have relatively high status among experienced MDMA users. It is sold in the ecstasy market and is often in tablet form physically indistinguishable from ecstasy. It is also found in powder and liquid form imported from abroad or diverted from medical or veterinary sources. In ‘closed’ settings, it is used for psychic exploration.			

Health risks — The main acute risks are accidents as a result of lack of knowledge about dose and fast-acting anaesthetic effects and risk of triggering psychiatric symptoms. Tolerance resulting in psychological dependence is highlighted as a risk for a limited number of individuals.

Mode and scope — Reports suggest that ketamine is not widely used and, although it may be sold as 'ecstasy' or another stimulant drug, it is different in a number of important ways. For a number of reasons related to factors associated with drug diffusion, it is unlikely to gain the widespread popularity of MDMA.

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The Centre's main goal is to provide 'objective, reliable and comparable information at European level concerning drugs and drug addiction and their consequences'.

Through the statistical, documentary and technical information it gathers, analyses and disseminates, the Centre provides its audience — whether policy-makers, practitioners in the drugs field or European citizens — with an overall picture of the drug phenomenon in Europe.

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- improving data-comparison methods;
- disseminating data; and
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