KETAMINE: AN UPDATE 2000-2004

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1.   Introduction

History

1.1

In 1959 Parke, Davis and Company in the US developed a new type of anaesthetic agent called Phencyclidine (PCP). Clinical trials were promising in that PCP did not induce sleep but a state of apparent catatonia where patients seemed dissociated from the environment without classical unconsciousness. It was termed a dissociative anaesthetic. However its potent psychoactive properties soon became evident. Ketamine was invented by Calvin Stevens and patented in Belgium in1963. PCP was soon abandoned as an anaesthetic in favour of ketamine, a less potent PCP derivative with a shorter duration of action. It was marketed as a rapidly acting anaesthetic with few side effects. However, dissociative and hallucinogenic symptoms were quickly reported. Despite these problems, the drug was the most widely used battlefield anaesthetic in the Vietnam War, but population exposure to the psychedelic effects may have contributed to the rise of ketamine and phencyclidine misuse in the 1970's. Street use of ketamine hydrochloride was first noted in 1971, although it is likely that it was misused soon after its discovery. Other forms of ketamine were documented in 1974 along with a variety of new street names including: K, Kay, Jet, Super Acid, 1980 Acid (Siegel 1978).

This Report

1.2

Increasing concerns from HM Customs and Excise of large seizures of ketamine in solution having been legitimately purchased in India and imported in solution primarily as 'Rosewater' has triggered this report. The MHRA have raised concerns that ketamine falls in between current legislation controlling prescription only medicines and the Misuse of Drugs Act 1971. Scientific papers quoted in this report were identified by Pub Med, cross referencing missing references from the bibliographies of relevant papers and from personal communication by the experts who have presented to the ACMD committee. An excellent review published by the EMCDDA in 2002 mentions the relevant scientific data prior to 2001 and so we do not mention anything other than the most salient older papers in this review.

# 2.   UK Prevalence / Availability / Price

UK Drug Situation

2.1

There is no reporting of ketamine use in standard surveys of drug use in the UK, such as the British Crime Survey. Several sources from the dance/club scene collect useful epidemiological data. Use of ketamine appears to have become more popular in the mid 1990's as a drug taken in the dance/club scene. Seizures of tablets of ketamine rose and peaked in 1997. The tablets were often indistinguishable from those sold as 'ecstasy' sharing the same logos and markings. There have been several surveys of people involved in the club/dance scene. Release Drugs and Dance Survey (Release 1997) reported that 31% of responders surveyed at 'dance venues' had tried K (n=200) compared with 85% who had used Ecstasy. However the inaccuracy of such surveys is highlighted by a repeat survey by the same group in 1999 (Bloomfield and Kerr 2000). This reported that 10% had tried ketamine and 73% Ecstasy. The dance/club music magazine Mixmag has published an annual drugs survey since 1999. The data is compiled from approximately 1000 postal respondents. The results are not robust and are a self-selected population but give an indication of ketamine use. A more rigorous scientific study shows that 90% of drug users in dance club venues are in employment or full time education, and 20% of this population had tried ketamine (Riley 2001). These data indicate a recent increase in use that has peaked and settled to approximately 10% of respondents taking it at least one in the past month. Ketamine was usually taken with alcohol or Ecstasy (Craske 2001, 2002, French 2003). These data, although only useful as a guide, show that ketamine has an established user base in the dance/club scene in the UK.
See appendices 2 & 3 by Dr White and John Corkery for detailed accounts

2.2

The National Poisons Information Service (NPIS) supplies information and advice for drugs taken by accident, as an overdose or recreationally. The calls are recorded and these data provide an indication of the trends of drug use. The number of enquiries regarding ketamine increased between 1995 and 2001 and then shows a fall in 2002 although there was still a small rise when these enquiries are represented as a percentage of total calls received.

Ketamine enquiries to the NPIS London
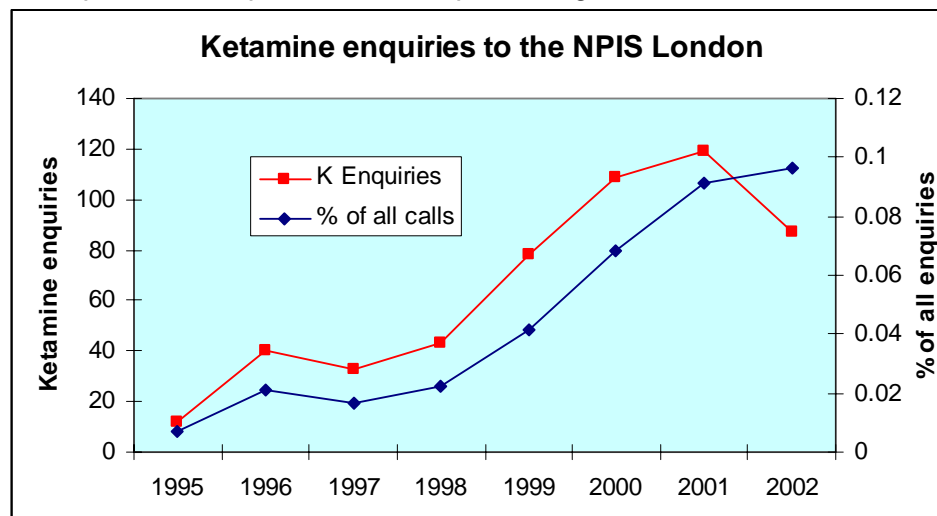
These data indicate the level of problems caused by ketamine with enquiries only accounting for 0.1% of all enquiries to the London NPIS in 2002. No deaths were reported to the NPIS for those enquiries made.

UK Availability and Price
2.3
There are several sources of drug price from law enforcement bodies to user reports documented in lifestyle media. These sources appear to have a good correlation. Data collected by NCIS (National Criminal Intelligence Service) is published to a restricted circulation in *Streetwise* and not recorded here. The dance/club magazines comment upon the price of drugs in their surveys mentioned above and mirror the data collected by NCIS. The reported price of Ecstasy had steadily dropped in the survey to a mean of £3.95 a 'pill' in the 2002 (French 2003). The price of ketamine powder in the 2001 report had halved in a year to £25 per gram. A 'pill' cost £6.32 and a 'line' £4 (Craske 2002). The price of ketamine has continued its downward trend, its value at time of writing being £20 a gram. The cost of ecstasy has also fallen considerably over the last 10 years and it is this that is primarily responsible for the change in the pattern of ketamine use. In the mid 1990's most ketamine was purchased and taken orally as a tablet, often unwittingly by the consumer who believed they were taking ecstasy. The ketamine tablets were marketed as ecstasy and made with ecstasy logos imprinted upon them. At this time ketamine was much cheaper than ecstasy it was more profitable to pass off ketamine tablets as ecstasy. By approximately 1998 the cost of ecstasy had become equal to or less than that of ketamine, and as users often experienced ketamine negatively there was no economic sense in continuing this type of supply. Currently clubbing users tend to purchase ketamine as a powder and use intranasally and this is reflected in the police seizure records submitted to the FSS *(see appendix 2 by Dr White).*

Current Legal Situation in the UK
2.4
Ketamine is currently controlled under the Medicines Act 1968 and the Medicines for Human Use 1994 legislation. Customs report that large quantities of ketamine are being seized on route to the UK from India. Ketamine is legally purchased in India at a very low price and then imported into the UK via the postal system or specialist parcel delivery companies and has the potential to be sold on for a large profit. Currently it is imported covertly in solution and declared as various substances including rosewater, toothpaste and massage oils.
See appendices 4,5 and 6 by Joe Onofrio, David Robinson and Ric Treble for detailed accounts

2.5
There has been one prosecution for importation and supply of ketamine, R v. Veiga, Widger and Siddi 2003 at Kingston Crown Court. The defendants were found guilty of a range of drug related charges involving drugs scheduled under the Misuse of Drugs Act. The barristers acting for the prosecution,

Allison Hunter and James Barratt at Furnival Chambers, London, have requested that current law be reviewed, and take the view that ketamine should be scheduled under the Misuse of Drugs Act. These barristers argue that current law hinders effective prosecution and sentencing powers are inadequate. Under present legislation the sentencing power of the court is limited to a maximum of two years imprisonment, and the barristers feel that and the legal position of ketamine remains confused between the two legislative powers mentioned above. In this case, sentences of six years were imposed as the offence charged was one of attempting to supply ecstasy. It is felt that ketamine supply represents low risk and high gains to organised criminals and the public is not adequately protected. The barristers concede that they are not qualified to assess the medical risk of ketamine but strongly advocate from their legal perspective the inclusion of ketamine under the Misuse of Drugs Act.

Methods and doses used

2.6

Ketamine can be taken as a tablet, snorted in powder form or injected in solution intramuscularly, subcutaneously or intravenously. The differing routes of use affect the onset and effect of the drug. However, the experiences produced by a drug are more affected by the state and situation of the user. It is dependent upon their experience with the drug, their surroundings, their underlying mental state, their personality traits, their knowledge of the drug's effects and other drugs taken concomitantly. In recreational use, typical doses are:

    75-125mg intramuscularly or subcutaneously;
    60-250mg intranasally
    50-100mg intravenously
   200-300mg orally

There are reports on the internet of ketamine being smoked with tobacco or cannabis, although the smell is unpleasant, and used rectally (EMCDDA 2002).

2.7

Jansen suggests that ketamine used intranasally at low doses has a stimulant effect (Jansen 2003). However, ketamine is usually used in combination with other drugs such as Ecstasy or snorted directly with cocaine powder, known as CK, and it is likely that this concomitant use of the stimulant cocaine is the reason why users can retain ability to function physically. Ketamine is rapidly absorbed with intravenous and intramuscular injection, the time for maximal absorption being 5-15 minutes. Maximal blood levels are reached after approximately 20 minutes by nasal administration and 30 minutes orally (EMCDDA 2002). Oral administration results in high levels of the metabolite norketamine, this has mainly analgesic effects and users report a different type of drug effect because of this. Therefore experienced repeat users tend to use intravenously and those users taking ketamine expecting ecstasy often report a negative drug experience. The duration of the pleasurable effects last approximately one hour, dependent upon route of use, although the effects of the metabolites will persist for longer.

3.   Ketamine use in other countries

Europe

3.1

Ketamine has a varied legal status across the European Union. It has been scheduled as a drug of abuse in Ireland and is subject to legal controls and/or sanctions in Greece, Belgium, France and Luxembourg. In contrast in some countries such as Germany, Spain, The Netherlands, Austria and Sweden it is subject to control through medicinal legislation as in the UK. In 2000 the EMCDDA performed a risk assessment on ketamine and GHB (EMCDDA 2002). The committee concluded that as a common minimum ketamine should be controlled under medicinal legislation.

3.2

A Dutch report into ketamine use (Nabben 2000) reports that in 1998 4% of clubbers had tried ketamine at least once. A group of ketamine users were identified, they were older, more likely to be male and better educated than drug users who had not experience ketamine. They appeared to be divided into two different groups dubbed 'psychonauts' and 'partygoers'. The partygoers appeared to be similar to those described in the UK dance/club literature, using their drugs outside the home and mixing with other drugs. The psychonauts tended to use at home, were older, used intravenously and used the drug to travel to 'inner worlds' and to achieve deeper understanding.

USA and Canada

3.3

Ketamine was made a Schedule III drug in the United States in 1999. This means it is recognised as having potential for abuse but lower than Schedule I and II drugs. It may lead to dependence but that the drug has an accepted medical use. The national survey on drug use and health (SAHMSA 2003), the primary epidemiological tool for prevalence and patterns of drug use in the US, does not collect data on ketamine use. However, the large national Monitoring the Future Survey, conducted by the University of Michigan's Institute for Social Research found that 2.6% of high school seniors in the United States used the drug at least once the year prior to survey (Johnston 2003). One study reports high levels of ketamine within the gay 'circuit party' scene in the US with 58% of responders reporting use in the last year (Mansergh 2001). A paper from Canada reports a significant rank order for the sequence of drug use with ketamine used last by experienced drug users (Gross 2002).

The Rest of the World

3.4

Ketamine has been made a controlled drug in the state of Victoria, Australia and in Singapore. Dillon (Dillon 2003) reports two surveys of Australian Ecstasy users. In 1997 16% of respondents had used ketamine at least once in their lifetime and 6% had used it in the last 6 months. This figure rose to 31% and 15% respectively in 2001. The study interviewed 100 ketamine users, 70% of the samples were male and 40% were homosexual. The sample was well educated and informed, and they had an extensive drug-using repertoire. The usual route of use was snorting (82%) with 11% reporting intravenous use.

4.   The Biology of Ketamine

Pharmacokinetics and pharmacodynamics
4.1
Ketamine is a non-competitive NMDA-receptor antagonist. It binds to the so-called PCP-binding site and blocks the flow of ions across the cell membrane. As such it blocks the actions of excitatory amino acids that work via the NMDA receptor system; glutamic acid, aspartic acid and glycine. Ketamine is known as a dissociative anaesthetic. This refers to the functional dissociation between the higher centres of the brain and the areas responsible for basic emotional functioning but also refers to the sensation of dissociation between mind and body.

4.2
Ketamine acts rapidly; a feeling of dissociation becomes apparent some 15 seconds after intravenous administration of an anaesthetic dose, unconsciousness occurring after 30 seconds (distribution half-life 24 seconds). Anaesthetic dose is between 1-4.5 mg/kg intravenously and 6.5-13 mg/kg intramuscularly. A dose of 140mg intravenously will result in result in approximately 10 minutes of surgical anaesthesia for an average healthy person. The terminal plasma half-life, the time taken for the level of the drug in blood to reduce by half, is fast being only 150-180 minutes. Ketamine undergoes extensive metabolism in the liver. The main metabolite norketamine is pharmacologically active itself, is easily detectable and is the preferred method for detection of ketamine as it lasts longer in the body. Very little ketamine (2%) is excreted unchanged in the urine. Ketamine is likely to be excreted in breast milk and can cross the placenta but in amounts that are unlikely to be of clinical relevance. It is indicated for use in caesarean sections and does not seem to have any effects on the neonate. It causes increased cardiovascular responses and is therefore contraindicated for medical use in patients who have suffered a recent heart attack, stroke or who have raised intra-cranial pressure. Its use is not recommended in those patients with psychiatric illnesses but there is little evidence of risk in these groups (see later). There is little effect on the respiratory system and patients can maintain their own airway even during prolonged ketamine anaesthesia (ABPI compendium 1999-2000).

Neurochemical pathways of action
4.3
As described above, ketamine acts primarily via the NMDA receptor system. It also has effects at many of the other neurochemical systems including the opiate system, the dopamine system and the serotonin/5-HT (5-hydroxytryptophan) system. These systems are responsible for the actions of other drugs of abuse such as heroin, cocaine and ecstasy respectively. As well as targeting specific neurochemical pathways, imaging research has investigated the changes in brain blood flow and brain metabolism in response to ketamine. These techniques allow direct characterisation of drug action in the brain.

4.4
Positron Imaging Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) are two brain-imaging techniques that have been used to identify the brain areas activated when ketamine is used. A complex study using three different PET imaging ligands has been used to demonstrate the change in regional cerebral blood flow (rCBF), regional cerebral metabolic activity (rCMR02) and regional cerebral blood volume (rCBV) in response to ketamine in normal volunteers (Langsjo 2003). Increased blood flow in response to ketamine was seen in the anterior cingulate nucleus, the thalamus, putamen, frontal cortex and insula. However there was no corresponding significant increase in brain metabolism as measured by increased oxygen use, although trends were seen. The blood volume was increased in the frontal cortex only. The areas identified are regions commonly activated by drugs that are abused although the authors comment that these structures relate to pain processing. Increased anterior cingulate blood flow after ketamine has been demonstrated in normal volunteers and schizophrenic patients in two studies employing similar techniques (Holcomb 2001, Lahti 1995). In the former study ketamine also produced increased flow in medial and inferior frontal cortices. Ketamine produced an increase in regional brain metabolism in the pre-frontal cortex (Breier 1997). Conceptual disorganisation, a psychotic symptom produced in the normal volunteers, correlated to ketamine activated prefrontal metabolism.

4.5
The effects of ketamine on the brain have been studied with fMRI (Abel 2003a, 2003b). Ketamine was used to model the disrupted facial emotional perception seen in schizophrenia. The differences between ketamine and placebo were measured whilst performing a facial emotional perception task. Ketamine abolished the normal pattern of neural response to fearful faces seen in the limbic and visual cortex and produced increased flow in visual cortex to neutral faces. However, despite objective neuropsychological effects in both studies in response to ketamine, only subtle changes in signal change were demonstrated between ketamine and placebo conditions.

4.6
Several research groups have investigated the effect of ketamine on dopamine in humans using the PET ligand 11C-raclopride. There is conflicting evidence as to whether acute doses of ketamine releases dopamine. Dopamine is released in the brain by many drugs of abuse and is released in response to a range of pleasurable experiences. Work in rats using direct measurement has shown that ketamine causes release of dopamine in the medial prefrontal cortex (Lorrain 2003). In humans the focus of research has been measurement in the striatum because this is the only region with high enough dopamine release to allow detection using imaging techniques. Two groups report that dopamine is released here in response to ketamine in normal volunteers using 11C-raclopride PET (Smith 1998, Volenweider 2000). Breier et al (1998) report a study comparing dopamine release in response to intravenous placebo, ketamine and amphetamine, which has a direct action on the brain to release dopamine. Results indicated that ketamine caused a significant increase in striatal dopamine compared with placebo but less than

that caused by amphetamine, although this difference was not significant. The interaction between ketamine and amphetamine on brain dopamine release has been studied using single photon emission computed tomography (SPECT) imaging technique (Kegeles 2000). Ketamine significantly enhanced the amount of dopamine released in response to amphetamine. Although the test conditions were done in the same sequence test/retest studies showed no evidence of tolerance or sensitisation to amphetamine. The authors suggest this ketamine model of psychosis demonstrates evidence for abnormal regulation of dopaminergic cell activity in schizophrenia.

4.7
However two recent studies that have been well designed and controlled have not shown any dopamine release in the brain in response to ketamine (Kegeles 2002, Aalto 2002). This was despite ketamine producing marked dissociative and psychotic effects in the subjects and calls into question the findings of previous studies. Taken together it would appear no conclusion could be drawn as to whether ketamine releases dopamine or not.

4.8
Research into the opiate receptor system is scarce and limited to animal studies. An investigation on the effects of ketamine at the mu, kappa and delta opioid receptors in hamster ovary cells reported that ketamine caused displacement of the opioid receptor radioligand [3H]diprenorphine indicating that it produces effects at these receptors (Hirota 1999). A similar study in rats demonstrated displacement of the radioligand [3H]naloxone by ketamine (Smith 1980). Further investigation suggests that ketamine acts as an opioid receptor agonist but some antagonist activity could not be ruled out. The affinity of ketamine for the opioid receptor was much lower than that of classic opioid receptor agonists and antagonists. There is a report of ketamine reversing opioid tolerance (Shimoyama 1996) a phenomenon reported for other NMDA receptor antagonists, but it can not be inferred from this that ketamine acts on the opioid receptor system.

Interactions with other recreational drugs
4.9
Ketamine is mostly used in combination with other drugs and alcohol, It is therefore important to understand the interactions between these drugs. Work in rats suggests that some of the effects of ketamine and alcohol are neutralised by each other (Silvestre 2002). The rats used were voluntary chronic alcohol consumers and the researchers measured anxiety effects and exploration-assisted locomotor effect of the drugs. The tissue distribution of co-administered cocaine and ketamine versus each drug alone has been demonstrated in rats (Rofael 2003). Tissue contents of cocaine was significantly reduced at 5, 15, and 30 minutes when given with ketamine compared with cocaine alone. Cocaine did not have an effect on the tissue disposition of ketamine. With the data available so far no clear conclusions can be drawn as to the interactions of ketamine with recreational drugs or alcohol. It is likely that ketamine has a synergistic effect with cocaine.

4.10

The likely main toxic interactions of recreational drugs and ketamine fall into two groups: CNS / Respiratory depressants and sympathomimetic agents. Although ketamine itself does not cause respiratory depression it is likely that the dissociative effects of ketamine makes an individual less aware of this consequence of other drug use. Hence two potent respiratory depressants, alcohol and opiates are the most common drugs found in the toxicology of ketamine associated deaths (see 6.2). Other classes of drug that are likely to have similar effects are benzodiazepines and barbiturates.

4.11

Ketamine stimulates the cardiovascular system (see 6.6). It will act synergistically with other sympathomimetics (drugs that cause inhibition of central catecholamine re-uptake or increasing levels of circulating catecholamines). Cocaine (crack) is the most potent sympathomimetic that is likely to be co-abused. This combination has the potential to exacerbate the cardiovascular risks of cocaine although no research evidence is yet available to quantify this risk. There is evidence that ketamine and cocaine powder is mixed and sold together as cK (after the designer logo for Calvin Kleine). Other recreational drugs that have this potential for interaction include amphetamines and ecstasy.

Related drugs

4.12

Ketamine is a less potent derivative of PCP with a shorter duration of action. In the late 1970's PCP was one of the most prevalent abused drugs in the USA and achieved notoriety for aggressive and violent behaviours in users. It was noted that PCP intoxication resulted in marked increase in muscle tone and produced brisk tendon reflexes. In the 1980's PCP was reclassified under USA law from schedule III to schedule II. In the UK it is described as a class A drug under the Misuse of Drugs Act. PCP acts at the same site on the NMDA receptor as ketamine and would be expected to produce the same effects as ketamine. However PCP produces unique behavioural effects because it also blocks presynaptic monoamine reuptake, thus directly increasing synaptic levels of dopamine and noradrenaline (Zukin 1995). Not only is this likely to be responsible for the stimulatory behavioural and physiological effects of PCP at high doses, it also serves to increase its dependence potential.

4.13

Tiletamine is a dissociative anaesthetic similar to ketamine and phencyclidine. It is used in veterinary practice as telazol, a combination of tiletamine hydrochloride 50mg/ml and zolazepam hydrochloride 50 mg/ml (a benzodiazepine used to minimise the muscle hypertonicity and seizures associated when tiletamine is used alone). In this respect tiletamine is more like PCP than ketamine. There are two cases of fatalities due to telazol (Chung 2000, Cording 1999). In the former case from South Korea, cause of death was solely due to intoxication with tiletamine and zolazepam (blood levels 850 ng/mL and 3300 ng/mL for tiletamine and zolazepam respectively). In the later case of a 45 year old veterinarian from the USA, death was

recorded as unclassified and ketamine was found as a co-intoxicant. In this case the blood levels of tiletamine and zolazepam were much lower (295 ng/mL and 1710 ng/mL respectively, and the ketamine level was also very low (0.037 micrograms per mL, therapeutic range 1-6 micrograms per mL) (see 6.3).

4.14
There is one further case reported of telazol abuse (Quail 2001). This is the case of a 30 year old female zoo employee who was brought unresponsive to the emergency department of hospital in Boston, USA. She recovered after medical treatment and admitted a history of recreational telazol use. The recreational use of this drug appears to be very small, mainly due to the restricted medical uses of the drug. However it is likely that abuse of telazol is more dangerous than ketamine and possibly PCP.

5.   Therapeutic Uses of Ketamine

Anaesthetics

5.1

There has been a gradual decline in use of ketamine as an anaesthetic agent in Europe. This is largely due to concerns about emergence phenomena such as hallucinations on coming out of the anaesthetised state. Ketamine continues to be used extensively in children and for short-term anaesthesia and analgesia in-patients with burns. Its use is expanding in developing countries due to the wide anaesthetic therapeutic range and good safety profile. As reported above large anaesthetic trials have proven the efficacy and safety of ketamine in medical practice. Recreational doses of ketamine are lower that that used in anaesthetic practice. For example an average anaesthetic dose intravenously would be 100-300mg whereas a recreational users dose would be between 50 and 100mg.

5.2

A brief survey of hospitals revealed that ketamine is kept in a variety of different conditions. Some hospitals treat ketamine as a controlled drug requiring documentation for ordering and dispensing to individual patients. In these cases ketamine is kept in double locked, alarmed cupboards. In other hospitals ketamine was not treated as a controlled drug in any way but these hospitals reported that this situation could change if there was evidence of diversion. In one hospital were ketamine is treated as a controlled drug theatre staff were reportedly unhappy about the restrictions to its use.

Analgesia

5.2

Ketamine is being increasingly used in acute pain management and in palliative care, and is now being prescribed for patients to use at home. In Accident and Emergency departments ketamine is used as sedation and analgesia when resetting fractures and dislocations and to allow investigation and examination of children. A recent Cochrane review examined the benefits and harms of adjuvant ketamine for cancer pain (Bell 2003). Benefits were noted in the trials identified and ketamine was well tolerated, but no significant conclusion could be drawn due to insufficient numbers. Ketamine has been shown to reduce the level of morphine required post-operatively in a randomised, double-blind placebo controlled study (Guillou 2003). There are many case studies advocating the value of ketamine for pain management but few large trials. In this field it seems that there is some evidence of benefit and ketamine appears not to cause significant side effects.
See Appendix 7 by Dr Power for detailed account

Psychiatry and psychotherapy

5.3

Ketamine has been postulated as a treatment in a wide range of psychiatric disorders. Soon after ketamine's invention NMDA antagonists were postulated

as a treatment for depression. A small double blind placebo controlled study of the antidepressant effect of a single dose of ketamine has been published (Berman 2000). Depressed patients showed a marked improvement in symptoms following ketamine when compared with placebo. A larger study investigated the effect of ketamine on post-operative pain and depression versus placebo in depressed patients (Kudoh 2002a). There was a significant improvement in mood in the ketamine group and less reported pain. The authors conclude that although pain and mood are closely linked, analysis with an earlier paper investigating post-operative pain in depressed patients demonstrates that the ketamine is alone responsible for the improvement in depressive symptoms. The same group found that ketamine used as an anaesthetic agent produced less confusion and psychotic symptoms in postoperative schizophrenics than standard anaesthesia (Kudoh 2002b).

5.4
Krupitsky has pioneered the use of ketamine assisted psychotherapy for alcoholics and heroin addiction. Improvements in one year abstinence from 24% of patients in the control group to 66% in the ketamine assisted group are reported (Krupitsky 1997). It is postulated the effect is produced by ketamine antagonism of the NMDA glutamate system, a receptor system also disrupted in alcohol dependence (Krupitsky 2001). Improved 2-year abstinence rates in heroin addicts were reported between very low dose and psychedelic doses of ketamine (Krupitsky 2002). In summary there is some evidence that ketamine has therapeutic uses in the field of psychiatry. The studies produced so far are relatively small and yet to be replicated. Ketamine appears to be well tolerated in psychiatric patients.

Veterinary practice
5.5
Ketamine remains a very important anaesthetic agent in veterinary practice. It is used across a wide range of species, in small animal, farming and exotic animal practices. As in humans, it is an extremely effective field agent when it can be used safely in poor conditions and with little support. It has a wide dose range in animals. The ability to deliver ketamine orally, intravenously and intramuscularly is another advantage. In small animals and in other situations when intravenous access is limited, this property is invaluable. The maintenance of cardiovascular tone, respiratory drive and airway allows ketamine to be given safely despite a veterinarian being unsure how a particular animal will respond.

5.6
Veterinarians are increasingly appreciating the analgesic properties of ketamine. Opiate use is undoubtedly limited due to their controlled drug status. The conditions that opiate drugs must be kept and the documentation necessary for their use prohibits many vets from using them. The veterinary profession believes the scheduling of ketamine under the Misuse of Drugs Act would have a negative impact on veterinary practice in the UK if it received a high class and schedule. However it was noted that benzodiazepines are used with little restriction by the profession. The veterinary professional body

has recently updated guidelines as to the storage of ketamine to be more stringent than those conditions required for class C scheduled drugs. Therefore categorising ketamine as a class C drug with a minimally restrictive schedule of III or IV would have little effect on practice.
See Appendix 8 by Dr Taylor for detailed account

6.   Harmful Effects of Ketamine

Deaths and accidents

6.1

There are several acute complications of ketamine intoxication and its use may result in death. It is difficult to quantify the specific danger of ketamine as it is usually used in combination with other drugs. However, ketamine has a very good safety profile when used in medical practice. Its advantages as an anaesthetic are that it has very little effect on the gag reflex and causes little respiratory depression. As such it can be used safely in emergency situations and by people with basic medical training, such as on the battlefield. These properties are also useful to vets where it can be difficult to judge the amount of anaesthetic agent needed. Ketamine has a wide therapeutic range of use and so over-sedation will not lead to death of the animal.

6.2

UK records of deaths where ketamine was detected on post-mortem has been reviewed *(see appendix 2 by John Corkery)*. Nine deaths were identified from 1993 to 2003. This is not an exhaustive check and many cases where ketamine is involved will be missed, as it is unlikely that it is routinely screened for. In only one death was ketamine the sole drug identified, unfortunately there is very little data on this case. Opiates and alcohol were the most common other substances found at toxicology. A report from New York City examined all the ketamine positive deaths over a two year period (Gill 2000). 87 deaths were identified but only 12 of these were incidents where ketamine had not been given as part of medical treatment. In no instance was a fatal intoxication caused exclusively by ketamine. Opiates were the most common co-intoxicant, followed by amphetamines and cocaine.

6.3

Further data on this subject is limited to case studies. Jansen (2003) accounts the death of the author Marcia Moore. Having become a regular user of ketamine, she died when she went into a forest, injected herself with a large dose of ketamine and froze to death. A report of a homicide in Italy (Licata 1994) accounts large doses of ketamine in the tissues but does report other drugs detected on toxicology. Ketamine levels in the blood at post-mortem (27.4 micrograms per mL) far exceeded the anaesthetic therapeutic range (1-6 micrograms per mL). Breitmeier et al (2002) report on a death involving ketamine. The death was reported as an autoerotic accident, with ketamine levels within the therapeutic range (2.5 micrograms per mL). Although tablets of diazepam and paracetamol were found beside the fatality these were not found in the venous toxicology. The subject had restricted their airway by use of a stiff collar and had inserted a rubber ball in his oral cavity. It was reported that ketamine may have contributed to the hypoxia. The case study of the death of a young female polydrug user is discussed by Gaillard et al (1998). Ketamine was detected on hair sampling as well as 5 other abused substances including heroin and cocaine. Two ketamine related fatalities from the US were reviewed (Cording 1999, Moore 1997). In the former ketamine

was identified along with another anaesthetic agent tiletamine and the benzodiazepine derivative zolazepam which are commonly used together in veterinary practice (see 4.13). In this case the blood level (0.037 micrograms per mL) was well below that used medically. The second fatality had a high blood alcohol level (170 mg per dL), although not high enough to cause death on its own. The blood ketamine level was low (1.8 micrograms per mL) but within the therapeutic range. The EMCDDA review (EMCDDA 2002) identifies 8 further fatalities involving ketamine but there is insufficient information recorded to evaluate these.

6.4
To summarise the information from the case studies above, it appears that ketamine does not cause fatalities alone. The one exception is the very high dose reported when ketamine was used as a homicidal agent. However it appears more dangerous when used in combination with other drugs, including alcohol. It appears that being intoxicated with ketamine will increase the likelihood of accidents and misadventure. The doctor and neuroscientist John Lilly is reported to have been involved in several accidents, such as a near drowning, whilst under the influence of ketamine (Jansen 2003). The reports above appear to represent few cases when compared with the epidemiological data demonstrating levels of use in the population. This may be due to under-detection post-mortem as ketamine does not form part of 'routine' screens for drugs of abuse, rather than it being a safe recreational drug.

Medical complications
6.5
Ketamine has been widely used in medical practice for many years and so the medical complications are extensively reported. The primary reason it is not used for more anaesthetic procedures is due to emergence phenomena, which are characteristically hallucinations on wakening. However, there is very little published evidence as to the complications of recreational use. Weiner et al (2000) have published a prospective observational case series of all cases of ketamine intoxication presenting to Connecticut emergency departments over one year. Data for 20 patients was available from 27 who self-presented and identified themselves as having used ketamine. By the time of assessment the most common outcome was having no remaining symptoms (10 of 20). The most common presenting symptom was of anxiety (8 of 20) followed by palpitations (3 of 20). None of the patients required admission although five were sufficiently agitated to require a dose of a benzodiazepine for sedation.

6.6
Ketamine causes stimulation of the cardiovascular system unlike most anaesthetic agents (White 1996). There is usually an increase in heart rate, cardiac output and blood pressure although the reverse occurs rarely in some situations. The safety of ketamine is highlighted by its use as a sole general anaesthetic for major surgery in the developing world (Bananno 2002). No anaesthetic fatalities were recorded during 64 major operations in the

absence of ventilatory equipment and with only an assistant trained in counting the carotid pulse manually, and with diazepam used as an adjunct. In only one case did the pulse rise by more than 20 beats per minute and spontaneous ventilation was maintained throughout. It was noted that there was an increase in salivation and lacrimation. This could potentially cause a problem for recreational users, although the doses used are significantly lower than those used for anaesthesia. No dystonia was noted although this has been reported in one recreational user who self presented to hospital (Jansen 2003). Ketamine has a bronchodilatory effect, but pharyngeal and laryngeal reflexes are maintained (Reich 1989).

6.7
In summary ketamine causes some cardiovascular effects and it is unlikely that a recreational user would be at risk from cardiovascular or respiratory collapse in the absence of co-administered drugs although there is a theoretical risk in persons with co-existing cardiovascular disorders such as ischaemic heart disease. However, stimulants, such as cocaine, also cause an increase in cardiovascular responses that may be synergistic.

6.8
Ketamine has minimal effects on the respiratory system but may lead to greater sensitivity to the respiratory depressant effects of other drugs such as heroin. This is reflected in the high rate of opiates as a co-intoxicant in the New York City deaths study relative to the reported co-use of drugs (Gill 2000). A postulated mechanism for this is that the dissociation achieved with ketamine results in a reduced self-awareness of the usual signs of opiate overdose with which opiate addicts are very familiar.

Neurotoxicity and use during pregnancy
6.9
Ketamine does cause localised neurotoxic effects at high doses in rats but not in humans and other primates (EMCDDA 2002). The more potent NMDA-antagonists phencyclidine (known as PCP or angel dust) can result in some cell death in adult rats although such compounds have been suggested to be neuroprotective for human strokes (Olney 1989, 1991). Moreover, the most toxic NMDA antagonist dizocilpine injected in primates does not cause neurotoxic changes.

6.10
Ketamine is a drug with a rich and varied pharmacology in that it has effects at many different receptor types. It is this property that is postulated as the difference between rats and primates, its action at other receptors switching off the excitation before it becomes excessive. Rats must be subjected to repeated intravenous injections to produce permanent brain changes so it is very unlikely ketamine used recreationally has direct neurotoxic effects. Many substances have been shown to be protective against ketamine toxicity in rats including benzodiazepines, LSD and amphetamine like substances (4-methyl-2,5-dimethoxy-amphetamine) (Jansen 2003).

6.11

Ketamine has not been shown to cause teratogenic effects in several mammals (EMCDDA 2002). However, evidence of histopathological changes in rat foetuses has been demonstrated at repeated doses 10 times those used in human anaesthesia (Kochhar 1986). It has been postulated that ketamine could have a neurotoxic effect on the developing foetal rat brain during a 'window of vulnerability'. This is a proposed mechanism for foetal alcohol syndrome due to alcohol's effects on the NMDA and GABA(A) receptors (Olney 2002). A combination of ketamine and cocaine, and each drug alone has been compared for their teratogenic effects in foetal rats (Abdel-Rahman 2000). Decreases in foetal weight and length were recorded in the combined group and skeletal effects noted in the cocaine and combined groups. The combination of ketamine and cocaine was shown to be most toxic. The result must be interpreted with caution as no dose response relationship was demonstrated and the effect on maternal food consumption may account for the combined teratogenic effect (Fantel 2000). Research showing potential teratogenic effects has only been shown in rodents. No evidence has come to light of brain damage in humans despite ketamine having been used as an anaesthetic agent during pregnancy and in children.

Psychological and psychiatric complications
6.12 In medical practice.
The principle psychiatric sequelae of ketamine use in medical practice is of 'emergence phenomena'. These are usually described as hallucinations upon waking from an anaesthetic dose. These are easily managed with benzodiazepines and are unlikely to cause lasting distress to the patient. Research into the safety profile of ketamine is well established and rigorous. Jansen (Jansen 2003) reports on two early studies into use of ketamine as an anaesthetic. Of 1,400 patients, only three suffered prolonged hallucinations, the longest lasting for 3 weeks. In another, ketamine anaesthesia appeared to have the same psychological consequences as other anaesthetic agents. It is concluded that ketamine is unlikely to cause any permanent changes in personality or intellect. However, the context ketamine is used for in medical practice is very different to its recreational use.

6.13 Acute psychedelic effects.
The acute effects of ketamine at recreational doses have been studied in an open uncontrolled study (Hansen 1988). The experiences described by the researchers, who administered repeated and variable doses and routes to each other, are those sought after by recreational users of the drug. The effects were short onset (30 seconds I/V, 2 minutes I/M and 20 minutes orally) and short-lived; the subjects were able to be the study observers after 3 hours. Oral administration resulted in weaker but less predictable effects. Mostly the subjects were calm and introverted but occasionally were exhibiting co-ordinated motor activity or excited speech.

6.14
Common experiences included lightness or out of body experience, distorted shape or sense of body, absence of time sense, insight into the self or

existential understanding, visual hallucinations, synaesthesia and an affective change, often happiness or anxiety. Observable signs of intoxication such as grimacing, lip smacking and facial exploration, were similar to other drugs of abuse and suggest that ketamine may share neurochemical pathways with such drugs. Although two subjects had an intense recollection of their ketamine experience (sometimes referred to as a flashback), none reported any side effects up to a year after the event.

6.15
The effects of four different ketamine doses in normal controls was investigated with intravenous saline used as a control (Bowdle 1998). The subjects reported similar effects to those described above, and the effects were dose related. The intensity of the effects was greatest for psychedelic symptoms and lowest for anxiety and meaning. As in the previous study the effects were well tolerated and rarely experienced as negative. The experiences of these volunteers were on the whole pleasant and uncomplicated. However their experiences were different to the recreational user in terms of context, security and psychological mindedness. Such factors significantly shape an individuals drug experience and may have protected these participants from negative consequences.

6.16 Effects on cognitive function.
Ketamine intoxication has profound affects on cognitive function. Attention, memory, organisational abilities and verbal fluency are affected by acute sub-anaesthetic doses of ketamine when administered to normal controls (Adler 1998, Harbourne 1996, Krystal 2000, Malhotra 1996, Newcomer 1999).

6.17
The longevity of these deficits in cognitive performance has been studied (Curran 2000). Thirty-nine polydrug-using participants were identified using a snowballing sampling technique at private parties and night-clubs. The group was divided into those who had used ketamine within 30 minutes of participation in the study and those who had not and had little or no prior ketamine use. The ketamine use group (n=20) showed significant deficits in attention, learning and episodic, semantic and working memory when intoxicated as compared with controls. Implicit memory was not affected. All subjects were tested again 3 days later having not taken ketamine again. The ketamine group's overall performance improved to match the controls on most measures. However the ketamine users remained in deficit on semantic memory tasks and this could not be explained by a lack of practice due to the initial intoxication.

6.18
A study using 26 normal volunteers also demonstrated reduced episodic memory but this was due to impaired encoding in contrast to the above study (Hetem et al 2000). Curran used the same methodology for a second study to investigate the cognitive effects of regular versus infrequent ketamine use (Curran et al 2001). The same acute cognitive deficits were seen directly after ketamine use in both groups and replicated the previous study (Curran et al 2000). However the frequent users did not show the degree of recovery of

cognitive facilities seen in the infrequent users. Measures of episodic memory were particularly affected. This is our memory for personally experienced events and has been shown to be a predictor of everyday memory performance.

6.19
The acute and chronic effects of ketamine in 54 normal volunteers using a double-blind placebo controlled design are reported in two papers (Morgan 2003a, 2003b). As in other studies acute doses of ketamine produced impairments in cognitive function, particularly memory functions. Ketamine was subjectively reinforcing especially at the lower dose studied (0.4 mg/kg). There were no residual effects from the ketamine when tests were repeated three days after the initial infusion. This taken with evidence of residual effects for chronic ketamine abusers at three days (Curran 2000,2001) suggest that ketamine can cause chronic memory impairment. It is difficult to quantify how much the level of impairment demonstrated would affect an individual's performance and whether an individual or others would be able to detect these subtle differences.

6.20
Taken together these findings suggest that regular ketamine users would experience memory problems in their daily lives and would potentially impact on working ability. There is some current evidence that memory deficits persist beyond three days in chronic users of ketamine. This raises concerns as to the consequences of long term recreational ketamine use.

6.21 Psychotic effects in normal subjects.
Ketamine has been widely used as a model for schizophrenia in normal controls and for relapse in schizophrenic patients. In these studies ketamine is given in single doses and in controlled research environments. The research subjects were free from the problems of concomitant drug use seen in recreational users. Ketamine produces a clinical syndrome with aspects that resemble key symptoms of schizophrenia including positive psychotic and negative symptoms (for a review see EMCDDA 2002). Studies use symptom scales such as BPRS (brief psychiatric rating scale), SANS (scale for the assessment of negative symptoms and SAPS (scale for the assessment of positive symptoms) that are used extensively to study and monitor schizophrenia as well as the CADSS (clinician administered dissociative states scale) to directly measure ketamine's dissociative properties.

6.22
There has been a great deal of research testing the ketamine model of psychosis using measures which are thought to reflect underlying brain pathological mechanisms found in chronic schizophrenia. Prepulse inhibition (PPI) of the startle reflex has shown to be decreased in chronically ill, medicated schizophrenics. Ketamine was found to have the opposite effect in normal volunteers despite ketamine inducing changes in their psychosis scores characteristic of psychotic relapse (Abel 2003). One study has shown that the typical antipsychotic agent haloperidol reduced the effects on

prepulse inhibition of ketamine but ketamine alone was without effect (Oranje 2002).

6.23
Eye tracking deficits as those seen in schizophrenia have been demonstrated in volunteers given ketamine (Avila 2002, Oranje 2000). Mismatch negativity (MN) is another detectable processing deficit commonly found in chronically ill schizophrenic patients and reflects a failure to use transient memory traces. A similar deficit was found in subjects given ketamine who experienced psychotic symptoms and this correlated with the severity of the symptoms (Umbricht 2002).

6.24
In summary it is established that ketamine causes psychotic symptoms as measured by rating scales in normal volunteers and some of the neurocognitive abnormalities present in schizophrenics can be replicated. However it is unsurprising that ketamine causes such changes, as these are the sensations sought by those who are recreational users. None of the studies postulate that ketamine causes schizophrenia or that the symptoms last beyond the acute phase of use.

6.25 Effects on schizophrenic patients.
Ketamine has been used in patients suffering from schizophrenia to mimic psychotic relapse. This has been subject to strict ethical control as relapse can be associated with risk to the patient in terms of their health and potentially to society. A review of all data from North American ketamine studies involving schizophrenic subjects has been published (Carpenter 1999). Psychosis induced was mild and brief and was similar to previous episode of a patient's illness, there was no evidence of prolonged adverse events. Prolonged psychotic relapse was extremely rare and clinically managed successfully in a short time period. Anxiety associated with the presence of psychotic symptoms was mild and brief.

6.26
The difference in symptoms produced between schizophrenics and normal controls has been studied (Lahti 2001). Both groups experienced increases in positive symptoms, but the normal volunteers reported more symptoms on the psychosis and withdrawal sub-scales. The paper concludes that there is little difference between the symptoms experienced by the normal volunteers and the psychotic symptoms re-experienced by the schizophrenic sufferers. In summary, it appears that ketamine does not induce or cause psychoses even in those with a high propensity for psychosis. However, in these trials patients are only given very few ketamine doses and so caution should be used in applying these data to the recreational setting.

Ketamine dependence

6.27

Dependence is a clearly defined syndrome of symptoms as outlined by international classification manuals, DSM-IV and ICD-10 (see table 1).

6.28

Tolerance to ketamine develops rapidly. This property of ketamine discourages repeated use as ever increasing doses must be taken in order to achieve the same psychedelic effects, and the ability to remember the experience is impaired (Jansen 2003).

6.29

There is no evidence that cessation of regular ketamine use results in a withdrawal syndrome. Some case reports pertain to individuals having difficulty giving up the drug although withdrawal phenomena are not described.

6.30

Unlike other psychedelic drugs such as LSD and psilocybin, ketamine appears to lead to compulsive drug taking in some individuals although descriptions of this in the literature are rare (EMCDDA 2002). Many users who try ketamine for the first time are put off by the dissociative effects, which are often perceived as unpleasant. One study reports that ketamine administered to normal volunteers was positively reinforcing (Morgan 2003b). The positive subjective ratings of drug experience were found to be related to response inhibition. Impaired response inhibition, the self-regulation of goal directed behaviour, and salience attribution, how a drug effect is felt, has been proposed to underlie drug addiction (Goldstein and Volkow 2002). The way ketamine is first experienced is therefore very important, with many reporting it as an aversive event; this will have a protective effect.

6.31

Individuals who use compulsively have been called 'psychonauts', they tend to be older, well-educated professionals who migrate to intravenous use. There is evidence of continued use in this group despite harm to social and work life. Reports of such users are mainly historical. These subjects were usually involved in some way with the medical profession and had an easy supply route. The 'partygoers' use is not compulsive but used expertly together with a cocktail of other drugs to produce specific effects.

6.32

Ketamine does have some effects similar to drugs such as cocaine, which is widely abused in society. There are conflicting reports in the literature as to whether ketamine causes significant release of dopamine. Several groups claimed increased striatal dopamine in response to ketamine (Breier 1998, Smith 1998, Vollenweider 2000) but the more recent studies found no such effect and no specific intra-striatal effect (Aalto 2002, Kegeles 2002). Dopamine release is postulated as a common mechanism of addiction for most abused drugs (Koob 1998) and if ketamine also acts by this mechanism this would add weight to its dependence potential. Imaging techniques have

also highlighted the areas of the brain affected by ketamine use. There is some evidence that ketamine stimulates brain regions involved in reward in common with other abused drugs (see chapter 4).

6.33

In summary ketamine use can fulfil the criteria for dependent use. However published reports of ketamine dependence are on a case by case basis and largely historical. The change in the demographics of users towards the younger 'partygoers', and more widespread use may result in the emergence of greater numbers of ketamine-dependent individuals. This seems unlikely as the co-abused drugs have much greater dependence potential and this group does not generally use ketamine in a compulsive manner. Greater awareness of ketamine abuse and controls on the drug will impact on the supply of those regular users involved with the medical and veterinary professions. However controls on the drug are likely to increase its profitability to the dealer network and a greater shift in the demographic of users towards the younger 'partygoers'.

Effects on society

6.34

Ketamine has the potential to cause a wide range of disruptions to users' working and family life, as well as to society in general. Intoxication with ketamine would severely affect competence to drive. The dissociative effects are likely to prohibit a person even considering a complex task such as driving. However if mixed with other drugs it may be possible to maintain enough focus to attempt driving which, would be extremely hazardous. There are no published reports of ketamine being implicated in a 'drug driving' incident. However, 'drug driving' is an under-reported occurrence and detection of ketamine is more unlikely as it does not form part of routine toxicology screens and it has a very short half-life of less than 5 hrs.

6.35

Intoxication with ketamine increases a person's vulnerability to accidents, and thus distress to others. A user is likely to be unaware of potential dangers and to make poor decisions, case reports of death whilst intoxicated are prime examples of this (EMCDDA 2002). Furthermore, ketamines analgesic property has the potential to cause injury to an individual by their unawareness of a trauma, for example heat, being inflicted upon a part of the body. There are no reports of primary ketamine drug rape although this is a possibility. Under reporting may be a factor but ketamine has a distinctive and unpleasant taste, a property that does not lend itself to use in drug rape.

6.36

Ketamine does not cause a user to become more violent or aggressive but may lead to automatic behaviours in response to internal hallucinogenic experiences. These behaviours have the potential to be forceful. Persons suffering acute psychotic symptoms are at greater risk of harm to others. However this risk is small even for schizophrenics suffering uncontrolled symptoms so it is likely to be minimal for brief ketamine induced symptoms.

6.37

The impact to others from the result of crime is likely to be small. Ketamine is not a drug that causes widespread dependence and financial hardship and so users are unlikely to become involved in acquisitive crime through its use. Users tend to be in employment and of a high educational background, fitting the profile of ecstasy users rather than that of heroin and crack cocaine users. Theft of ketamine by veterinary practice burglary has been reported in France and the USA; this has the potential to be violent. Most ketamine is acquired via importation from countries such as India and through diversion from legitimate medical supply, which poses minimal risk to the public in itself.

6.38

One author states that legal control of ketamine in the USA caused an increase in the profitability of ketamine to the dealer network and thus greater involvement in its distribution (Jansen 2003), although this claim has yet to be substantiated. The risk to the public from discarded needles is very small given the small numbers using by this route and the typical profile of users. In summary it is likely that the greatest risk to others from ketamine is through involvement in an accident.

6.39

Ketamine has the potential to cause disruption to family and work life. Epidemiological data shows the majority of ketamine users are in employment. Cognitive deficits persisting up to 3 days after use of ketamine demonstrates the negative impact of use on working performance (Curran 2000). This effect would be magnified in regular users (Curran 2001). The deficit in episodic memory would impair ability to perform skilled and professional work efficiently. A person using ketamine in a compulsive and dependent way would severely compromise their ability to work. Such use would cause detachment from family life and damage relationships. Ketamine users report becoming introspective and distant when taking the drug and these effects cause strain to their family and personal relationships.

Table 1: The ICD-10 definition of dependence syndrome.
A diagnosis of dependence should be made if three or more of the following have occurred together for at least one month or occurred together repeatedly at some time during the last year.
- A strong **desire** or compulsion to take the substance
- Difficulties in **controlling** substance taking behaviour
- Physiological **withdrawal** state when substance use has ceased or been reduced, or substance use to relieve or avoid withdrawal symptoms
- Evidence of **tolerance**, such that increased doses of the substance are required to achieve effects originally produced by lower doses
- Progressive **neglect** of alternative pleasures or interests because of substance use and increased amount of time necessary to obtain or take the substance or to recover from its affects
- **Persisting** with substance use despite clear evidence of overtly harmful consequences (physical or mental)

7. Prevention of Ketamine Misuse

Public Health Measures
7.1
Ketamine use rose significantly in the mid 90's but the last five years has seen its popularity stabilising and possibly diminishing (see 2.2). This contrasts to the use of ecstasy that started as a niche drug but is now seen as mainstream. It seems that many people use ketamine only once and are put off by the dissociative effects that are often described as unpleasant. Knowledge of ketamine use and its effects is still low. The consequences of an education programme must be carefully considered. There is a small risk of publicising the effects of ketamine and enhancing its acceptability in society. Ketamine appears to be a relatively safe drug used recreationally and there may be little benefit of an educational programme to minimise risks if these risks are already very small. Ketamine users tend to be well-educated and experienced who are often well informed as to how to use the drug safely. They are people who are confident with the internet which has numerous sites promoting the safe use of ketamine.

Treatment of Dependence
7.2
Ketamine dependence is scarcely reported. It is possible to use a wide variety of substances in a compulsive fashion and treatment regimes use techniques to tackle behaviours common to all addictions. Opiate drugs such as heroin can be managed by prescription of a pharmacological substitute to gain regulation of drug intake. There is no such substitute for ketamine and so addiction must be treated primarily using psychological methods, as is dependence on drugs such as cocaine and ecstasy. A patient referred with ketamine dependence to a specialist addiction service should expect effective treatment using this method. However, relapse rates for addictive behaviours remain high and this is likely to be the case for ketamine dependence although lack of rush and lack of availability would mitigate against this. There are several non-statutory organisations that would offer support such as Narcotics Anonymous.

7.   Testing for Ketamine

Tests available

8.1

Testing for ketamine, primarily by detection of its more stable metabolite norketamine, is a well-established technique. Widely available methods are used, principally gas chromatography-mass spectrometry. It is possible to identify ketamine using this method in blood, urine and bodily tissues. Hair sampling can be used to give a more longitudinal history of ketamine use. Unfortunately epidemiological data collection is hampered by a lack of testing for ketamine in routine toxicological sampling of suspicious deaths and driving incidents. Therefore deaths and accidents involving ketamine are likely to be under-reported.

8.2

There are three papers discussing testing for ketamine in the recent published literature. Feng et al (1995) report development of gas chromatography-mass spectrometry method with selected ion monitoring. The authours report this is a sensitive method for detection of ketamine that has been developed to measure low plasma concentrations in volunteers participating in ketamine schizophrenia research. The United States department of defence report using urine testing to detect ketamine use in subjects under criminal investigation (Moore 2001). A rise in requests for testing from 1 in 1997 to 116 in 2000 prompted the department to evaluate the effectiveness of urine testing. A liquid chromatography-mass spectrometry method was used which had the advantage of reducing the amount of artefact dehydronorketamine that was produced using the gas chromatography method. The method described displays good sensitivity for ketamine and its metabolites but more investigation is essential to validate the method. Sporkert and Pragst (2000) describe a method for detecting lipophilic basic drugs, including ketamine, from hair samples. All these testing methods only report small numbers and there is no reliable test to match intoxication or recent use with a positive ketamine or metabolite level. However with greater levels of testing these methods will become better understood and more reliable.

Bibliography

ABPI compendium of data sheets and summaries of product characteristics. London: Datapharm 1999-2000

Aalto S, Hirvonen J, Kajander J, Scheinin H, Nagren K, Vilkman H et al. Ketamine does not decrease strialtal dopamine D2 receptor binding in man. *Psychopharmacology* 2002;**164**(4):401-6

Abel KM, Allin MP, Hemsley DR, Geyer MA. Low dose ketamine increases prepulse inhibition in healthy men. *Neuropharmacology* 2003;**44**(6):729-37

Abel KM, Allin MP, Kucharska-Pietura K, Andrew C, Williams S, David AS et al. Ketamine and fMRI BOLD signal: distinguishing between effects mediated by change in blood flow versus change in cognitive state. *Hu Brain Mapp* 2003a;**18**(2):135-45

Abel KM, Allin MP, Kucharska-Pietura K, David A, Andrew C, Williams S et al. Ketamine alters neural processing of facial emotion in healthy men: an fMRI study. *Neuroreport* 2003b;**14**(3):387-91

Abel-Rahman MS, Ismail EE. Teratogenic effect of ketamine and cocaine in CF-1 mice. *Teratology* 2000;**61**(4):291-6

Adler CM, Goldberg TE, Malhotra AK, Pickar D, Breier A. Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. *Biol Psychiatry* 1998;**43**(11):811-16

Avila MT, Weiler MA, Lahti AC, Tamminga CA, Thaker GK. Effects of ketamine on leading saccades during smooth-pursuit eye movements may implicate cerebellar dysfunction in schizophrenia. *Am J Psychiatry* 2002;**159**(9):1490-96

Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2003;(1):CD003351

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;**47**(4):351-354

Bloomfield R and Kerr J. Matters of substance. *Time Out* April 2000;1547;18-24

Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury* 2002;**33**(4):323-327

Bowdle TA, Radant AD, Cowley DS, Karasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology* 1998;**88**(1):82-8

Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D. Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in health volunteers. *Am J Psychiatry* 1997;**154**(6):805-11

Breier A, Adler CM, Weisenfeld N, Su TP, Elman I, Picken L. Effects of NMDA antagonism on striatal dopamine release in healthy subjects: application of a novel PET approach. *Synapse* 1998;**29**(2):142-7

Breitmeier D, Passie T, Masouri F, Albrecht K, Kleeman WJ. Autoerotic accident associated with self-applied ketamine. *Int J Legal Med* 2002;**116**(2):113-6

Carpenter WT. The schizophrenia ketamine challenge study debate. *Biol Psychiartry* 1999;**46**(8):1081-91

Chung H, Choi H, Kim E, Jin W, Lee H, Yoo Y. A fatality due to injection of tiletamine and zolazepam. *J Anal Toxicol* 2000;**24**(4):305-08

Cording CJ, DeLuca R, Camporese T, Spratt E. A fatality related to the vetinary anesthetic telazol. *J Anal Toxicol* 1999;**23**(6):552-5

Curran HV and Morgan C. Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* 2000;**95**(4):575-590

Curran HV and Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001;**96**(5):749-760

Craske V, Stevenson N, Halfin M and French P. The Mixmag drugs survey 2000. *Mixmag* Feb 2001;117:54-56

Craske V, Robinson K, Harris I, Van der Buek J and Fielding A. The Mixmag drugs survey 2001. *Mixmag* Feb 2002;129:84-109

Dillon P, Copeland J and Jansen K. Patterns of use and harms asscoiated with non-medical ketamine use. *Drug and Alcohol Depend* 2003;**69**(1)23-8

EMCDDA. Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs. Luxembourg: Office for official publications of the European Communities 2002

Fantel AG, Shepard TH. Potential role of maternal toxicity in the developmental effects of ketamine and cocaine in mice. *Teratology* 2000;**62**(4):177

Feng N, Vollenweider FX, Minder EI, Rentsch K, Grampp T, Vonderschmitt DJ. Development of a gas chromatography-mass spectrometry method for

determination of ketamine in plasma and its application to human samples. *Ther Dryg Monit* 1995;**17**(1):95-100

French P. The Mixmag drugs survey 2002. *Mixmag* Mar 2003;117:54-56

Gaillard Y, Pepin G. Evidence of polydrug use using a hair analysis: a fatal case involving heroin, cannabis, chloroform, thiopental and ketamine. *J Forensic Sci* 1998;**43**(2):435-8

Gill JR and Stajic M. Ketamine in non-hospital and hospital deaths in New York City. *J Forensic Sci* 2000;**45**(3):655-8

Gross SR, Barrett SP, Shestowsky JS and Pihl RO. Ecstasy and drug consumption patterns: a Canadian rave population study. *Can J Psychiatry* 2002;**47**(6):546-51

Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Pyschiatry* 2002;**159**(10):1642-1652

Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Malledant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care patients after major abdominal surgery. *Anesth Analg* 2003;**97**(3):843-7

Hansen G, Jensen SB, Chandresh L, Hilden T. The psychotropic effect of ketamine. *J of Psychoactive Drugs* 1998;**20**(4):419-425

Harborne GC, Watson FL, Healy DT, Groves L. The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers. *J of Psychopharm* 1996;**10**(2):134-40

Hetem LA, Danion JM, Diemunsch, Brandt C. Effect of subanaesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. *Psychopharmacology* 2000;**152**(3):283-8

Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. *Anesthesiology* 1999;**90**(1):174-82

Holcomb HH, Lahti AC, Medoff, Weiler M, Tamminga CA. Sequential regional cerebral blood flow brain scans using PET with H2(15)O demonstrate ketamine actions in CNS dynamically. *Neuropsychopharmacology* 2001;**25**(2):165-72

Jansen KLR. Ketamine: further observations on use, users and consequences. *In press: Addiciones* 2003

Johnston LD, O'Malley PM and Bachman JG. Monitering the future national results on adolescent drug use: overview of key findings 2002. Berthesda MD: NIDA

Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL et al. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for humans. *Biol Psychiatry* 2000;**48**(7):627-40

Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O et al. NMDA antagonist effects on striatal dopamine release: postitron emission tomography studies in humans. *Synapse* 2002;**43**(1):19-29

Kochhar MM, Aykac I, Davidson PP, Fraley ED. Teratologic effects of d,1-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride (ketamine hydrochloride) in rats. *Res Commun Chem Pathol Pharmacol* 1986;**54**(3):413-16

Koob GF, Rocio M, Carrera A, Glod LH, Heyser CJ, Maldonado-Irizarry C et al. Substance dependence as a compulsive behaviour. *J of Psychoparm* 1998;**12**(1):39-48

Krystal JH, Bennett A, Abi-Saab D et al. Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. *Biol Psychiatry* 2000;**47**(2):137-43

Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* 2002a;**95**(1):114-18

Kudoh A, Katagai H, Takazawa T. Anesthesia with ketamine, propofol, and fentanyl decreases the frequency of postoperative psychosis emergence and confusion in schizophrenic patients. *J Clin Anesth* 2002b;**14**(2):107-10

Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs* 1997;**29**(2):165-83

Krupitsky EM, Burakov AM, Romanova TN, Grinenko NI, Grinenko AY, Fletcher J et al. Attenuation of ketamine effects by nimodipine pretreatment in recovering ethanol dependent men: pschoparmacologic implications of the interaction of NMDA and l-type calcium channel antagonists. *Neuropsychopharmacology* 2001;**25**(6):936-47

Krupitsky E, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko A. Ketamine psychotherapy for heroin addiction: immediate effects and two year follow up. *J Subst Abuse Treat* 2002;**23**(4):273-83

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport* 1995;**6**(6):869-72

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA. Effect of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* 2001;**25**(4):455-67

Langsjo JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V et al. Effects of sub-anaesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 2003;**99**(3):614-23

Licata M, Pierini G, Popoli G. A fatal ketamine poisoning. *J Forensic Sci* 1994;**39**(5):1314-20

Lorrain DS, Baccei CS, Bristow LJ, Anderson JJ, Varney MA. Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release an the rat prefrontal cortex: modulation by a group II selective metabotropic glutamate receptor agonist LY379268. *Neuroscience* 2003;**117**(3):697-706

Malhorta AK, Pinals DA, Weingartner H et al. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 1996:**14**(5):301-7

Mansergh G, Colfax GN, Marks G, Rader M, Guzman R, Buchbinder. The circuit party men's health survey: findings and implications for gay and bisexual men. *Am J Public Health* 2001;**91**(6):953-8

Moore KA, Kilbane EM, Jones R, Kunsman GW, Levine B, Smith M. Tissue distribution of ketamine in a mixed drug fatality. *J Forensic Sci* 1997;**42**(6):1183-5.

Moore KA, Sklerov J, Levine B, Jacobs AJ. Urine concentrations of ketamine and norketamine following illegal consumption. *J Anal Toxicol* 2001;**25**(7):583-588

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 2003a Nov 5 [Epub ahead of print]

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose response study. *In press: Psychopharmacology* 2003b

Nabben T and Korf DJ. Ketamine (English summary). Thela Thesis 2000, Amsterdam.

Newcomer JW, Farber NB, Jevtovic-Todorovic V et al. Ketamine induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* 1999;**20**(2):106-18

Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 1990;**244**(4910):1360-2

Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA. NMDA antagonist neurotoxicity: mechanism and prevention. *Science* 1991;**254**(5037):1515-8

Olney JW, Wozniak DF, Farber NB, Jevtovic-Todorovic V, Bittigau P, Ikonomidou C. The enigma of fetal alcohol neurotoxicity. *Ann Med* 2002;**34**(2):109-19

Oranje B, van Berckel BN, Kremner C, van Ree JM, Khan RS, Verbaten MN. The effects of a sub-anaesthetic dose of ketamine on human selective attention. *Neuropsychopharmacology* 2000;**22**(3):293-302

Oranje B, Gispen-de-Weied CC, Verbaten MN, Khan RS. Modulating sensory gating in healthy volunteers: the effects of ketmaine and haloperidol. *Biol Psychiatry* 2002;**52**(9):887-95

Quail MT, Weimersheimer P, Woolf AD, Magnani B. Abuse of telazol: an animal tranquilizer. *J Toxicol Clin Toxicol* 2001;**39**(4):399-402

Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989;**36**(2):186-97

Release. Release drugs and dance survey: an insight into the culture. *Release* 1997 388 Old Street, London.

Shimoyama N, Shimoyama M, Inturrisi CE, Elliot KJ. Ketamine attenuates and reverses morphine tolerance in rodents. *Anesthesiology* 1996;**85**(6):1357-66

Silvestre JS, Pallares M, Nadal R, Ferre N. Opposite effects of ethanol and ketamine in the elevated plus-maze test in wistar rats undergoing a chronic oral voluntary consumption procedure. *J Psychopharmacol* 2002;**16**(4):035-12

Smith DJ, Pekoe GM, Martin LL, Coalgate B. The interaction of ketamine with the opiate receptor. *Life Sciences* 1980;**26**(10):789-795

Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA et al. Glutamate modulation of dopamine measured in vivo with positron emission tomography and 11C-raclopride in normal human subjects. *Neuropsychopharmacology* 1998;**18**(1):18-25

Sporkert F, Pragst F. Use of headspace solid-phase microextraction (HS-SPME) in hair analysis for organic compounds. *Forensic Sci Int* 2000;**107**(1-3):129-48

Substance Abuse and Mental Health Services Administration. Overview of findings from the 2002 National Survey on Drug Use and Health. Office of Applied Studies 2003, Rockville, MD.

Stiegel R K. Phencyclidine and ketamine intoxication: A study of four populations of recreational users. *NIDA Research Monograph* 1978 21:**6**;119-147

Rofeal HZ, Abdel-Rahman MS. Reduction of tissue concentration of cocaine in rat by ketamine. *J Toxicol Environ Health A* 2003;**66**(3):241-51

Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol Psychiatry* 2002;**51**(5):400-406

Vollenweider FX, Vontobel P, Oye I, Hell D, Leenders KL. Effects of the (S)-ketamine on striatal dopamine a 11C-raclopride PET study of a model of psychosis in humans. *J Psychiatric Res* 2000;**34**(1):35-43

Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* 2000;**18**(4):447-51

White MJ and Ryan C. Pharmacological properties of ketamine. *Drug and Alc Review* 1996;**15**:145-55

Zukin SR. Phencyclidine (or phencyclidine –like)-related disorders. In Kaplan and Sadock's Comprehensive Textbook of Psychiatry Seventh Edition. Lippincott, Williams and Wilkins 1995.

ACMD Technical Committee – Ketamine Report
Forensic Science Service contribution
Dr Mike White
December 2003

Introduction
The Forensic Science Service (FSS) examines drugs seizures from over 80% of Police forces in England and Wales and the FSS Drugs Intelligence Unit (DIU) maintains a database of the results of examination of these seizures. Since July 1996 the FSS has also examined drug seizures from HM Customs and Excise.

In this report a *seizure* relates to a quantity of drug(s) seized at a particular location on a particular date and usually results in a single *submission* to the FSS. A seizure may comprise one or more *seizure records* each relating to a discrete part of the *seizure*.

Forensic examination of ketamine seizures is usually limited to identification of the drug itself and any other drugs present. The proportion of ketamine in powders and the ketamine content of tablets, capsules and liquids are not routinely undertaken. Ketamine in pharmaceutical products is usually present as the hydrochloride salt, however, forensic examination of ketamine seizures does not normally include identification of the salt form of the drug nor identification of the solid or liquid matrix containing the drug.

Police seizures
The first seizures of ketamine were encountered by the FSS in 1990. The number of seizures increased through the early 1990's, but by 1995 submissions to the FSS had stabilised at around 250 per annum. In 1995, around 91-92% of ketamine seizure records related to tablets and around 5-7% related to powder, with the remaining records being capsules. In 1999 the number of tablet seizures decreased sharply and the number of powder seizures started to increase. This was probably due to the closure of a large ketamine tablet making facility by the National Crime Squad in 1998. By 2002, the number of police ketamine seizures had declined to about 150 per annum.

Provisional data for 2003 show that Police seizures of ketamine have increased from 146 in 2002 to 195 in 2003 and only 20 of these seizures included ketamine tablets. However, ketamine seizures are still at a relatively low level compared to 'ecstasy' (e.g. over 5000 MDMA seizure records in the first 10 months of 2003). The amount of ketamine seized by the Police over the last 5 years amounted to approximately 150,000 doses whereas the Police seized over 1.06 million MDMA tablets in 2002 alone.

Over the last 10 years the FSS has seen 43 different ketamine tablet designs in a variety of colours. The majority of these designs have also been seen on 'ecstasy' tablets. Ketamine is usually found mixed with a stimulant drug such

as amphetamine, ephedrine or caffeine, although other drugs including procaine, MDMA, diazepam, selegilene, tiletamine, and methylamphetamine have been encountered. The use of such mixtures may be intended to mimic the effects of ecstasy [Ref 1]. The design and composition of ketamine tablets suggests that the manufacturers of these tablets have been targeting the 'ecstasy' market. Other drugs were found in ketamine tablets in around 95% of seizure records and a controlled drug was found in about 30% of seizure records.

Ketamine powders submitted to the FSS are generally fine white powders similar in appearance to cocaine. Many seizures are packaged in paper and plastic wraps much like those used for cocaine and amphetamine. The content of these wraps varies from less than 100 milligrams to a gram. There is very little quantitative information on the ketamine content of these powders, as there is no requirement to measure purity. Other drugs were only found in ketamine powders in about 20% of seizure records and a controlled drug was only found in about 15% of seizure records. The range of other drugs found was similar to that for tablets, with the exception of cocaine, which is not normally encountered in tablets but was encountered in 6% of ketamine powders.

Licit ketamine products (KETALAR, VETALAR and CALYPSOL) have been encountered only occasionally and usually in very small amounts, typically only one or two vials.

Prior to 2002, police seizures of liquids containing ketamine (other than identifiable licit products) were rarely encountered and were usually only small volumes or residues in a syringe.   In July 2002, the Metropolitan Police seized a DHL parcel containing 15 litres of ketamine solution in thirty 500 millilitre translucent plastic bottles labelled "Rose Water" from Mumbai (Bombay) in India. The suspect stated that he boiled the liquid in a microwave oven to obtain ketamine powder. Other drugs found at two premises during the investigation included, amphetamine, methylamphetamine and MDMA tablets ('ecstasy'). Following this seizure there have been at least four further police seizures of plastic bottles containing ketamine solutions.

Ketamine is often seized along with other controlled drugs and over the last 18 months, 62% of police ketamine seizures submitted to the FSS included one or more controlled drugs. The drugs most frequently seized along with ketamine are MDMA tablets (47% of seizures), cannabis resin or herbal cannabis (24% of seizures), cocaine powder (16% of seizures) and amphetamine (14% of seizures).

Customs seizures
Ketamine first appeared in Customs seizures submitted to the FSS in December 2002. The drug was usually found dissolved in liquid and concealed in one-litre opaque, white plastic bottles labelled 'Rose Water' or as some other perfume fragrance. According to information provided by Customs and Excise, these seizures originated from packages sent to the UK from Goa in India. Customs seizures of this description are only submitted for

forensic examination where forfeiture is contested and even then only a sample of the seized bottles is submitted for examination. Meaningful seizure statistics are not therefore available from FSS records.

Further examination of some seizures confirmed that the drug was present as ketamine hydrochloride and the liquid was consistent with being water. The liquids however had a strong sweet-floral odour, which suggest that they do actually contain "Rose Water". The first Customs seizures contained 50-80 grams of ketamine (calculated as base) in each litre bottle (1 gram of ketamine base is equivalent to 1.15 grams of ketamine hydrochloride).

More recent Customs seizures have been found to contain saturated solutions of ketamine hydrochloride with significant amounts of solid drug. The solubility of ketamine hydrochloride in water is about 200 grams per litre. In two cases, 213 and 219 grams of crystalline powders, with ketamine hydrochloride purities of about 97%, were recovered from one-litre, opaque-white plastic bottles. The use of opaque bottles would hide the presence of any solids in the liquid.

Other smuggling methods encountered in Customs cases have included concealment in clear liquid in shampoo bottles and as an off-white solid in a toothpaste tube.

No other drugs have been detected in Customs seizures of ketamine solutions and no other drugs have been seized along with ketamine in these cases.

General Toxicology Submissions
The Forensic Science Service (FSS) undertakes forensic toxicology at its London and Chorley laboratories in criminal cases and in some Coroners' cases. Due to the relatively low incidence of ketamine as a drug of abuse it is not included in a routine 'drugs of abuse' screen. However, ketamine is tested for in drug facilitated sexual assault cases and where the drug is specifically mentioned or where the circumstances indicate the possible involvement of the drug. Furthermore, at the FSS Chorley laboratory, ketamine would be included in most toxicology screens undertaken in criminal or Coroner's cases unless the customer specified that testing be confined to commonly abused drugs.

There have been very few cases where ketamine has been identified during these screens. The exact figure is not available but it is unlikely to exceed 10 cases since the early 1990's, when the drug was first included in routine toxicology testing, to the present day. At the FSS London laboratory, ketamine has been detected in only 3 out of more than a thousand drug facilitated sexual assault cases and in all instances the findings were thought to be incidental and not due to surreptitious administration of ketamine.

In those cases where ketamine has been detected, information is not readily available on ketamine levels or details of other drugs found.

Drugs Driving Submissions

Since 2001, ketamine has not been included in routine tests carried out in drugs driving cases, but ketamine is tested for when indicated by the circumstances. To date ketamine has only been found in about two cases of 'driving under the influence of drugs' and in both cases other drugs were also found. Prior to 2001, drugs driving submissions were included in the general toxicology work described above.

References

D. Shewan, P. Dalgarno and L. A. King, "Tablets often contain substances in addition to, or instead of, ecstasy ... such as ketamine" [Letter], British Medical Journal 313, 424, 1996.

Appendix: Charts and Tables

Police Ketamine Seizures 1994 - 2003

Police Seizure Records for Ketamine 1994 - 2003

Frequency Distribution of Ketamine Wrap Size

No. of Records (y-axis, 0 to 9) vs Weight (grams) (x-axis)

Weight (grams)	No. of Records
0 - 0.1	4
0.2	3
0.3	6
0.4	6
0.5	8
0.6	4
0.7	5
0.8	8
0.9	4
1	3
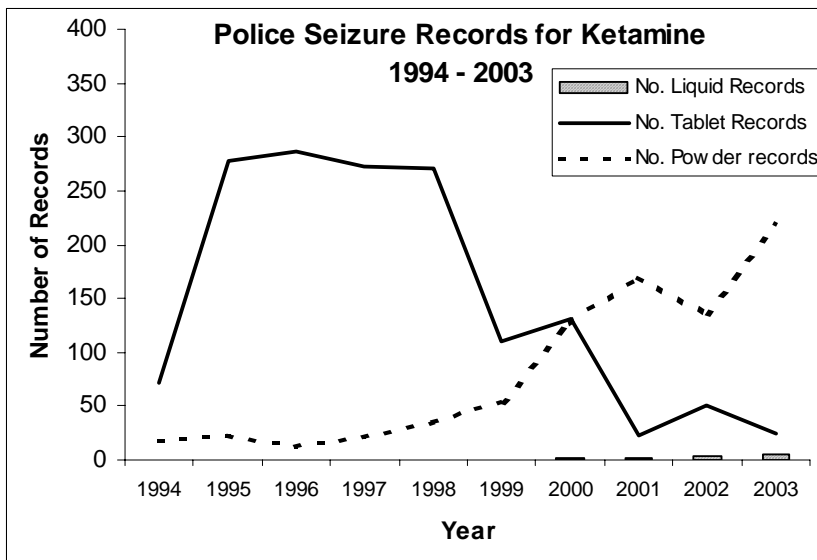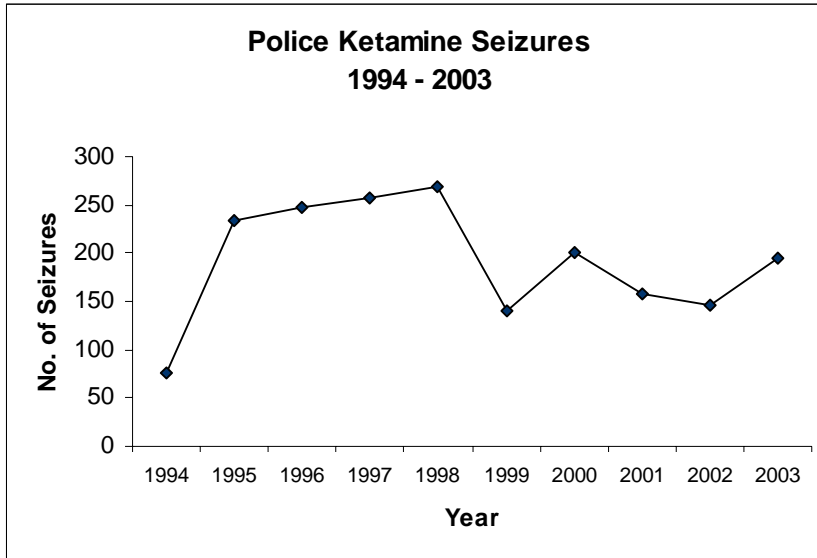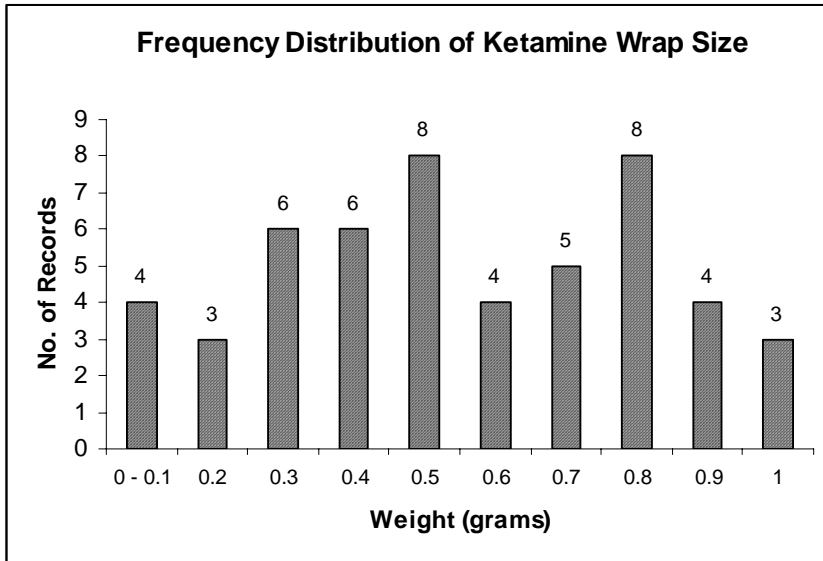
Frequency of other drugs encountered with ketamine in Police siezures.

Other Drugs Seized	Class	Proportion of Seizures**
MDMA	Class A	47.3%
Cocaine powder	Class A	16.4%
Herbal Cannabis*	Class B	15.5%
Amphetamine	Class B	14.5%
Cannabis Resin*	Class B	12.1%
LSD	Class A	4.3%
Benzodiazepines	Class C	4.3%
Heroin	Class A	3.4%
Psilocybin ('Magic Mushrooms')	Class A	2.9%
Methadone	Class A	1.4%
Crack cocaine	Class A	1.0%
2C-B	Class A	1.0%
GHB	Class C	1.0%
MDEA	Class A	1.0%
Hash Oil*	Class B	0.5%
2C-I	Class A	0.5%

*   As of 29 January 2004 all forms of Cannabis are Class C
**   The total is greater than 100% as some seizures include more than one controlled drug

Appendix 3

ACMD Technical Committee – Ketamine Report
Ketamine use on the recreational scene in the UK
John M Corkery
February 2004

INTRODUCTION

Ketamine is not included as a specific drug in general household or school surveys in the UK. It is thus difficult to say very much about its prevalence or incidence in the general population.

Some information is available from face to face interviews at dance venues (Release 1997; Deehan and Saville 2003). Another source of information is the surveys conducted at pop festivals and other outdoor events by the Independent Drug Monitoring Unit (Atha and Davis 2003).

Additional, limited information is available from postal surveys of readers of magazines (such as *Ministry*, *Mixmag* and *Time Out*) aimed at those attending clubs and dance venues. It should be borne in mind that the respondents to these surveys were self-selecting and are probably not representative of either the general public or the readership of the magazines in question. However, the results do tell us some about part of that recreational drug using population.

Data on ketamine from these various sources are presented below. Information on GHB and ecstasy is also included so as to provide some points of comparison. Comparisons are drawn between ecstasy and ketamine as the former is much more widely used and is typically used in similar situations. Reference is made to GHB since, until July 2003, it too was not a substance controlled under the Misuse of Drugs Act 1971.

The aim of this paper is to draw together what can be distilled from these sources to inform us on the nature and extent of recreational ketamine use in the UK over recent years.

FACE TO FACE INTERVIEWS

Release 1997

Probably the first detailed UK research to ask about ketamine use in the recreational scene was that undertaken by *Release*. This organisation conducted face to face interviews (n = 520) in 18 dance venues in London and the South East of England between March and November 1996 (*Release*, 1997). The results relating to ecstasy and ketamine are now presented.

Use

Males are more likely to have used both these substances than females (Table 1). The likelihood of ever having used ketamine increases with age, but it is unclear whether this is an age or cohort effect (page 12). Lifetime use of ketamine is 2.7 times less than that for ecstasy - 31% compared to 82%. Regular use of ketamine is even less common than for ecstasy (13 times lower) - see Table 2. But regular use of ketamine follows the same pattern as lifetime use. Regular use appears to peak in the over 29 age group for both ecstasy and ketamine. About 7 in 10 said that ecstasy was their favourite drug to take at dance venues, compared to only 3 in 100 for ketamine (Table 3).

Males are much more likely than females to consider ketamine as their favourite drug at a dance venue, whereas for ecstasy there is no difference. There is little difference the age groups in the proportion of people likely to consider ecstasy as their favourite dance drug. For ketamine there is a distinct difference; the choice is highest amongst 20-24 year olds. Ketamine is clearly less likely to be the favourite drug for users generally compared to ecstasy (14 times less likely). Nearly 84% of all those who ever taken a drug had tried a drug to 'chill out' with; of these 12% had tried ecstasy and 3% ketamine.

Table 1: Ever use (%) amongst *Release* respondents

	Ecstasy	Ketamine
Male	85	34
Female	83	25
15-19	80	22
20-24	86	31
25-29	86	34
> 29	92	44
All	85	31
n = 501		

Table 2: Of those *Release* respondents who had ever taken a drug, the proportion who had used or intended to use that evening (%)

	Ecstasy	Ketamine
Male	53	4
Female	52	2
15-19	53	2
20-24	49	3
25-29	54	6
> 29	61	7
All	53	4
n = 493		

Table 3: Of those _Release_ respondents who had ever taken a drug, their favourite drug to take at dance events (%)

	Ecstasy	Ketamine
Male	67	5
Female	68	1
15-19	67	2
20-24	68	5
25-29	67	3
> 29	73	1
All	68	3
Favourite drug to take generally	28	2
n = 493		

Effects

A wider range of effects - both negative and positive - was experienced with ecstasy than with ketamine; for ecstasy the average was two negative and in excess of 6.5 positive effects compared to one negative and in excess of two positive effects for ketamine (Tables 4 and 5).

Table 4: Problems experienced with ecstasy and ketamine (%) by _Release_ respondents

Problem	Ecstasy	Ketamine
None	49	76
Amnesia/vagueness	10	6
Blurred vision	20	14
Depression	17	7
Excessive mood swings	17	5
Fatigue	16	5
Headaches	11	5
Insomnia	12	6
Irregular periods	5	1
Nausea	22	9
Panic attacks/anxiety	7	3
Paranoia	15	6
Passing out	5	5
Skin problems	9	2
Stomach pain	12	3
Vomiting	20	7
Weight loss	19	3
Number who had ever tried the drug	425	156

Three-quarters of those who used ketamine said they had experienced no problems compared to one half of ecstasy users. The four most common problems experienced by ketamine users were blurred vision (14%), nausea (9%), depression (7%) and vomiting (7%). Three out of five ketamine users reported no positive effects compared to only one-sixth of ecstasy users. The five most common positive effects of ketamine reported are: hallucinations (21%), relaxation (18%), escape from worries, happiness and heightened perception (all 15%).

Table 5: Positive effects experienced with ecstasy and ketamine (%) by *Release* respondents

Problem	Ecstasy	Ketamine
None	16	58
Compassion	49	5
Confidence	62	6
Empathy	43	6
Energy	69	9
Escape from worries	24	15
Hallucinations	21	21
Happiness	75	15
Heightened perception	44	15
Humour	53	12
In touch with body	52	9
Oneness with world	17	8
Realisation and understanding	7	6
Relaxation	37	18
Sexual excitement	30	5
Sociability	50	8
Wisdom	28	4
Number who had ever tried the drug	425	156

Legal status

About one-third of all those surveyed that it should be illegal to possess ketamine compared to one-sixth who responded in a similar manner for ecstasy (Table 6). There were higher proportions of users who had tried these drugs than had not tried them that agreed with the statement that the drugs should be illegal (Table 7). Nearly half of those surveyed thought it should be legal to sell ecstasy compared to only one-sixth in favour of the legal sale of ketamine (Table 8). The proportions who thought that it should be illegal to possess ketamine or ecstasy fell with age; the proportions who thought it should be legal to sell these drugs rose with age.

Table 6: *Release* respondents thinking it should be illegal to possess (%)

	Ecstasy	Ketamine
Male	15	33
Female	18	37
15-19	17	43
20-24	20	36
25-29	16	23
> 29	10	29
All	17	35
n = 520		

Table 7: Should be illegal by whether drug had ever been tried (%) by *Release* respondents

	Ecstasy	Ketamine
Not tried	32	38
Ever tried	14	25
Ratio	2.3:1	1.5:1
n = 520		

Table 8: *Release* respondents thinking it should be legal to sell ketamine (%)

	Ecstasy	Ketamine
Male	54	17
Female	42	14
15-19	42	8
20-24	48	17
25-29	48	16
> 29	67	30
All	49	16
n = 520		

Other studies

Other research using face to face interviews usually reports only lifetime use of ketamine. Deehan and Saville (2003a and 2003b) report on interviews with 760 clubbers and 26 in-depth interviews conducted in January and February 2000. These involved interviews at 8 events at 6 night clubs in South East England. Lifetime use for the sample as a whole was 17% for ketamine compared to 6% for GHB. However, when the interviewees were divided into current and lapsed drug users there was an important difference. Among current users 35% had taken ketamine and 13% GHB, but these rates fell to 7% and 3% respectively for lapsed users.

This lifetime rate of 17% for ketamine is higher than the 10% found by the earlier *CREW 2000* (1997) study of clubbers in Edinburgh, but lower than that found by *Release* (1997). It is worth noting that the most recent study by *CREW 2000* found that last year use of ketamine was 15% compared to 82% for ecstasy. This study was conducted in February and March 2001 at 7 dance events and pre-club pubs in Edinburgh, and involve questionnaires being administered to 122 self-selected respondents (*CREW 2000* 2001). The British Dance Culture survey by *Release* in 1999 of London "techno" venues found that 10% of respondents had ever taken ketamine, compared to the 73% who had used ecstasy (quoted in Bloomfield & Kerr 2000).

Bellis, Hughes, Bennett and Thomson (2003) conducted surveys using anonymised questionnaires at Ibiza airport of young holiday-makers returning to the UK from the resort. There were 846 respondents in 1999 and 868 in 2002. Between these dates the proportion of ketamine, esctasy and GHB being used in Ibiza rose. The proportion of individuals having used GHB or ketamine in 2002 more than doubled from those on their first visit to Ibiza compared to those returning for a fourth or further visit. The rise for ketamine in 1999 was from 7.9% to 18.3%, and in 2002 was from 6.5% to 19.5%. For newer drugs such as GHB and ketamine a large proportion of all users in Ibiza had never used in the UK but were recruited into use while on holiday (18.8% in 1999 and 18.4% in 2002 for ketamine). These new recruits represent a significant percentage of users of that drug.

READERS' SURVEYS

Time Out

The *Time Out* survey of 2000 (sample size not stated) found that no one took ketamine regularly whereas 4% took ecstasy (Bloomfield and Kerr 2000). However, 10% of respondents said they had tried ketamine compared to 32% who had ever used ecstasy and 6% who tried GHB.

Ministry

A survey by the magazine *Ministry* found that 16% of the 1000 plus respondents had taken ketamine compared to the 91.6% who claimed to have used ecstasy (and 30.9% several times a week). Ecstasy was mentioned in 7 out of the top 10 favourite drug combinations (*Ministry* 2000). (GHB and ketamine were either not included in the list of drugs asked about or did not appear in this list.)

Mixmag

The *Mixmag* drugs survey has included some information on ketamine from its annual postal survey of about 1000 respondents, 1560 in 2003 (Craske, Stevenson, Halfin and French 2001; Craske, Robinson, Harris, Van der Buek and Fielding 2002; French 2003; Craske 2004; Mitcheson 2004).

Current use of ketamine appears to have peaked in 2000 at 30% with substantially lower use in both the preceding twelve months (4%) and the three following years between 10% and 16%). Lifetime use was report at only 4% in 1999 but since has been considerably higher and stable at around 39% to 47% (Table 9). Last year use in 2003 was 27.1%. Ketamine is tried and consumed regularly far less than ecstasy but is more popular than GHB among this population (Table 10).

Table 9: Ketamine use amongst *Mixmag* readers

Year	Last month (%)	Lifetime (%)
1999	3.9	4
2000	29.7	46.5
2001	10	39.7
2002	12.6	40.8
2003	16.0	38.9

Table 10: Use of ketamine compared to GHB and ecstasy by *Mixmag* readers

Drug	Last month (%) (and ranking)			Lifetime (%)	Age of first use
	1999	2000	2001	2000	2000
Ecstasy	85.6	84.7 (1)	71.2 (2)	97.7 (2)	19 yrs 6 months
Ketamine	3.9	29.7 (5)	12.6 (5)	46.5 (8)	21 years 4 months
GHB	3.4	25.8 (7)	4.1 (6)	23.8 (11)	22 years 6 months

In 2000 over 7% of those who had tried ketamine had done so by the age of 17; in 2003 this proportion had nearly doubled (to 13.6%). Nearly half of those who have tried ketamine did so by the age of 20 (49.7% in 2003). In 2000 the average age of first trying ketamine was given as 21 years 4 months compared to 19 years 8.5 months for ecstasy. Thee was little change in the average age for trying ketamine in 2003 (21 years 9.6 months), although the most common (modal) age for experimentation was 18 years.

Respondents in 2001 said that if they regularly took ketamine, they took it with alcohol or ecstasy but not with amphetamine, GHB or cocaine. GHB (16.2%) was the top drug which people said they would like to try, whilst ketamine was in fifth place (5.1%). One in eight (12.1%) of respondents in 2003 said they next wanted to try ketamine (the same proportion also wanted to experiment with GHB).

When asked about their intention to use ketamine, more than half (56.1%) of those who answered said they did not want to use ketamine. This figure comprises 36.6% who have never tried ketamine and do not want to and 19.6% who have used it but would not do so again. One fifth (18.3%) had never tried ketamine but might. Another fifth (20.3%) regarded themselves as occasional or current users and only 6.4% as regular users.

No information is given on the route of administration of ketamine. In 2000, the most usual method of taking ecstasy was to swallow it. However, 64.4% of those taking ecstasy said they had snorted it, 43.4% had smoked it, 1% injected, and 3.4% anally. Most users of GHB swallowed it as a liquid (71.5%), 15.4% swallowed it as a powder, 10.1% had injected it, and 3% either snorted or smoked it. The average number of ecstasy tablets taken in a session was: 1999 - 2.82; 2000 - 3.7; 2001 - 3.4; and 2002 - 3.7.

The main way in which ketamine was stated to be used in 2003 was at 'chill outs' (47%). Ketamine was taken in small doses whilst dancing by 18.3% compared to 6.3% of respondents using large doses at parties. Only a small percentage (4.5%) reported using ketamine on their own. A quarter (24.3%) said that used the drug in a range of other situations.

OUTDOOR VENUES

Surveys of populations likely to contain high proportions of drug users have been conducted each year between 1998 and 2002 by the Independent Drug Monitoring Unit (IDMU). IDMU use anonymous questionnaires distributed at pop festivals and other outdoor events. These surveys are likely to capture elements of the populations covered by the music magazine readership surveys and face to face interviews at clubs and similar venues.

Use

Over the period 1998-2002 14.8% of respondents said they had ever used ketamine (range 13.0% to 18.4%), and 3.0% regarded themselves as current users (range 2.4% to 6.5%). The highest rates were reported in 2001 but this may be a sampling effect since the majority of respondents in that year were from the London region, and the sample size was smaller than in other years.

The majority of ketamine users asked in 2001 and 2002 said that only used one or two tablets/doses a week. Only 0.2% of ketamine users had used it on the day they completed the questionnaire. This suggests that the drug is not usually consumed at pop festivals. The mean amount spent on ketamine each month was £19, although the mode appears to have been about £10.

Initiation

The mean age of initiation to ketamine use over the period 1998-2002 was 22 years 9 months, ranging from 21 years 8 months to 23 years 7 months. Most individuals had first tried the drug between the ages of 18 and 30.

Attitudes towards ketamine

The overwhelming majority (87%) of those who had never used ketamine said they would never use it. Only 13% indicated that they might try ketamine in the future.

There appears to have been a fall in subjective ratings of the drug since 1999. As might be expected, the ratings appear to be associated with frequency of use or intention to use. The lowest ratings were given by those who stated they would never ketamine; the highest ratings were given by regular (weekly/monthly) users.

Price

The prices quoted for ketamine appear to vary considerably, but the sample sizes on which the figures are based are comparatively small. The price of a tablet/dose was fairly stable, being about £11.42 on average (n = 241). The mean price for 10 tablets/one gram was £25.65 (n = 60). The mean price for an ecstasy tablet fell from £9.46 in 1998 to £7.45 in 2002.

Table 11: Ketamine and ecstasy prices (£) from IDMU surveys, 1998-2002

	Unit			
	Dose/tab	Gram/10 tabs	Ounce/100 tabs	Ecstasy tablet
1998				
N	0	38	4	429
Mean	N/A	15.14	212.50	9.46
1999				
N	73	7	1	541
Mean	12.23	35.71	0	8.38
2000				
N	63	6	2	400
Mean	10.37	51.75	300.00	6.99
2001				
N	21	2	1	111
Mean	13.67	100.00	350.00	6.24
2002				
N	84	7	6	533
Mean	10.93	29.00	176.67	5.47
1998-2002				
N	241	60	14	2014
Mean	1.42	25.65	204.29	7.45

DISCUSSION AND CONCLUSIONS

Introduction to ketamine (and GHB) is more likely to occur at a party rather than at a club (Deehan and Saville 2003a). This is in line with the findings that ketamine is used more to 'chill out' than at parties or dance venues. The research by Bellis et al (2003) suggests that initiation and increased consumption take place in situations away from the constraints of work, study or family. This does not contradict Deehan and Saville's conclusions.

The average age of initiation for ketamine is 21 or 22 years, with nearly half of users having first tried it by the age of 20. There appears to have been an increase in the proportion of users having been under 17 when they experimented with the drug. The average age of first use of ketamine tends to be higher than that for ecstasy. Ketamine use increases with age.

Ketamine is used far less than ecstasy but more than GHB. Ketamine appears to be less attractive than GHB in its appeal to those who have not tried either substance. Many of the respondents to the *Mixmag* survey in 2003 who had tried the drug said they did not want to use it again. The *IDMU* surveys results suggest that ketamine is losing its appeal despite the fact that its lifetime rate appears to have been stable over recent years, and there may have been a modest increase in monthly use amongst clubbers since 2001.

Lifetime use of ketamine amongst those attending club and dance venues ranges between 10 and 47%, and between 13 and 18% amongst those attending pop festivals and other outdoor events. Rates for regular or current users are much lower, typically in the range 4 to 30% according to the *Mixmag* surveys and 2 to 7% according to the *IDMU* surveys.

The type of venue and the type of music played there appear to affect the use of ketamine. For example, lifetime use is likely to be higher amongst those who frequent 'techno' venues rather than attend 'garage' events. O'Hagan (1999) reports lifetime rates of 40% for 'techno' and 11% for 'garage'. This may explain the differences between the *Release* surveys of 1997 and 1999.

Ketamine is reputed to have both less negative effects/problems and less positive effects than ecstasy.   Its main reported positive effects - hallucinations, relaxation, escape from worries, happiness and heightened perception - underline its choice as an aid to 'chilling out'. It appears to occupy a niche spot in a relatively small and stable market; hence the stability in relatively high prices compared to the ever available and increasingly purer and cheaper ecstasy tablet.

The *Release* survey of 1997 reported that one quarter of those who had ever tried ketamine thought it should be illegal compared to two-fifths who had not tried the drug. Overall, only 16% thought it should be illegal to sell ketamine.

Bringing ketamine under the control of the Misuse of Drugs Act 1971 would not deter regular users from consuming the drug, but might reduce experimentation. Neither would it reduce the little diversion that there is from medical or veterinary sources. However, reducing the supply of ketamine to this niche market would probably require changes to existing legislation to close certain loopholes to prevent its illegal importation into the UK.

REFERENCES

Atha, M. and Davis, S. T. (2003). *Ketamine Usage in the UK 1998-2002*. Report commissioned by the Advisory Council on the Misuse of Drugs Ketamine Working Group. Wigan: Independent Drug Monitoring Unit.

Bellis, M.A., Hughes, K., Bennet, A. and Thomson, R. (2003). 'The role of an international nightlife resort in the proliferation of recreational drugs'. *Addiction*, 98(12): 1713-1721.

Bloomfield, R and Kerr, J. (2000). 'Matters of Substance'. *Time Out*, April 12-19 2000, 1547: 18-24.

Craske, V., Stevenson, N., Halfin, M. and French, P. (2000). 'The Mixmag drugs survey 2000'. *Mixmag*, February 2001, 117:54-65.

Craske, V., Robinson, K., Harris, I., Van der Buek, J. and Fielding, A. (2002). 'The Mixmag drug survey 2001'. *Mixmag*, February 2002, 129:84-109.

Craske, V. (2004). 'Drug Britain: A nation of caners - what state are you in?'. *Mixmag*, February 2004, 153:32-35.

CREW 2000. (1997). *Young People's Drug Use at Rave Dance Events*. First draft.

CREW 2000. (2001). *Drug use survey 2001*.
http://www.crew2000.co.uk/drug_use_survey Accessed 31/01/2004 15:30.

Deehan, A. and Saville, E. (2003a). *Recreational drug use among clubbers in the South East of England*. Findings 208. London: Home Office Research Development and Statistics Directorate. Available at:
http://www.homeoffice.gov.uk/rds/pdfs2/r208.pdf

Deehan, A. and Saville, E. (2003b). *Calculating the risk: recreational drug use among clubbers in the South East of England*. On-Line Report 43/03. London: Home Office Research Development and Statistics Directorate. Available at:
http://www.homeoffice.gov.uk/rds/pdfs2/rdsolr4303.pdf

French, P. (2003). 'The Mixmag drug survey 2003'. *Mixmag*, March 2003, 142:74-80.

Ministry. (2000). 'The *Ministry* drug survey', April 2000, 27:60-62.

O'Hagan, C. (1999). British Dance Culture: sub-genres and associated drug use. Unpublished MSc thesis. Liverpool John Moore's University.

Mitcheson, L. (2004). Personal communication to author, 23 January and 4 February.

Release. (1997). *Release drugs and dance survey: An insight into the culture*. London: Release.

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ACMD Technical Committee – Ketamine Report
Importation of Ketamine concealed in Rosewater and other substances
Joe Onofrio
December 2003

Background

During 2001/2002 HMC&E identified an emerging trend relating to the importation of Ketamine in solution as Rosewater. The Ketamine was concealed in parcels labelled as Indian Rosewater and were mainly being imported into the UK using courier parcel companies.

Following a Police operation in early 2002 a number of recipients of Parcels containing Ketamine were identified throughout the UK. During a search of Premises by the Police in London in Feb 2002 a total of 1,198 bottles of Rosewater contain Ketamine (533 Litres) were found.

All the Rosewater had been imported from Goa, India, monies raised from the sale of the Ketamine were sent to India by telegraphic transfer. In this one case some £150,000 was sent back to India from the sale of Ketamine.

HMC&E Seizures

The bulk of the parcels were destined initially to the London area but later the majority of the parcels were for the Nottingham and Derby areas. A number of addresses received multi-parcel deliveries. 9 x 50 Litre parcels were delivered to one address in Derby in one day.

All the parcels were originally declared as solutions such as Rosewater (gifts) and normally contained Indian handicrafts, normally of low value and Rosewater. The parcels contained between 10 to 50 Litres of Rosewater, which were of an identical i.e. White Plastic Bottles with Red Tops wrapped in Adhesive tape around the bottles' neck.

The average cost to send a parcel by a courier company is approximately £100 and £40 by Indian Surface Mail. It's quite clear that a number of parcels have been imported and that importations continue.

A recent search of premises by the Police in Farnham Surrey revealed that at least 75 parcels had been imported successfully to one particular address. The total amount of Rosewater and other solutions containing Ketamine seized since February 2003 is approximately 1000 Litres.

FSS Analysis

Samples of the Rosewater have been submitted to the FSS who confirmed they contained Ketamine. They assess that one litre of Rosewater would yield

between 50-80 Grammes of Ketamine. Extraction of the Ketamine from the Rosewater is apparently a simple process using a microwave.

Street Price

The street price of ketamine is approximately £25 per gram. The cost of use a courier parcel service is the only major outlay for illicit importers of ketamine as the drug itself can be purchase cheaply in developing countries. The current importers of ketamine as are making substantial profits as with other drugs of abuse.

Smuggling Organizers.

The organisers behind this particular smuggling method use fictitious sending addresses and false recipients' names in the UK.

It's suspected that the parcels are sent to addresses in the UK, which are merely drop addresses. The Rosewater is then taken for conversion to Ketamine at various unknown locations. Intelligence sources indicate that this method of importation has been operating for over 12 years.

There is little intelligence known about the organisers themselves. Enquires in India with the Indian Authorities have not yielded any intelligence that would assist us in identifying the suppliers and exporters of Ketamine from India.

Ketamine is not a controlled drug in India.

HMC&E Action

Prior to February 2003 HMC&E had not taken any action against the importation of these parcels but it became clear that the number of parcels was increasing rapidly. As Ketamine is not a controlled Drug HMC&E could not take any action under the Misuse of Drugs Act. Ketamine is subject to the Medicines Control Act 1968. (S 45 refers)

There is no legislation in force prohibiting the importation of Ketamine, the MHRA are of the view that Medicines Act 1968 is not the proper statute to prosecute Ketamine importation. However, ketamine is a Medicinal Product and as it was being concealed in Rosewater and other solutions the view was taken that HMC&E could seize these imported parcels under S167 Customs & Excise Management Act 1979 (I.e. failure to correctly declare the contents of the parcels). The Rosewater contained a medicinal product that was not being declared.
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Joe Onofrio
HM Customs & Excise
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Synthetic Drugs   & Precursor Chemicals.

ACMD Technical Committee – Ketamine Report
Medicines and Healthcare Regulatory Authority (MHRA) contribution
David Robinson
December 2003

A medicinal product is defined in Article 1 of Directive 2001/83 as:

"Any substance or combination of substances presented for treating or preventing disease in human beings.

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological function in human beings is likewise considered a medicinal product."

This definition is part of UK national legislation through the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 (as amended). There is no doubt that a finished product containing ketamine falls within the second limb of the definition because of its pharmacological effect on human beings.

However, the determination as to whether a particular product is a medicinal product is made on a case by case basis. The MHRA has published guidance on the interpretation of the definition in Guidance Note 8 *A guide to what is a medicinal product.* UK medicines legislation does not provide positive lists of substances which are always medicinal. Thus it is possible for a product to avoid the controls of medicines legislation if it is not a form ready for consumption or administration.

Ketamine hydrochloride is a chemical substance that is the active pharmaceutical ingredient used in the formulation of ketamine hydrochloride injection, a medicinal product indicated for the induction and maintenance of anaesthesia.

Ketamine is currently listed in column 1 of schedule 1 of The Prescription Only Medicines (Human Use) Order 1997 [S.I. 1997/1830] as a substance which if included in a medicinal product makes that medicinal product a Prescription only Medicine (POM).

A product containing ketamine would not be regarded as a medicinal product if it could not be administered to or taken by a human being without further processing. Thus if ketamine was mixed with a solvent (for example) and had to be recovered from solution before it could be administered; it would fall outside the definition of a medicinal product and would not, therefore, come under the Medicines Act framework.

A summary of the UK legislation in respect of the manufacturer and distribution of a medicinal product is provided below.

UK legislation relating to medicinal products is in accordance with European Community Directives[1]. Specifically the Medicines Healthcare products Regulatory Agency (MHRA) regulate medicinal products for human use on behalf of the Licensing Authority in accordance with The Medicines for Human use (Marketing Authorisations Etc) Regulations 1994 [S.I. 1994/3144], the Medicines Act 1968 "the Act" and Regulations made thereunder.

Medicines Act
A medicinal product, which is either manufactured or distributed in the UK or is sourced in another Member State or imported from a third country and is placed on the UK market is subject to Regulation 3(1) which provides that '…*no relevant medicinal product shall be placed on the market'* and *'no such product shall be distributed by way of wholesale dealing unless a marketing authorisation in respect of that product has been granted…'.*

The only exemption to this requirement is the supply of *unlicensed* medicinal products (commonly described as 'specials'), under strictly limited conditions. This provides amongst other things, that subject to certain conditions, an unlicensed product may be supplied in response to the order of a doctor, and on his personal responsibility, to meet the special needs of an individual patient. The conditions include that the distributor, manufacturer or importer must be authorised.

The ketamine (if determined as constituting a medicinal product) imported within rosewater bottles does not hold an MA and so is classified as unlicensed. This is an offence.

Sourcing medicinal products
Persons who source either a licensed or unlicensed medicinal product from a licensed manufacturer in another Member State of the European Economic Area (EEA), i.e. the EC plus Norway, Iceland and Liechtenstein, must hold a **Wholesale Dealer's License.**

Persons importing either a licensed or unlicensed medicinal product from a third country i.e. outside the EEA must hold a **Wholesale Dealer's Import License.**

Manufacturers and/or assemblers of a medicinal product are required to hold a **manufacturers licence** to conduct manufacturing and assembly activities. This is required by Section 8(2) of the Act 1968. Manufacturers of 'specials' are required to hold a **manufacturer's 'specials' licence**.

Section 8 (3) of the Act requires a distributor of a medicinal product to hold a wholesale dealer's licence to store and distribute medicinal products.

The act of manufacturing, assembling, and/or sourcing unlicensed ketamine (if determined as constituting a medicinal product) requires specific licences, as noted above. Carrying out any of these activities without the requisite licence is an offence.

The maximum sentence under the Medicines Act 1968 is a two-year custodial sentence and/or unlimited fine.

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[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

ACMD Technical Committee – Ketamine Report
The importation of ketamine – an example of a lacuna between the
misuse of drugs and medicines acts.
R D Treble
January 2004

An extensive range of naturally occurring or synthetic psychoactive substances exists. Many of these substances can be formulated in a variety of different presentations, including solutions of the material in a variety of solvents. The two key legal instruments available to control the importation and distribution of these potentially dangerous substances are the Misuse of Drugs Act and the Medicines Act, and their supporting legislative instruments.

There is also a demand for psychoactive materials by current and potential drug misusers which results in a continuing search, by individuals or groups, for 'loopholes' in, or between, these two acts which might be utilised to permit such materials to reach the marketplace without encountering legal restrictions. It appears that such a loophole has been utilised to permit the importation of ketamine.

The two acts operate in different ways:

> The **Misuse of Drugs Act** is based on lists of named materials, or their derivatives, which are controlled under the act. The lists include both drugs which have medicinal uses and drug which are not permitted for medicinal purposes. Consideration of which materials represent a sufficient danger to society to be brought under control of this act hinges primarily on the nature of the active ingredient, rather than its presentation, although there are some exemptions for formulations containing low levels of the controlled ingredient.

> The **Medicines Act**, by contrast, addresses only those presentations of materials which fall within the definition of a 'medicinal product', as explained by the Medicines and Healthcare Regulatory Agency's (MHRA) submission to the ketamine committee (appendix 5). Psychoactive substances can therefore avoid this control by this act if presented in a form other than a medicinal product.

The combined result is that a psychoactive substance which is not controlled by the Misuse of Drugs Act and which is presented in a form other than a medicinal product can evade control under either act.

In the case of ketamine, as this is not currently controlled under the Misuse of Drugs Act, control can only be applied via the medicines legislation. The importation route which has been identified involves initial conversion overseas of a medicinal product into another form, or at least into another packaging, so that the material enters this country described as something other than a medicinal product. Although there are controls under the

medicines legislation which could be applied if the material were subsequently to be found being offered for supply, the importers have effectively evaded the act's controls on importation by presenting it in a form other than a medicinal product.

The current considerations of ketamine have therefore identified a scenario whereby psychoactive pharmaceutical material not listed in the Misuse of Drugs Act can be imported without restriction if it is brought into the country in a form outwith the definition of a 'medicinal product'. Once imported, it can then disappear into the 'underground' distribution system to be reformulated into presentations which can be used by 'recreational' users.

Admittedly, if the degree of misuse becomes significant, it can be expected that, as in the case of ketamine, the ACMD will be asked to consider the addition of the substance to the list of materials controlled by the Misuse of Drugs Act. If this is decided on, legal restrictions on the importation of the material, in whatever form, are then created and the loophole is closed. However, in the interim period, or should it be decided that the harm to society is not sufficient to justify addition to the Misuse of Drugs Act lists, there are no effective powers to prevent the large scale importation of a psychoactive, and potentially harmful, material.

Potential approaches to effect closure of this loophole could include establishing emergency provisions under the Misuse of Drugs Act to control importations for a time sufficient to permit evaluation by the ACMD, or amendment of the medicines legislation to enact controls over the importation of the active ingredients of medicinal products, in whatever form. However, both these approaches would appear to require primary legislation, and are therefore unlikely to be rapidly effective.

ACMD Technical Committee – Ketamine Report
Medical practice contribution
Dr Ian Power
December 2003

KETAMINE HYDROCHLORIDE

Ketamine hydrochloride is a phencyclidine derivative introduced to the market in 1965. It is a powerful intravenous anaesthetic agent that produces a state of 'dissociative anaesthesia'. When given at low, sub-anaesthetic, doses ketamine is a very powerful analgesic for acute, chronic or cancer pain.

Physical characteristics
Ketamine is soluble in water and is presented in a solution of sodium chloride at 10 mg/kg, which is isotonic. Higher concentrations are also available in multi-dose phials containing preservatives: 50 or 100 mg/kg.

Ketamine is a very lipid soluble drug and after intravenous injection it produces anaesthesia in 30 to 60 seconds, and this lasts for 10 to 15 minutes. If given by intramuscular injection at similar doses, it produces anaesthesia within 3 to 4 minutes, and this last for 15 to 25 minutes. When given in lower doses (see below) intravenous, subcutaneous, or intramuscular injection can produce analgesia, with minimal sedation.

EEG changes produced by administration of ketamine are different from those seen with other intravenous anaesthetics. There is an increase in cerebral metabolic rate, with a consequent rise in cerebral blood flow and intracranial pressure. Ketamine also increases arterial blood pressure (by up to 25%), hear rate, cardiac output and myocardial oxygen consumption. The heart becomes more sensitive to circulating catochlamines. In general, ventilation is well maintained after a dose of ketamine, although there is always the risk of a period of apnoea after administration, and a loss of upper airway reflexes. Notably, bronchial muscle tone falls. Other features seen after ketamine administration includes an increase in skeletal muscle tone; spontaneous movements; and a rise of salivation.

Doses
For anaesthesia an average intravenous dose of 2 mg/kg is required. To maintain anaesthesia, additional doses of 1 to 1½ mg/kg are required about every 5 to 10 minutes. When given intramuscularly for anaesthesia, the ketamine dose required is 8 to 10 mg/kg.

Adverse effects
Upon emergence from anaesthesia delirium, nightmares and hallucinations are common, especially in adults. In some patients hypertension and tachycardia may be significant. Other patients may suffer from excessive salivation and intracranial pressure increases.

<u>Indications</u>
A. Anaesthesia
1. High-risk patients. Ketamine is a very useful drug in patients who have a low blood pressure.
2. Paediatric anaesthesia. Ketamine remains a useful drug in children, where the risk of emergence hallucinations is reduced. Ketamine especially has found a place in anaesthesia for short procedures such as minor surgery, some investigations, radiotherapy, and ophthalmic examinations.
3. Anaesthesia in difficult situations. Ketamine can be very useful for an anaesthetic at the site of accidents when life-saving procedures have to be performed urgently.
4. In some developing countries, ketamine is used extensively for anaesthesia, perhaps because of the shortage of other drugs and trained anaesthetists.

B. Analgesia for acute pain
Ketamine is a very useful drug when given in sub-anaesthetic doses, to produce analgesia for painful procedures. For example, ketamine is used to provide analgesia for patients who have suffered severe burns and require daily dressing changes. Such dressing changes can be extremely painful, producing the stress that cannot be controlled with opioids alone. In this situation ketamine is often used to produce intense analgesia with some sedation to allow these dressing changes. Similarly, ketamine is sometimes used to produce short-term pain relief in patients with fractures, including fracture neck of femur.

C. Chronic Pain
When given in sub-anaesthetic doses the NMDA receptor blocking properties of ketamine can be very useful for the prevention and treatment of chronic pain. That is, there is some evidence to suggest that ketamine may be useful in preventing the features of central sensitisation and opioid tolerance. This is important because a significant number of individuals develop significant chronic pain states, often with a neuropathic basis, after surgery or trauma. The most obvious example is post-amputation, where patients may suffer the distress of phantom limb pain in up to 70% of cases. Much current research is being produced to look at the possibilities of using drugs such as ketamine to prevent the establishment of such chronic pain states.

In addition to the possibility of using ketamine to prevent chronic pain, its role in the treatment of neuropathic pain is well established. Neuropathic pain differs from 'nociceptive' pain, in that the clinical features include: increasing pain after healing; burning or shooting pain; alodinea (severe pain in response to minor stimulation); dysasthesias (abnormal sensations); spontaneous pain; pain spreading beyond the injured area; and a relative refractory response to opioid therapy. In low doses, ketamine can be used to alleviate such pain.

Certain patients suffering chronic pain, often develop 'opioid-resistant pain'. This means that their pain, which was previously controlled successfully by opioids, now becomes less well treated. It has been shown in a number of situations that the administration of ketamine in such a situation may restore the opioid responsiveness of their pain. This is extremely valuable in some chronic pain sufferers, but is perhaps especially relevant in individuals suffering cancer pain where a prolonged response to a relatively short-term infusion of ketamine has been demonstrated.

Doses for analgesia

For the relief of pain, the doses of ketamine required are much lower than for anaesthesia. For example, for the treatment of neuropathic pain the dose given by infusion (intravenous or subcutaneous) is of the order of 5 to 20 mg/hour. Sometimes, to check that the pain state is responsiveness to ketamine, an infusion of 0.15 mg/kg is given over 20 minutes. This is used to test the patients responsiveness to the drug, and thereafter much lower doses may be considered to control the patients pain in the long term.

Certain patients suffering chronic pain, perhaps most notably those suffering cancer pain, may be sent home on an infusion of ketamine either by the subcutaneous or intravenous route.

Unfortunately, ketamine has an oral bioavailabilty of around 10 to 20% with a marked inter-patient variability. Therefore the oral doses required to control a patient's pain may be significantly higher than the intravenous or subcutaneous doses.

Of course, the remaining concern in treating patients at home with this drug is the abuse potential of ketamine.

Summary

Ketamine has significant viable anaesthetic and analgesic properties. While its use in anaesthetic practice is diminishing as newer induction agents have been developed, it is still used in certain important situations. For the treatment of acute pain, the control of chronic pain, and the potential prevention of chronic pain states, it is likely that the use of ketamine will increase. Certain patients may benefit greatly from being treated by continuous intravenous or subcutaneous infusions of ketamine at home.

ACMD Technical Committee – Ketamine Report
The role of ketamine in veterinary medicine
Dr Polly Taylor
December 2003

Background

Veterinary medicine, in contrast with human medicine, is concerned with a wide range of different species, both domestic and exotic. There is considerable knowledge of species specific physiology and pharmacology in domestic animals, allowing for appropriate adjustment for both species and breed variations. However, in non-domestic species there may be little knowledge of specific physiology and pharmacology; even normal values for vital cardiovascular and respiratory function may be unknown. This applies to a wide range of animals, and includes not only mammals but also birds and reptiles. The problems of anaesthesia of unhandled, wild and free ranging animals are also exacerbated by the stress of capture, which may elicit a marked "fight-flight' response. Convalescence and postoperative care are also difficult to provide. In such animals anaesthesia is usually required for diagnosis and treatment, rather than the case in man and domestic animals, where a preoperative examination ensures the patient is fit for anaesthesia.

It is not uncommon in routine clinical veterinary treatment that the veterinarian is the anaesthetist, the nurse and the surgeon, and those operating conditions are less than ideal. "Field surgery" is often required for large animals that may be difficult or uneconomical to transport to a suitable operating theatre. Hence availability of a predictable anaesthetic that is straightforward to use is essential.

Ketamine

Ketamine is widely used in veterinary medicine as an anaesthetic that is relatively safe and behaves in a similar manner in most species, including mammals, birds and reptiles. Ketamine is a dissociative anaesthetic, which in comparison with most other anaesthetic agents, causes very little cardiovascular or respiratory depression, allows a wide dose range to be used (high therapeutic index; 2-50 mg/kg) and can be given by many routes.

No anaesthetic is safe, the very process of anaesthesia inherently carries the risk of death, usually through cardiac or respiratory depression, or from physical injury during induction or recovery. However, as a result of the limited inherent cardio-respiratory depressant effects of ketamine and its very high therapeutic index, ketamine is safer than many. It is of particular value where there is limited knowledge of the normal physiology of the species and of the animal's health status. In many ways, ketamine can be regarded as the "if in doubt - use it" anaesthetic

Current veterinary use of ketamine

Routine anaesthesia of domestic species

Ketamine is widely used for induction as well as for maintenance of anaesthesia for relatively short procedures. It is commonly used in combination with sedatives such as the benzodiazepines and the alpha-2 adrenoceptor agonists. Use of ketamine in such combinations produces better relaxation and allows smaller doses to be used to produce more conventional anaesthesia than ketamine alone. Ketamine is also used in high risk cases because of its limited cardiodepressant properties.

Ketamine is used for routine surgical procedures such as ovarohysterectomy in <u>dogs</u>, always in combination with sedatives. In such cases it is used for induction before maintenance with an inhaled volatile agent or a single induction dose may be sufficient for the whole procedure. Ketamine is also used in high risk surgical canine cases, particularly where anaesthesia is required in the systemically ill.

Ketamine is now increasingly used as an analgesic in dogs. Both professional and public appreciation of the need for good pain management of animals has led to a range of new approaches to analgesia in animals. It is now widely accepted that good pain control is essential for animals undergoing surgery or that have suffered trauma or chronic disease. Ketamine given by infusion (2-10 µg/kg/min) has proved efficacious during and after major surgery in dogs. A single small dose (around 0.5 mg/kg) given before surgery has been shown to improve post operative pain control in this species.

<u>Cats</u> are now the most common domestic pet (several million in the UK alone), and most undergo at least one surgery in their lifetime, for neutering. Ketamine has a very long and successful history as an anaesthetic in cats. Even well humanised domestic cats may be difficult to handle for intravenous injection and the intramuscular route is commonly used, well suited to ketamine, particularly in combination with sedatives as described above. Ketamine is also beginning to be used for analgesia in this species as in dogs.

<u>Horses</u> have a high risk of anaesthetic-associated death (1 in 100), probably at least partly due to the marked anaesthetic-induced cardiovascular depression seen in this species. There is also a considerable risk of serious injury during induction and recovery when this large and heavy animal must lie down and stand up. Ketamine is generally preferred over barbiturates and other injectable anaesthetics in this species. It is widely used for induction of anaesthesia before maintenance with a volatile agent as well as for total intravenous anaesthesia, particularly for short procedures such as castration "in the field".

<u>Farm animals</u> may not often undergo general anaesthesia but have a very special need for ketamine as there are very few drugs licensed for food animals. Under European law, for a drug to receive market authorisation for use in a food animal, it must have had minimum residue limits (MRL) established that are deemed safe for human consumption. Establishment of MRL is a costly process and most anaesthetic drugs have not undergone the

procedure. Ketamine is considered sufficiently safe to be included in "Annexe 2" where an MRL is not required. Drugs in this list may be used in a food animal as long as it is not sent for human consumption within the statutory withdrawal period of 28 days. Hence ketamine is the only injectable anaesthetic that can legally be used in food animals. On welfare grounds alone it is essential that a general anaesthetic can be given when necessary, hence availability of ketamine is vital for these animals.

Laboratory animal anaesthesia
Ketamine has a long history of successful and frequent use in laboratory animal anaesthesia and in children's "small furry" pets. Ketamine is of particular value in these small species as there is usually no easy intravenous access, the range of species is considerable, the actual dose is critical as very low body weight leaves little margin for error.

There is particular need to ensure the welfare of animals used in scientific procedures, particularly when there is no benefit to the animal involved. Public concern with humane use of such animals is entirely justifiable and must be respected. The UK has an unsurpassed reputation for ethical and humane handling of animals used in scientific procedures and this must be maintained at all costs. Ketamine is probably the single most important injectable anaesthetic for laboratory animals and has the added benefit of providing good analgesia as well as anaesthesia. It is essential that ketamine is available for the many thousands of laboratory animals used each year in the UK.

Wild, zoo and exotic animal anaesthesia
Ketamine is the single most important anaesthetic for wild and exotic animals, including birds and reptiles. It is used for capture where the ability to use the intramuscular route is essential and where precise knowledge of body weight is not essential. Lack of marked cardiovascular and respiratory depression is also an important consideration under these circumstances.

Ketamine and analgesia
Recent increased understanding of the physiology of pain and development of better ways to manage it has revolutionised pain management in both man and animals. Ketamine's clinical pharmacology in pain management has led to an exciting and effective new role for this old drug, with very considerable benefits to animal welfare, particularly where the alternative is likely to be a schedule 2 controlled opiate. Western concern with welfare of animals and professional appreciation of the benefits of good welfare and improvement in post operative recovery make pain management the fastest growing and most topical area in veterinary medicine.

Ketamine is used to provide analgesia through low single doses (less than 1 mg/kg), intravenous infusions, epidural injection and as a sedative in treatment of animals after physical injury.

Potential effects of controlling ketamine

Ketamine has a major role in veterinary medicine on grounds of animal welfare and suitability for a wide range of species and conditions. Increased statutory control of ketamine, above a class C drug, would be likely to have deleterious effects on animal welfare as the drug would become difficult to use, particularly in the less than ideal "field" conditions where it is perhaps of most value with fewest alternatives. The schedule applied to ketamine would have a variable effect on practice.

Ketamine is voluntarily kept under secure conditions in most veterinary practices, and the most recent RCVS Guide to Professional Conduct recommends that it should be kept in the controlled drugs cupboard and an informal register kept. In this way ketamine is well cared for, but unconventional needs for the emergency, high risk and field case are unhindered. Current statutory control of opioids undoubtedly restricts their use in animals who would benefit from them. Mu-agonist opioids are often withheld or simply not even purchased because of the paperwork. Recent changes for buprenorphine have discouraged its use.

To summarise:
- Ketamine is the single most universally-used veterinary drug
- Ketamine is the only suitable anaesthetic under many conditions encountered
- Restrictions would incur time & effort leading to limited use of ketamine and inevitable detriment to animal welfare
- Restrictions would lead to difficulties for all types of field use
- Appropriate, informal, self-regulating control of ketamine use and storage in veterinary practices is effective
- The RCVS & BVA encourage good codes of conduct
- Regular BVA/SPVS pharmacy courses teach good pharmacy practice
- There is already a legal requirement to record batch numbers of all drugs as they are administered or dispensed.
- Health & Safety Regulations & risk assessment ensure that local rules are drawn up and followed.