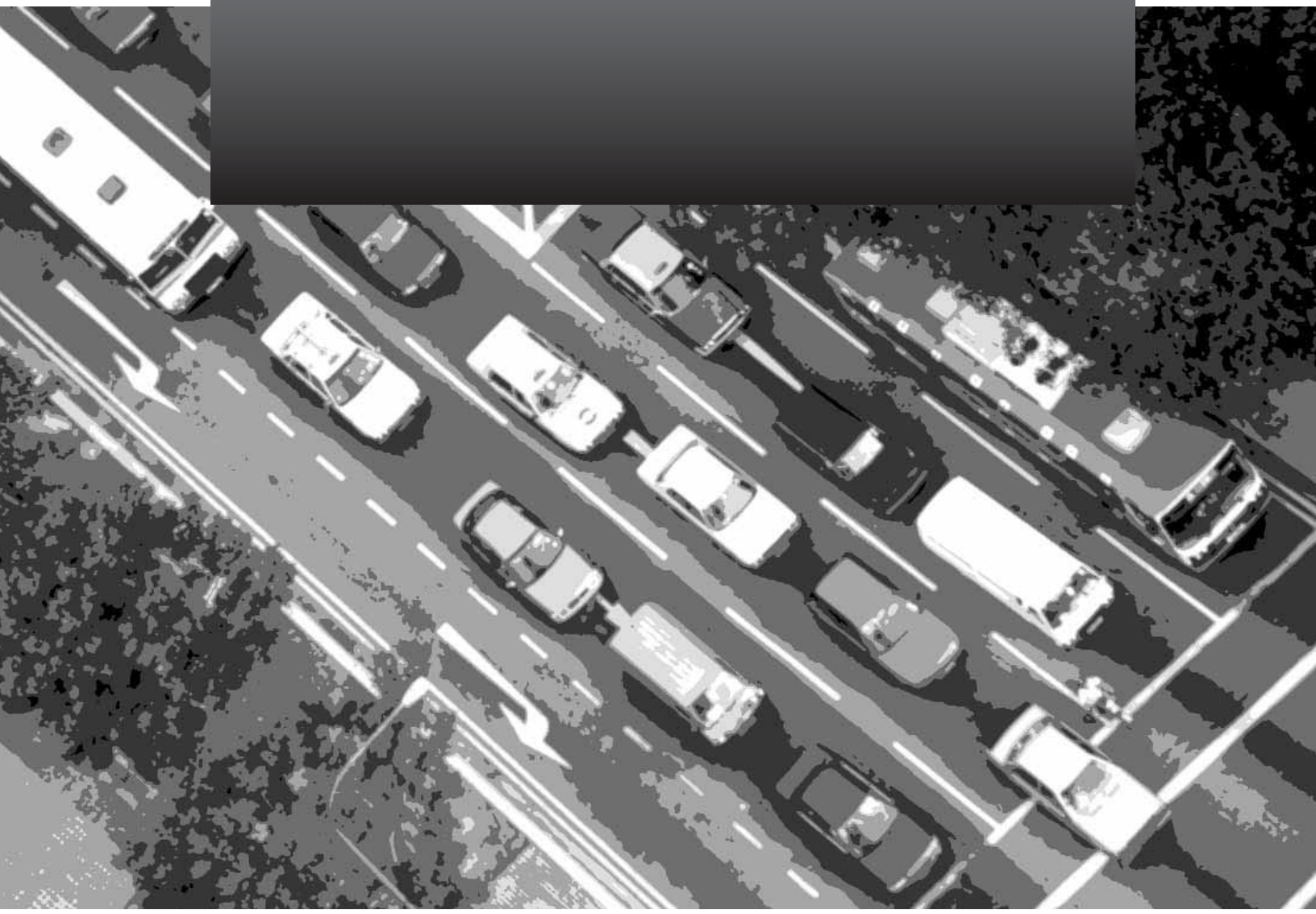
NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION

Drugs and Human Performance Fact Sheets



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16. Abstract

A panel of international experts on drug-impaired driving met in Seattle during August 2000 to review developments in the field of drugs and human performance over the last 10 years; to identify the specific effects that both illicit and prescription drugs have on driving; and to develop guidance for others when dealing with drug-impaired driving problems. Delegates represented the fields of psychopharmacology, behavioral psychology, drug chemistry, forensic toxicology, medicine, and law enforcement experts trained in the recognition of drug effects on drivers in the field.

These Fact Sheets represent the conclusions of the Panel and include the state of current scientific knowledge in the area of drugs and human performance for the 16 drugs selected for evaluation. The selected drugs include over-the-counter medications such as dextromethorphan and diphenhydramine; prescription medications such as carisoprodol, diazepam and zolpidem; and abused and/or illegal drugs such as cocaine, GHB, ketamine, LSD, marijuana, methadone, methamphetamine, MDMA, morphine, PCP and toluene.

Keyword continuation: illicit and licit drugs and traffic safety, drugs and driving, drug-impaired driving.

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Introduction

The use of psychoactive drugs followed by driving has been an issue of continual concern to law enforcement officers, physicians, attorneys, forensic toxicologists and traffic safety professionals in the U.S. and throughout the world. At issue are methods for identifying the impaired driver on the road, the assessment and documentation of the impairment they display, the availability of appropriate chemical tests, and the interpretation of the subsequent results. A panel of international experts on drug-related driving issues met to review developments in the field of drugs and human performance over the last 10 years; to identify the specific effects that both illicit and prescription drugs have on driving; and to develop guidance for others when dealing with drug-impaired driving problems.

This publication is based on the deliberations of the International Consultative Panel on Drugs and Driving Impairment held in Seattle, WA in August 2000. This meeting was sponsored by the National Safety Council, Committee on Alcohol and other Drugs; the State of Washington Traffic Safety Commission; and the National Highway Traffic Safety Administration. Delegates represented the fields of psychopharmacology, behavioral psychology, drug chemistry, forensic toxicology, medicine, and law enforcement experts trained in the recognition of drug effects on drivers in the field. The Fact Sheets reflect the conclusions of the Panel and have been designed to provide practical guidance to toxicologists, pharmacologists, law enforcement officers, attorneys and the general public on issues related to drug impaired driving.

Sixteen drugs were selected for review and include over-the-counter medications, prescription drugs, and illicit and/or abused drugs. The selected drugs are cannabis/marijuana, carisoprodol, cocaine, dextromethorphan, diazepam, diphenhydramine, gamma-hydroxybutyrate, ketamine, lysergic acid diethylamide, methadone, methamphetamine/amphetamine, methylenedioxymethamphetmaine, morphine/heroin, phencyclidine, toluene, and zolpidem.

The Fact Sheets are based on the state of current scientific knowledge and represent the conclusions of the panel. They have been designed to provide practical guidance to toxicologists, pharmacologists, law enforcement officers, attorneys and the general public to use in the evaluation of future cases. Each individual drug Fact Sheet covers information regarding drug chemistry, usage and dosage information, pharmacology, drug effects, effects on driving, drug evaluation and classification (DEC), and the panel's assessment of driving risks. A list of key references and recommended reading is also provided for each drug. Readers are encouraged to use the Fact Sheets in connection with the other cited impaired driving-related texts.

The information provided is uniform for all the Fact Sheets and provides details on the physical description of the drug, synonyms, and pharmaceutical or illicit sources; medical and recreational uses, recommended and abused doses, typical routes of administration, and potency and purity; mechanism of drug action and major receptor sites; drug absorption, distribution, metabolism and elimination data; blood and urine concentrations; psychological and physiological effects, and drug interactions; drug

effects on psychomotor performance effects; driving simulator and epidemiology studies; and drug recognition evaluation profiles. Each Fact Sheet concludes with general statements about the drugs' ability to impair driving performance. The authors strongly believe that all the above information needs to be taken into account when evaluating a drug.

Case interpretation can be complicated by a number of factors and one of the main limitations of the Fact Sheets is that they primarily relate to single drug use. Other factors which influence the risk of effects on driving for any drug include the dose, the dosage frequency, acute and residual effects, chronic administration, route of administration, the concentration of the drug at the site of action, idiosyncrasies of metabolism, drug tolerance or hypersensitivity, and the combined effects of the drug with other drugs or alcohol, to name but a few.

Individual Fact Sheets

Cannabis/Marijuana
Carisoprodol (and Meprobamate)
Cocaine
Dextromethorphan
Diazepam
Diphenhydramine
Gamma-Hydroxybutyrate (GHB, GBL, and 1,4-BD)
Ketamine
Lysergic acid diethylamide (LSD)
Methadone
Methamphetamine (and Amphetamine)
Methylenedioxymethamphetamine (MDMA, Ecstasy)
Morphine (and Heroin)
Phencyclidine (PCP)
Toluene
Zolpidem (and Zaleplon, Zopiclone)

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Disclaimer

The information contained in the Drugs and Human Performance Fact Sheets represents the views of the contributors and not necessarily those of their place of employment or the National Highway Traffic Safety Administration.

Cannabis / Marijuana (Δ^9-Tetrahydrocannabinol, THC)

Marijuana is a green or gray mixture of dried shredded flowers and leaves of the hemp plant *Cannabis sativa*. Hashish consists of resinous secretions of the cannabis plant. Dronabinol (synthetic THC) is a light yellow resinous oil.

Synonyms: Cannabis, marijuana, pot, reefer, buds, grass, weed, dope, ganja, herb, boom, gangster, Mary Jane, sinsemilla, shit, joint, hash, hash oil, blow, blunt, green, kilobricks, Thai sticks; Marinol®

Source: Cannabis contains chemicals called cannabinoids, including cannabinol, cannabidiol, cannabinolidic acids, cannabigerol, cannabichromene, and several isomers of tetrahydrocannabinol (THC). One of these isomers, Δ^9-THC, is believed to be responsible for most of the characteristic psychoactive effects of cannabis. Marijuana refers to the leaves and flowering tops of the cannabis plant; the buds are often preferred because of their higher THC content. Hashish consists of the THC-rich resinous secretions of the plant, which are collected, dried, compressed and smoked. Hashish oil is produced by extracting the cannabinoids from plant material with a solvent. In the U. S. , marijuana, hashish and hashish oil are Schedule I controlled substances. Dronabinol (Marinol®) is a Schedule III controlled substance and is available in strengths of 2.5, 5 or 10 mg in round, soft gelatin capsules.

Drug Class: *Cannabis/Marijuana*: spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen. *Dronabinol*: appetite stimulant, antiemetic.

Medical and Recreational Uses: *Medicinal*: Indicated for the treatment of anorexia associated with weight loss in patients with AIDS, and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy. *Recreational*: Marijuana is used for its mood altering effects, euphoria, and relaxation. Marijuana is the most commonly used illicit drug throughout the world.

Potency, Purity and Dose: THC is the major psychoactive constituent of cannabis. Potency is dependent on THC concentration and is usually expressed as %THC per dry weight of material. Average THC concentration in marijuana is 1-5%, hashish 5-15%, and hashish oil ≥ 20%. The form of marijuana known as *sinsemilla* is derived from the unpollinated female cannabis plant and is preferred for its high THC content (up to 17% THC). Recreational doses are highly variable and users often titer their own dose. A single intake of smoke from a pipe or joint is called a hit (approximately 1/20th of a gram). The lower the potency or THC content the more hits are needed to achieve the desired effects; 1-3 hits of high potency sinsemilla is typically enough to produce the desired effects. In terms of its psychoactive effect, a drop or two of hash oil on a cigarette is equal to a single “joint” of marijuana. Medicinally, the initial starting dose of Marinol® is 2.5 mg, twice daily.

Route of Administration: Marijuana is usually smoked as a cigarette (‘joint’) or in a pipe or bong. Hollowed out cigars packed with marijuana are also common and are called

`. Joints and blunts are often laced with adulterants including PCP or crack cocaine. Joints can also be dipped in liquid PCP or in codeine cough syrup. Marijuana is also orally ingested.

Pharmacodynamics: THC binds to cannabinoid receptors and interferes with important endogenous cannabinoid neurotransmitter systems. Receptor distribution correlates with brain areas involved in physiological, psychomotor and cognitive effects. Correspondingly, THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature.

Pharmacokinetics: Absorption is slower following the oral route of administration with lower, more delayed peak THC levels. Bioavailability is reduced following oral ingestion due to extensive first pass metabolism. Smoking marijuana results in rapid absorption with peak THC plasma concentrations occurring prior to the end of smoking. Concentrations vary depending on the potency of marijuana and the manner in which the drug is smoked, however, peak plasma concentrations of 100-200 ng/mL are routinely encountered. Plasma THC concentrations generally fall below 5 ng/mL less than 3 hours after smoking. THC is highly lipid soluble, and plasma and urinary elimination half-lives are best estimated at 3-4 days, where the rate-limiting step is the slow redistribution to plasma of THC sequestered in the tissues. Shorter half-lives are generally reported due to limited collection intervals and less sensitive analytical methods. Plasma THC concentrations in occasional users rapidly fall below limits of quantitation within 8 to 12 h. THC is rapidly and extensively metabolized with very little THC being excreted unchanged from the body. THC is primarily metabolized to 11-hydroxy-THC which has equipotent psychoactivity. The 11-hydroxy-THC is then rapidly metabolized to the 11-nor-9-carboxy-THC (THC-COOH) which is not psychoactive. A majority of THC is excreted via the feces (~65%) with approximately 30% of the THC being eliminated in the urine as conjugated glucuronic acids and free THC hydroxylated metabolites.

Molecular Interactions / Receptor Chemistry: THC is metabolized via cytochrome P450 2C9, 2C11, and 3A isoenzymes. Potential inhibitors of these isoenzymes could decrease the rate of THC elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.55

Interpretation of Blood Concentrations: It is difficult to establish a relationship between a person's THC blood or plasma concentration and performance impairing effects. Concentrations of parent drug and metabolite are very dependent on pattern of use as well as dose. THC concentrations typically peak during the act of smoking, while peak 11-OH THC concentrations occur approximately 9-23 minutes after the start of smoking. Concentrations of both analytes decline rapidly and are often < 5 ng/mL at 3 hours. Significant THC concentrations (7 to 18 ng/mL) are noted following even a single puff or hit of a marijuana cigarette. Peak plasma THC concentrations ranged from 46-188 ng/mL in 6 subjects after they smoked 8.8 mg THC over 10 minutes. Chronic users can have mean plasma levels of THC-COOH of 45 ng/mL, 12 hours after use; corresponding

THC levels are, however, less than 1 ng/mL. Following oral administration, THC concentrations peak at 1-3 hours and are lower than after smoking. Dronabinol and THC-COOH are present in equal concentrations in plasma and concentrations peak at approximately 2-4 hours after dosing.

It is inadvisable to try and predict effects based on blood THC concentrations alone, and currently impossible to predict specific effects based on THC-COOH concentrations. It is possible for a person to be affected by marijuana use with concentrations of THC in their blood below the limit of detection of the method. Mathematical models have been developed to estimate the time of marijuana exposure within a 95% confidence interval. Knowing the elapsed time from marijuana exposure can then be used to predict impairment in concurrent cognitive and psychomotor effects based on data in the published literature.

Interpretation of Urine Test Results: Detection of total THC metabolites in urine, primarily THC-COOH-glucuronide, only indicates prior THC exposure. Detection time is well past the window of intoxication and impairment. Published excretion data from controlled clinical studies may provide a reference for evaluating urine cannabinoid concentrations; however, these data are generally reflective of occasional marijuana use rather than heavy, chronic marijuana exposure. It can take as long as 4 hours for THC-COOH to appear in the urine at concentrations sufficient to trigger an immunoassay (at 50ng/mL) following smoking. Positive test results generally indicate use within 1-3 days; however, the detection window could be significantly longer following heavy, chronic, use. Following single doses of Marinol®, low levels of dronabinol metabolites have been detected for more than 5 weeks in urine. Low concentrations of THC have also been measured in over-the-counter hemp oil products – consumption of these products may produce positive urine cannabinoid test results.

Effects: Pharmacological effects of marijuana vary with dose, route of administration, experience of user, vulnerability to psychoactive effects, and setting of use.
Psychological: At recreational doses, effects include relaxation, euphoria, relaxed inhibitions, sense of well-being, disorientation, altered time and space perception, lack of concentration, impaired learning and memory, alterations in thought formation and expression, drowsiness, sedation, mood changes such as panic reactions and paranoia, and a more vivid sense of taste, sight, smell, and hearing. Stronger doses intensify reactions and may cause fluctuating emotions, flights of fragmentary thoughts with disturbed associations, a dulling of attention despite an illusion of heightened insight, image distortion, and psychosis.
Physiological: The most frequent effects include increased heart rate, reddening of the eyes, dry mouth and throat, increased appetite, and vasodilatation.

Side Effect Profile: Fatigue, paranoia, possible psychosis, memory problems, depersonalization, mood alterations, urinary retention, constipation, decreased motor coordination, lethargy, slurred speech, and dizziness. Impaired health including lung damage, behavioral changes, and reproductive, cardiovascular and immunological effects have been associated with regular marijuana use. Regular and chronic marijuana smokers may have many of the same respiratory problems that tobacco smokers have (daily cough

and phlegm, symptoms of chronic bronchitis), as the amount of tar inhaled and the level of carbon monoxide absorbed by marijuana smokers is 3 to 5 times greater than among tobacco smokers. Smoking marijuana while shooting up cocaine has the potential to cause severe increases in heart rate and blood pressure.

Duration of Effects: Effects from smoking cannabis products are felt within minutes and reach their peak in 10-30 minutes. Typical marijuana smokers experience a high that lasts approximately 2 hours. Most behavioral and physiological effects return to baseline levels within 3-5 hours after drug use, although some investigators have demonstrated residual effects in specific behaviors up to 24 hours, such as complex divided attention tasks. Psychomotor impairment can persist after the perceived high has dissipated. In long term users, even after periods of abstinence, selective attention (ability to filter out irrelevant information) has been shown to be adversely affected with increasing duration of use, and speed of information processing has been shown to be impaired with increasing frequency of use. Dronabinol has an onset of 30-60 minutes, peak effects occur at 2-4 hours, and it can stimulate the appetite for up to 24 hours.

Tolerance, Dependence and Withdrawal Effect: Tolerance may develop to some pharmacological effects of dronabinol. Tolerance to many of the effects of marijuana may develop rapidly after only a few doses, but also disappears rapidly. Marijuana is addicting as it causes compulsive drug craving, seeking, and use, even in the face of negative health and social consequences. Additionally, animal studies suggests marijuana causes physical dependence. A withdrawal syndrome is commonly seen in chronic marijuana users following abrupt discontinuation. Symptoms include restlessness, irritability, mild agitation, hyperactivity, insomnia, nausea, cramping, decreased appetite, sweating, and increased dreaming.

Drug Interactions: Cocaine and amphetamines may lead to increased hypertension, tachycardia and possible cardiotoxicity. Benzodiazepines, barbiturates, ethanol, opioids, antihistamines, muscle relaxants and other CNS depressants increase drowsiness and CNS depression. When taken concurrently with alcohol, marijuana is more likely to be a traffic safety risk factor than when consumed alone.

Performance Effects: The short term effects of marijuana use include problems with memory and learning, distorted perception, difficultly in thinking and problem-solving, and loss of coordination. Heavy users may have increased difficulty sustaining attention, shifting attention to meet the demands of changes in the environment, and in registering, processing and using information. In general, laboratory performance studies indicate that sensory functions are not highly impaired, but perceptual functions are significantly affected. The ability to concentrate and maintain attention are decreased during marijuana use, and impairment of hand-eye coordination is dose-related over a wide range of dosages. Impairment in retention time and tracking, subjective sleepiness, distortion of time and distance, vigilance, and loss of coordination in divided attention tasks have been reported. Note however, that subjects can often “pull themselves together” to concentrate on simple tasks for brief periods of time. Significant performance impairments are

usually observed for at least 1-2 hours following marijuana use, and residual effects have been reported up to 24 hours.

***Effects on Driving*:** The drug manufacturer suggests that patients receiving treatment with Marinol® should be specifically warned not to drive until it is established that they are able to tolerate the drug and perform such tasks safely. Epidemiology data from road traffic arrests and fatalities indicate that after alcohol, marijuana is the most frequently detected psychoactive substance among driving populations. Marijuana has been shown to impair performance on driving simulator tasks and on open and closed driving courses for up to approximately 3 hours. Decreased car handling performance, increased reaction times, impaired time and distance estimation, inability to maintain headway, lateral travel, subjective sleepiness, motor incoordination, and impaired sustained vigilance have all been reported. Some drivers may actually be able to improve performance for brief periods by overcompensating for self-perceived impairment. The greater the demands placed on the driver, however, the more critical the likely impairment. Marijuana may particularly impair monotonous and prolonged driving. Decision times to evaluate situations and determine appropriate responses increase. Mixing alcohol and marijuana may dramatically produce effects greater than either drug on its own.

DEC Category: Cannabis

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence present; pupil size normal to dilated; reaction to light normal to slow; pulse rate elevated; blood pressure elevated; body temperature normal to elevated. Other characteristic indicators may include odor of marijuana in car or on subject's breath, marijuana debris in mouth, green coating of tongue, bloodshot eyes, body and eyelid tremors, relaxed inhibitions, incomplete thought process, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: Low doses of THC moderately impair cognitive and psychomotor tasks associated with driving, while severe driving impairment is observed with high doses, chronic use and in combination with low doses of alcohol The more difficult and unpredictable the task, the more likely marijuana will impair performance.

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Carisoprodol (and Meprobamate)

Carisoprodol is a white, crystalline powder. Meprobamate is a white powder. Both are available in tablet form.

Synonyms: *Carisoprodol*: N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate; Soma®, Sodol®, Soprodol®, Soridol®. *Meprobamate*: Miltown®, Equanil®, Equagesic®, Meprospan®.

Source: Carisoprodol and meprobamate are available by prescription only. Carisoprodol itself is not a federally scheduled compound, while meprobamate is a Schedule IV drug. Soma® is available as a 350 mg strength round, white tablet; Soma® Compound is a 250 mg strength two-layered, white and light orange round tablet (also contains aspirin); and Soma® Compound with Codeine is a 250 mg strength two-layered, white and yellow oval tablet (also contains aspirin and codeine phosphate) and is a schedule III controlled substance. Miltown® is available as a 200 mg and 400 mg strength white tablet; Equanil® is a 200 mg and 400 mg strength tablet; and Equagesic® is a 200 mg strength two-layered, pink and yellow, round tablet (also contains aspirin).

Drug Class: *Carisoprodol*: muscle relaxant, CNS depressant; *Meprobamate*: antianxiety, CNS depressant.

Medicinal and Recreational Uses: Carisoprodol is a centrally acting skeletal muscle relaxant prescribed for the treatment of acute, musculoskeletal pain. Meprobamate is a major metabolite of carisoprodol, and is a CNS depressant in its own right, indicated for the management of anxiety disorders or for short-term treatment of anxiety symptoms. Use of these drugs begins with prescription for muscular pain or anxiety, and abuse develops for their sedative-hypnotic effects, resulting in increased dosage without medical advice, or continued use after pain or anxiety has subsided.

Potency, Purity and Dose: Carisoprodol is present as a racemic mixture. During treatment, the recommended dose of carisoprodol is for one 350 mg tablet taken three times daily and at bedtime (1400 mg/day). The usual dose for meprobamate is one 400 mg taken four times daily, or daily divided doses of up to 2400 mg. To control chronic pain, carisoprodol is often taken concurrently with other drugs, particularly opiates, benzodiazepines, barbiturates, and other muscle relaxants.

Route of Administration: Oral.

Pharmacodynamics: The pharmacological effects of carisoprodol appear to be due to the combination of the effects of carisoprodol and its active metabolite, meprobamate. Meprobamate is equipotent to carisoprodol. There is some evidence suggesting carisoprodol is a $GABA_A$ receptor indirect agonist with CNS chloride ion channel conductance effects. In animals, carisoprodol produces muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in the descending reticular formation and spinal cord. It is unknown if this mechanism of action is also present in humans. In addition to the desired skeletal muscle relaxing effects,

carisoprodol and meprobamate produce weak anticholinergic, antipyretic and analgesic properties.

Pharmacokinetics: Carisoprodol is rapidly absorbed from the gastrointestinal tract and rapidly distributed throughout the CNS. Protein binding is approximately 60%. Carisoprodol is predominantly dealkylated to meprobamate in the liver, and to a lesser extent hydroxylated to hydroxycarisoprodol and hydroxymeprobamate, followed by conjugation and excretion. The half-life of carisoprodol is approximately 100 minutes. Some individuals have impaired metabolism of carisoprodol, and exhibit a half life of 2-3 times that in normal subjects. The half-life of meprobamate is many times longer, between 6 and 17 hours. As a result of the significantly longer half-life of meprobamate relative to carisoprodol, accumulation of meprobamate during chronic therapy may occur.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 2C19 isoenzyme is responsible for the conversion of carisoprodol to meprobamate. Potential inhibitors of the 2C19 isoenzyme could decrease the rate of drug elimination if administered concurrently, while potential inducers of the 2C19 isoenzyme could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Data not available for carisoprodol; 3.3 to 5.0 for meprobamate.

Interpretation of Blood Concentrations: Following therapeutic doses of carisoprodol, blood concentrations are typically between 1 and 5 mg/L for carisoprodol, and between 2 and 6 mg/L for meprobamate. A single oral dose of 350 mg carisoprodol produced average peak plasma concentrations of 2.1 mg/L carisoprodol at one hour, declining to 0.24 mg/L at 6 hours. Following a single oral dose of 700 mg, average peak plasma concentrations of carisoprodol were 3.5 mg/L at 45 minutes, and meprobamate concentrations of 4.0 mg/L were obtained in 220 minutes. A single oral dose of 700 mg carisoprodol has also produced peak plasma concentrations of 4.8 mg/L carisoprodol. Following administration of meprobamate in the treatment of anxiety, concentrations are typically around 10 mg/L, but can range between 3 and 26 mg/L. A single oral dose of 1200 mg meprobamate produced concentrations of 15.6 mg/L at 4 hours. Plasma meprobamate concentrations of greater than 100 mg/L have been associated with deep coma; light coma between 60 and 120 mg/L; and patients with levels below 50 mg/L are invariably conscious.

Interpretation of Urine Test Results: Both drugs are excreted into the urine and are likely be detectable for several days following cessation of use. Less than 1% of a single oral dose of carisoprodol is excreted unchanged in the 24 hour urine, with meprobamate accounting for 4.7% of the dose. Following administration of meprobamate, up to 11% of a single dose is excreted in the urine in 24 hours.

Effects:
Psychological: Dizziness, drowsiness, sedation, confusion, disorientation, slowed thinking, lack of comprehension, drunken behavior, obtunded, coma.

Physiological: CNS depression, nystagmus (becoming more evident as concentrations increase), loss of balance and coordination, sluggish movements, slurred speech, bloodshot eyes, ataxia, tremor, sleep disturbances.

Side Effect Profile: Agitation, tremor, paresthesia, irritability, depression, facial flushing, headache, vertigo, postural hypotension, fainting, weakness, loss of balance and coordination, impairment of visual accommodation, tachycardia, nausea, vomiting, and stomach upset. In abuse or overdose, subjects are consistently sedated and obtunded, frequently becoming comatose. Overdose symptoms may include shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, paradoxical excitement and insomnia, convulsions, and possible death. Meprobamate overdose can produce drowsiness, ataxia, severe respiratory depression, severe hypotension, shock, heart failure, and death.

Duration of Effects: The effects of carisoprodol begin within 30 minutes of oral administration, and last for up to 4-6 hours. In overdose, coma may last from several hours to a day or more. Meprobamate has a much longer duration of effect than carisoprodol due to a much longer half-life.

Tolerance, Dependence and Withdrawal: Development of abuse and moderate physical and psychological dependence can occur with chronic use of both carisoprodol and meprobamate. Abrupt discontinuation of long-term use can be followed by mild withdrawal symptoms such as anxiety, abdominal cramps, insomnia, headache, nausea, vomiting, ataxia, tremor, muscle twitching, confusion, and occasionally chills, convulsions and hallucinations. Onset of withdrawal from meprobamate occurs within 12-48 hours following cessation of use, and can last a further 12-48 hours. Carisoprodol has been shown to produce cross-tolerance to barbiturates.

Drug Interactions: Alcohol enhances the impairment of physical abilities produced by carisoprodol, and increased sedation, extreme weakness, dizziness, agitation, euphoria and confusion may be observed. Alcohol also inhibits the metabolism of meprobamate and produces an additive depressant effect on the CNS that includes sleepiness, disorientation, incoherence and confusion. The concurrent administration of other centrally acting drugs such as opiates, benzodiazepines, barbiturates, and other muscle relaxants can contribute to impairment. Meprobamate may enhance the analgesic effects of other drugs.

Performance Effects: Very limited studies are available for carisoprodol, however, single oral doses of 700 mg have not been shown to affect psychomotor and cognitive tests within 3 hours of dosing, to a significant degree. In contrast, single doses of meprobamate are capable of causing significant performance impairment. Performance effects include impaired divided attention, impaired coordination and balance, slowed reflexes and increased reaction time. With chronic dosing of either drug, it is likely that decrements in psychomotor performance would be even more pronounced.

Effects on Driving: The drug manufacturer suggests patients should be warned that carisoprodol and meprobamate may impair the mental and/or physical abilities required

for the performance of potentially hazardous tasks, such as driving a motor vehicle. Reported signs of psychomotor and cognitive impairment in subjects found to be driving under the influence of carisoprodol/meprobamate include poor perception, impaired reaction time, slow driving, confusion, disorientation, inattentiveness, slurred or thick speech, slow responses, somnolence, lack of balance and coordination, unsteadiness, and difficulty standing, walking or exiting vehicles.

Logan et al., 2000 describes 21 driving under the influence cases where carisoprodol and/or meprobamate were the only drugs detected. The mean carisoprodol and meprobamate concentrations were 4.6 mg/L (range 0-15 mg/L) and 14.5 mg/L (range 1-36 mg/L), respectively. Signs of impairment were noted at blood concentrations as low as 1 mg/L of meprobamate, however, the most severe driving impairment and the most overt symptoms of intoxication occurred in drivers whose combined carisoprodol and meprobamate blood concentrations were greater than 10 mg/L. Signs consistent with CNS depression were typically observed, including poor balance and coordination, horizontal gaze nystagmus, slurred speech, dazed or groggy appearance, depressed reflexes, slow movements, disorientation to place and time, and a tendency to dose off or fall asleep. Many subjects were involved in accidents, and other observed driving behaviors included extreme lane travel and weaving, striking other vehicles and fixed objects, slow speed, and hit and run accidents where the subject appeared unaware they had hit another vehicle.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus may be present in high doses; lack of convergence present; pupil size normal to dilated; reaction to light slow; pulse rate normal to down; blood pressure normal to down; body temperature normal to down. Other characteristic indicators may include slurred speech, drowsiness, disorientation, drunken behavior without the odor of alcohol, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: A single therapeutic dose of carisoprodol is unlikely to cause significant performance impairment. However, single therapeutic doses of meprobamate and chronic doses of carisoprodol may produce moderate to severe impairment of psychomotor skills associated with safe driving.

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Cocaine

Cocaine hydrochloride is a white to light brown crystalline powder, shiny rather than dull in appearance. Cocaine base is white to beige in color; waxy/soapy to flaky solid chunks.

Synonyms: Methylbenzoylecgonine. *Cocaine hydrochloride*: coke, snow, flake, blow, cane, dust, shake, toot, nose candy, white lady. *Cocaine base*: crack, rock, free-base.

Source: Naturally derived CNS stimulant extracted and refined from the leaves of the coca plant (*Erythroxylon coca*), grown primarily in the Andean region of South America and to a lesser extent in India, Africa and Indonesia. The picked coca leaves are dried in the open air and then "stomped" as part of the process to extract the alkaloid, resulting in coca paste and eventually cocaine hydrochloride. It is illegal to possess and sell cocaine in the U.S. and cocaine is a Schedule II controlled substance. "Crack" is the street name given to cocaine that has been processed from cocaine hydrochloride. It is prepared by adding baking soda to aqueous cocaine hydrochloride and heating it until the free-base cocaine precipitates into small pellets. The mixture is cooled and filtered, and then the "rocks" are smoked in a crack pipe.

Drug Class: CNS stimulant, local anesthetic.

Medical and Recreational Uses: Minor use as a topical local anesthetic for ear, nose and throat surgery. Traditionally, the coca leaves are chewed or brewed into a tea for refreshment and to relieve fatigue. Recreationally, cocaine is used to increase alertness, relieve fatigue, feel stronger and more decisive, and is abused for its intense euphoric effects.

Potency, Purity and Dose: In ear, nose and throat surgery cocaine is commercially supplied as the hydrochloride salt in a 40 or 100 mg/mL solution. Depending on the demographic region, street purity of cocaine hydrochloride can range from 20-95%, while that of crack cocaine is 20-80%. The hydrochloride powder is often diluted with a variety of substances such as sugars for bulk (lactose, sucrose, inositol, mannitol), other CNS stimulants (caffeine, ephedrine, phenylpropanolamine), or other local anesthetics (lidocaine, procaine, benzocaine). Commonly abused doses are 10-120 mg. Repeated doses are frequently taken to avoid the dysphoric crash that often follows the initial intense euphoric effects. Cocaine is frequently used in combination with other drugs; injected with heroin ("speedball") or taken with alcohol to reduce irritability; smoked with phencyclidine ("tick"); and smoked in marijuana blunts ("turbo").

Route of Administration: Topically applied for use as a local anesthetic. Recreationally, coca leaves can be chewed, however, cocaine abusers typically smoke "crack" in a glass pipe or inject the hydrochloride salt intravenously. Cocaine hydrochloride can be smoked to some effect but this is very inefficient as the powder tends to burn rather than vaporize. Snorting (insufflation/intranasal) is also popular. Subcutaneous injection (skin-popping) is rarely used.

Pharmacodynamics: Cocaine is a strong CNS stimulant that interferes with the reabsorption process of catecholamines, particularly dopamine, a chemical messenger associated with pleasure and movement. Cocaine prevents the reuptake of dopamine by blocking the dopamine transporter which leads to increased extracellular dopamine, resulting in chronic stimulation of postsynaptic dopamine receptors. This results in the euphoric 'rush'. When dopamine levels subsequently fall, users experience a dysphoric 'crash'. Similarly, cocaine interferes with the uptake of norepinephrine and serotonin (5-HT), leading to accumulation of these neurotransmitters at postsynaptic receptors. As a local anesthetic, cocaine reversibly blocks the initiation and conduction of the nerve impulse. Cocaine additionally produces vasoconstriction and dilated pupils.

Pharmacokinetics: Cocaine is rapidly absorbed following smoking, snorting and intravenous administration. Bioavailability is 57% following snorting and ~70% following smoking. Cocaine is 91% bound in plasma. Cocaine is extensively metabolized to a variety of compounds: benzoylecgonine, ecgonine, and ecgonine methyl ester are the major metabolites and are centrally inactive. Benzoylecgonine is produced upon loss of the methyl group and is the major urinary metabolite. Norcocaine is a very minor metabolite, but is active and neurotoxic. Cocaethylene, formed following concurrent ingestion of cocaine and alcohol, is also active and is equipotent to cocaine in blocking dopamine reuptake. The apparent half-life for cocaine is short, approximately 0.8 ± 0.2 hours, while the half-life of benzoylecgonine is 6 hours.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 3A4 isoenzyme is responsible for the N-demethylation of cocaine to norcocaine. Potential inhibitors of the 3A4 isoenzyme could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination. Cocaine itself is an inhibitor of the CYP2D6 isoform.

Blood to Plasma Concentration Ratio: averages ~ 1.0

Interpretation of Blood Concentrations: The presence of cocaine at a given blood concentration cannot usually be associated with a degree of impairment or a specific effect for a given individual without additional information. This is due to many factors, including individual levels of tolerance to the drug and artifactual changes in cocaine concentrations on storage. There is a large overlap between therapeutic, toxic and lethal cocaine concentrations and adverse reactions have been reported after prolonged use even with no measurable parent drug in the blood. Typical concentrations in abuse range from 0-1mg/L, however, concentrations up to 5mg/L and higher are survivable in tolerant individuals. After single doses of cocaine, plasma concentration typically average 0.2-0.4 mg/L. Repeated doses of cocaine may result in concentrations greater than 0.75 mg/L.

Following intranasal administration of 106 mg, peak plasma concentrations of cocaine averaged 0.22 mg/L at 30 minutes, while benzoylecgonine concentrations averaged 0.61 mg/L at 3 hours. Oral administration of 140 mg/70 kg cocaine resulted in peak plasma concentrations averaging 0.21 mg/L of cocaine at 1 hour. Single 32 mg intravenous doses of cocaine produced an average peak plasma concentration of 0.31 mg/L of cocaine within 5 minutes. Smoking 50 mg of cocaine base resulted in peak

plasma cocaine concentrations averaging 0.23 mg/L at ~ 45 minutes and 0.15 mg/L of benzoylecgonine at 1.5 hours.

Interpretation of Urine Test Results: Urinary excretion is less than 2% for unchanged cocaine, 26-39% for benzoylecgonine, and 18-22% for ecgonine methyl ester. 64-69% of the initial dose is recovered after 3 days. Very low concentrations of cocaine may be detected in urine during the initial few hours, however, benzoylecgonine persists in urine at detectable concentrations from 2-4 days. Chronic, heavy use of cocaine can result in detectable amounts of benzoylecgonine in urine for up to 10 days following a binge.

Effects:
Early phase – Psychological: Euphoria, excitation, feelings of well-being, general arousal, increased sexual excitement, dizziness, self-absorbed, increased focus and alertness, mental clarity, increased talkativeness, motor restlessness, offsets fatigue, improved performance in some simple tasks, and loss of appetite. Higher doses may exhibit a pattern of psychosis with confused and disoriented behavior, delusions, hallucinations, irritability, fear, paranoia, antisocial behavior, and aggressiveness.
Physiological: Increased heart rate and blood pressure, increased body temperature, dilated pupils, increased light sensitivity, constriction of peripheral blood vessels, rapid speech, dyskinesia, nausea, and vomiting.
Late phase - Psychological: Dysphoria, depression, agitation, nervousness, drug craving, general CNS depression, fatigue, insomnia. *Physiological*: Itching/picking/scratching, normal heart rate, normal pupils.

Side Effect Profile: Nervousness, restlessness, tremors, anxiety, and irritability. Chronic use may lead to personality changes, hyperactivity, psychosis, paranoia, and fear. Cocaine overdose can be characterized by agitation, enhanced reflexes, hostility, headache, tachycardia, irregular respiration, chills, nausea, vomiting, abdominal pain, rise in body temperature, hallucinations, convulsions, delirium, unconsciousness, seizures, stroke, cerebral hemorrhage, heart failure, and death from respiratory failure. Cocaine excited delirium is a syndrome often caused by excessive cocaine use, and is associated with a dissociative state, violence to persons and property, exaggerated strength, hyperthermia, cardiorespiratory arrest and sudden death.

Burnt lips and fingers from crack pipes are frequently seen, as are rashes and skin reddening from scratching. Smokers may suffer from acute respiratory problems including cough, shortness of breath, and severe chest pains with lung trauma and bleeding. Prolonged cocaine snorting can result in ulceration of the mucous membrane of the nose. The injecting drug user is at risk for transmitting or acquiring HIV infection/AIDS if needles or other injection equipment are shared.

Duration of Effects: The faster the absorption the more intense and rapid the high, but the shorter the duration of action. Injecting cocaine produces an effect within 15-30 seconds. A hit of smoked crack produces an almost immediate intense experience and will typically produce effects lasting 5-15 minutes. Similarly, snorting cocaine produces effects almost immediately and the resulting high may last 15-30 minutes. The effects

onset more slowly after oral ingestion (~1 hour). General effects will persist for 1-2 hours depending on the dose and late phase effects following binge use may last several days.

Tolerance, Dependence and Withdrawal Effects: Cocaine is a powerfully addictive drug of abuse and an appreciable initial tolerance to the euphoric high may develop. Cocaine is psychologically addicting, particularly with heavy or frequent use, and possibly physically addicting as well. The short duration of effects is one reason leading to probability of addition. As effects wear off, more drug is frequently administered and a pattern of repeated use occurs. Following binge use of cocaine, the "crash" can last from 9 hours to 4 days and may consist of agitation, depressed moods, insomnia to hypersomnolence, and initial drug craving. Withdrawal symptoms can typically last from 1-3 weeks and may consist of alternating low and high drug craving, low to high anxiety, paranoia, dysphoria, depression, apathy, irritability, disorientation, hunger, fatigue, bradycardia, and long periods of sleep.

Drug Interactions: The combined use of cocaine and ethanol forms cocaethylene in the body, a substance which intensifies cocaine's euphoric effects while possibly increasing the risk of sudden death. In laboratory studies, cocaine has been shown to partially reverse some of the adverse effects of alcohol, but may contribute to the detrimental effects of marijuana.

Performance Effects: Most laboratory-based studies have been limited by the low doses of cocaine that were allowed. At these single low doses, studies have shown performance enhancement in attentional abilities and increased behavioral and cortical arousal, but have no enhancement of effects on learning, memory, and other cognitive processes. Faster reaction times and diminished effects of fatigue have been observed. Improvements were greatest in behaviorally impaired subjects (e.g. sleep deprived, fatigued, or concurrent use of ethanol) and least improvements were observed in well-rested, healthy subjects. More deleterious effects are expected after higher doses, chronic ingestion and during drug withdrawal, and include agitation, anxiety, distress, inability to focus on divided attention tasks, inability to follow directions, confusion, hostility, time distortion, and poor balance and coordination. Laboratory studies have also demonstrated increased risk taking (rapid braking or steering) and deleterious effects on vision related to mydriasis. Self-reported increases in sensitivity to light, seeing halos around bright objects, flashes or movement of light in peripheral field, difficulty focusing, blurred vision, and glare recovery problems have been reported.

Effects on Driving: Observed signs of impairment in driving performance have included subjects speeding, losing control of their vehicle, causing collisions, turning in front of other vehicles, high-risk behavior, inattentive driving, and poor impulse control. As the effects of cocaine wear off subjects may suffer from fatigue, depression, sleepiness, and inattention. In epidemiology studies of driving under the influence cases, accidents, and fatally injured drivers, between 8-23% of subjects have had cocaine and/or metabolites detected in their blood. An examination of 253 fatally injured drivers in Wayne County, Michigan between 1996-1998, found that 10% of cases were positive for blood cocaine and/or metabolites. On review of accident and witness reports, aggressive

driving (high speed and loss of vehicle control) was revealed as the most common finding. Ethanol was detected in 56% of these cases, and all of these drivers lost control of their vehicles. In Memphis, Tennessee in 1993, 13% of 150 drivers stopped for reckless driving were determined to be driving under the influence of cocaine based on observations of behavior and appearance, performance on field sobriety tests, and positive urine cocaine tests.

A 25 year-old male driver, who made an improper turn against oncoming traffic, had a blood cocaine concentration of 0.04 mg/L and 0.06 mg/L of benzoylecgonine, 2 hours after the collision. A 30 year-old female caused an accident after failing to stop at a traffic light; the driver admitted to ingesting a large amount of cocaine ~ 2.5 hours prior to the collision, and 0.32 mg/L cocaine was detected in her blood 1 hour post accident.

DEC Category: CNS stimulant.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include excessive activity, increased alertness, talkativeness, irritability, argumentativeness, nervousness, body tremors, anxiety, redness to nasal area and runny nose.

Panel's Assessment of Driving Risks: Single low doses of cocaine may improve mental and motor performance in persons who are fatigued or sleep deprived, however, cocaine does not necessarily enhance the performance of otherwise normal individuals. Cocaine may enhance performance of simple tasks but not complex, divided-attention tasks such as driving. Most laboratory studies have been limited by the low single doses of cocaine administered to subjects. At these low doses, most studies showed performance enhancement in attentional abilities but no effect on cognitive abilities. Significant deleterious effects are expected after higher doses, chronic ingestion, and during the crash or withdrawal phase.

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Dextromethorphan

Dextromethorphan is a white powder. Available primarily in tablet, capsule and liquid form.

Synonyms: 3-methoxy-17-methyl-9α, 13α, 14 α-morphinan hydrobromide monohydrate; dextromethorphan hydrobromide, DXM, "robbo tripping"; Anaplex-DM®, Diabe-Tuss DM™, Benylin®, Pertussin®, Delsym®, Sucrets®, Bromfed-DM®, Robitussin®, Vicks Formula 44, etc.

Source: Synthetic analog of codeine and *d*-isomer of 3-methoxy-N-methymorphinan. Available as lozenges, capsules, tablets, and cough syrups, in a variety of prescription medications and over-the-counter cough and cold remedies. Products contain dextromethorphan alone or in combination with guaifenesin, brompheniramine, pseudoephedrine, phenylephrine, promethazine, codeine, acetaminophen, and/or chlorpheniramine. For example, Diabe-Tuss DM™ syrup contains 15 mg dextromethorphan; Benylin® Adult and Pediatric contain 15 mg and 7.5 mg dextromethorphan, respectively; and Anaplex-DM® contains 30 mg dextromethorphan, 4 mg brompheniramine and 60 mg pseudoephedrine.

Drug Class: Non-opioid antitussive, cough suppressant, CNS depressant (in high doses).

Medical and Recreational Uses: Used as an antitussive for temporary relief of coughs caused by minor throat and bronchial irritation. Recreationally used for effects ranging from mild stimulation and intoxication, to dissociation.

Potency, Purity and Dose: As an antitussive, the recommended dosage for adults and children aged 12 years and older is 60-120 mg daily in divided doses; for children aged 6-12 years, 30-60 mg daily in divided doses; and for children aged 2-6 years, 15-30 mg daily in divided doses. Each brand contains different quantities of dextromethorphan, generally 20-30 mg per dose, and the majority contain other drugs as previously mentioned. Approximate recreational doses are: threshold dose 80-90 mg; light 100-200 mg; common 200-400 mg; strong 400-600; and heavy dose 600-1500 mg.

Route of Administration: Oral.

Pharmacodynamics: Dextromethorphan acts centrally to elevate the threshold for coughing, and has no significant analgesic or sedative properties at antitussive doses. It is proposed that dextromethorphan is a glutamate and NMDA antagonist, and blocks the dopamine reuptake site. It may also increase $5HT_{1A}$ activity possibly via NMDA antagonism.

Pharmacokinetics: Dextromethorphan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are reached in approximately 2.5 hours. Dextromethorphan is widely distributed, and is rapidly and extensively metabolized by the liver. Dextromethorphan is demethylated to dextrorphan, an active metabolite, and to

3-methoxymorphinan and 3-hydroxymorphinan. It is primarily excreted as unchanged parent drug and dextrorphan.

Molecular Interactions / Receptor Chemistry: The cytochrome P450 2D6 isoenzyme is responsible for the conversion of dextromethorphan to dextrorphan; and P450 3A4 and 3A5 isoenzymes are responsible for converting dextromethorphan to 3-methoxymorphinan and 3-hydroxymorphinan. Potential inhibitors of these isoenzymes could decrease the rate of dextromethorphan elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Data not available.

Interpretation of Blood Concentrations: A single 20 mg oral dose of dextromethorphan produced peak concentrations of 1.8 ng/mL in serum after 2.5 hours. Chronic oral dosing of 120 mg daily, in divided doses, resulted in peak plasma dextromethorphan concentrations of 0.5-5.9 ng/mL (mean 2.4 ng/mL) in extensive metabolizers, and 182-231 ng/mL (mean 207 ng/mL) in poor metabolizers.

Interpretation of Urine Test Results: In a 24 hour period, less than 2.5% of a dose is excreted unchanged in the urine, while up to 30% of the conjugated dextrorphan is excreted.

Effects: At recommended doses, dextromethorphan produces little or no CNS depression. At recreational doses, positive effects may include acute euphoria, elevated mood, dissociation of mind from body, creative dream-like experiences, and increased perceptual awareness. Other effects include disorientation, confusion, pupillary dilation, and altered time perception, visual and auditory hallucinations, and decreased sexual functioning. Recreational doses of approximately 100-200 mg have a mild, stimulant effect (likened to MDA); doses of 200-500 mg produce a more intoxicating effect (likened to being 'drunk and stoned'); 500-1000 mg may result in mild hallucinations and a mild dissociate effect (likened to a low dose of ketamine) and an overall disturbance in thinking, senses and memory; while doses over 1000 mg may produce a fully dissociative effect (likened to a high dose of ketamine). Recreationally abused doses are capable of impairing judgment, memory, language, and other mental performances.

Side Effect Profile: Adverse effects with recommended antitussive doses are rare. However, nausea, other gastrointestinal disturbances, slight drowsiness and dizziness can occur. Following acute doses of between 250-1500 mg, the following clinical and overdose symptoms have been reported: excitation, nausea, vomiting, drowsiness, dizziness, blurred vision, nystagmus, dilated pupils, body itching, rash, ataxia, sweating, hot/cold flashes, fever, hypertension, shallow respiration, urinary retention, diarrhea, opisthotonos (spasm where head and heels are bent back, and torso is bent forward), toxic psychosis (hyperactivity, marked visual and auditory hallucinations), coma, and an increase in heart rate, blood pressure and body temperature. Side effects can be serious if very large doses of the combined preparations are ingested; for example, guaifenesin and

dextromethorphan can cause severe nausea and vomiting; chlorpheniramine and dextromethorphan can cause seizure, loss of consciousness and bleeding.

Duration of Effects: Dextromethorphan exerts its antitussive effects within 15-30 minutes of oral administration. The duration of action is approximately 3-6 hours with conventional dosage forms.

Tolerance, Dependence and Withdrawal Effects: At recommended antitussive doses, addiction does not occur. Mild psychological dependence and depression may occur with regular use of increased doses. Abrupt discontinuation of higher doses may produce insomnia, dysphoria and depression. Poor metabolizers of dextromethorphan have been shown to tolerate lower doses of the drug compared to extensive metabolizers, and report greater sedation, dysphoria and psychomotor impairment. Preliminary evidence also suggests that extensive metabolizers may report a greater dextromethorphan abuse potential due to the increased rate of metabolism to the active metabolite dextrorphan.

Drug Interactions: Should not be taken with Monoamine Oxide Inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs) because of an apparent serotonin syndrome (fever, hypertension, arrhythmias). Should be used with caution in atopic children due to histamine release. Additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

***Performance Effects*:** Minimal at therapeutic levels, however, with high doses one can expect gross cognitive and psychomotor impairment.

***Effects on Driving*:** Little to no effect at therapeutic levels, however with high doses one could expect significant impairment. The drug manufacturer states that the combined preparation of promethazine and dextromethorphan may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle. Patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy. Similar effects could be seen with other combined dextromethorphan preparations.

DEC Category: CNS depressant

DEC Profile: Data not available; however, the profile for a CNS depressant is: horizontal gaze nystagmus present; vertical gaze nystagmus present at high doses; lack of convergence present; pupil size normal to dilated; reaction to light slow; pulse rate down; blood pressure down; body temperature normal. Such effects are more likely to be seen following recreational doses of dextromethorphan.

Panel's Assessment of Driving Risks: Minimal to no risk at therapeutic levels. Potentially mild to moderate driving risk with higher recreational use.

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Diazepam

Diazepam is a colorless, crystalline compound. Available primarily in tablet or liquid form.

Synonyms: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one; Valium®, Valrelease®, Vazepam®, Diaz Intensol®, Diastat®, Dizac®.

Sources: Diazepam is a Schedule IV controlled substance and is available by prescription in tablet, gel and injectable form. Valium® tablets are white (2 mg), yellow (5 mg) or blue (10 mg) round tabs with a cut out "V" design. Valium® Injectable is available in 5 mg/mL strength liquid.

Drug Class: Tranquilizer, sedative, CNS depressant.

Medical and Recreational Uses: Used medicinally in the management of anxiety disorders, as an adjunct for the relief of skeletal muscle spasm and for convulsive disorders/status epilepticus, and as a minor tranquilizer or sedative. Also used to suppress or dampen acute alcohol withdrawal, and anxiety-related gastrointestinal disorders such as stress ulcers. Diazepam is used recreationally as a sedative or to enhance the effects of alcohol or opioids. For example, administration of diazepam 30 minutes after a dose of oral methadone reportedly produces an augmented high. Diazepam is used by cocaine users to increase seizure threshold and by heroin users to enhance the effects of heroin, and by both of these users to reduce the impact of withdrawal symptoms between doses.

Potency, Purity and Dose: Commonly prescribed doses of Valium® are 5-40 mg daily. For anxiety, 2-10 mg is taken twice to four times daily; for alcohol withdrawal symptoms 10 mg is taken three to four times daily. For the injectable form, 2-20 mg is administered intramuscularly or intravenously. Street doses may consist of several tablets administered at once.

Route of Administration: Usually oral, but intravenous injection is possible after preparing a solution from crushed tablets. Commercially available liquid Valium® can be injected, and gel forms can be rectally administered.

Pharmacodynamics: Diazepam is a 1,4-benzodiazepine, which binds with high affinity to the $GABA_A$ receptor in the brain to reduce arousal and to affect emotions. Diazepam's action causes an increase in affinity of the major inhibitory neurotransmitter, GABA. GABA binds mainly to the α subunit while diazepam binds to the β subunit. The γ subunit is also essential for modulation of chloride transport by benzodiazepines. Diazepam increases chloride transport through ion-channels and ultimately reduces the arousal of the cortical and limbic systems in the CNS. Diazepam depresses the electrical after-discharge in the amygdala and hippocampus regions of the limbic system that affect emotions.

Pharmacokinetics: Diazepam is rapidly absorbed. Oral bioavailability is approximately 100%, and close to 99% is bound in plasma. The half-life of diazepam is 43±13 hours,

but ranges from 40-100 hours if the contribution from active metabolites is included. Diazepam is metabolized to nordiazepam which is an active metabolite with a half-life of 40-99 hours. Temazepam and oxazepam are minor active metabolites of diazepam. Diazepam is excreted in urine mainly as oxazepam conjugate (~33 %), and temazepam conjugate, with only traces of diazepam and nordiazepam.

Molecular Interactions / Receptor Chemistry: Diazepam is demethylated to nordiazepam via P450 2C19 and 3A4; and 3-hydroxylation to temazepam and oxazepam occurs via P450 3A4. Potential inhibitors of 2C19 and 3A4 could decrease the rate of diazepam elimination if administered concurrently, while potential inducers of these isoenzymes could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.55 and 0.70 reported; 0.59 for nordiazepam.

Interpretation of Blood Concentrations: Simple interpretation of blood concentrations without any knowledge of drug-taking history is ill advised. Given changing responses with repeated use and variability in response, blood concentrations will not provide a good indication of likely behavioral effects. Additionally, the long half-life of diazepam may cause accumulation to occur with repeated use. Blood concentrations may be several-fold higher after chronic use compared to single use, and there are significant increases in blood levels in the elderly

Therapeutic blood concentrations typically range from 0.1-1.0 mg/L. Single oral doses of 10 mg result in diazepam concentrations of 0.2-0.6 mg/L at 0.5-2 hours, while chronic doses of 30 mg produce steady state diazepam concentrations of 0.7-1.5 mg/L and nordiazepam concentrations of 0.35-0.53 mg/L. Plasma concentrations of 0.3-0.4 mg/L are recommended for anxiolytic effects, and > 0.6 mg/L for control of seizures. Higher concentrations might suggest misuse or abuse.

Interpretation of Urine Test Results: Urine concentrations of metabolites are detectable for several days to weeks after last use. Urinary excretion of unchanged drug is less than 1%.

Effects: At low doses, diazepam is a moderate tranquilizer, causing sleepiness, drowsiness, confusion, and some loss of anterograde memory. At high doses, excitement, disinhibition, severe sedation, and effects on respiration occur, particularly if respiration is impaired by other drugs or by disease. Diazepam can produce a state of intoxication similar to that of alcohol, including slurred speech, disorientation, and drunken behavior.

Side Effect Profile: Side effects may include dry mouth, blurred or double vision, headache, vertigo, urinary retention, excessive perspiration, nausea and vomiting, ataxia, tremor, depression, hypotension and diminished reflexes. The elderly are more likely to develop significant adverse CNS effects from the use of diazepam. In overdose, paradoxical reactions of anxiety, insomnia, stimulation, hallucination, and acute hyperexcited state may occur. Shallow breathing, clammy skin, dilated pupils, weak and rapid pulse, coma, and death are possible.

Duration of Effects: Dose-dependent, however, with therapeutic doses onset of effects occurs within 30 minutes and significant effects can last for 12-24 hours.

Tolerance, Dependence and Withdrawal Effects: Regular use will produce tolerance to most of the sedative and adverse effects, but tolerance may not occur for the anxiolytic benefits of diazepam. Tolerance may take several weeks or months to develop depending on dose and frequency of administration. Diazepam is capable of causing mild physical and psychological dependence and is regarded as having a significant abuse potential. Abstinence or abrupt withdrawal may produce excitement, restlessness, dysphoria, anxiety, apprehension, fearfulness, dizziness, headache, muscle stiffness, tremors, insomnia, and sensitivity to light and sound. More severe symptoms may include intense rebound nausea, vomiting, abdominal cramps, delirium, hallucinations, hyperthermia, sweating, panic attacks, confusional or paranoid psychoses, tachycardia, increased blood pressure, and occasionally seizures or convulsions.

Drug Interactions: Other benzodiazepines, alcohol, phenothiazines, narcotic analgesics, barbiturates, MAOI's, and other CNS depressants may potentiate action of diazepam. Alcohol enhances such effects as drowsiness, sedation, and decreased motor skills, and can also exacerbate the memory impairing effects of diazepam. Cimetidine delays clearance of diazepam. Valproate may potentiate the CNS depressant effects. Theophylline has an antagonistic action to some of the deleterious effects of diazepam.

Performance Effects*:* Laboratory studies have shown that single doses of diazepam (5-20 mg) are capable of causing significant performance decrements, with maximal effect occurring at approximately 2 hour post dose, and lasting up to at least 3-4 hours. Decreases in divided attention, increases in lane travel, slowed reaction time (auditory and visual), increased braking time, decreased eye-hand coordination, and impairment of tracking, vigilance, information retrieval, psychomotor and cognitive skills have been recorded. Lengthened reaction times have been observed up to 9.5 hours post dose. Lethargy and fatigue are common, and diazepam increases subjective perceptions of sedation. Such performance effects are likely to be exacerbated in the elderly. In drug users, diazepam has greater behavioral changes, including subjects' rating of liking and decrements in psychomotor and cognitive performance. Reduced concentration, impaired speech patterns and content, and amnesia can also be produced, and diazepam may produce some effects that may last for days. Laboratory studies testing the effect of ethanol on subjects already using benzodiazepines demonstrate further increases in impairment of psychomotor and other driving skills, compared to either drug alone.

Effects on Driving: The drug manufacturer suggests patients treated with diazepam be cautioned against engaging in hazardous occupations requiring complete mental alertness such as driving a motor vehicle. Simulator and driving studies have shown that diazepam produces significant driving impairment over multiple doses. Single doses of diazepam can increase lateral deviation of lane control, reduce reaction times, reduce ability to perform multiple tasks, decrease attention, adversely effect memory and cognition, and increase the effects of fatigue. Significant impairment is further increased when diazepam is combined with low concentrations of alcohol (0.05 g/100 mL). A number of

epidemiological studies have been conducted to evaluate the risk of crashes associated with the use of diazepam and other benzodiazepines. These show a range of relative risk, but most demonstrate increases in risk compared to drug free drivers. These increases have been twice to several fold. The elderly may have an increased risk of a motor vehicle crash.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate down; blood pressure down; body temperature normal. Other characteristic indicators may include behavior similar to alcohol intoxication without the odor of alcohol, staggering and stumbling, lack of balance and coordination, slurred speech, disorientation, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: The incidences of diazepam in drivers involved in road crashes and in drivers suspected of being under the influence, suggest an adverse effect of diazepam on road safety. Data are available to demonstrate that single therapeutic doses of diazepam can significantly impair psychomotor skills associated with safe driving, with some effects still observable the morning after a nighttime dose.

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Diphenhydramine

Diphenhydramine is a white, crystalline powder. Available primarily in tablet, capsule and liquid form.

Synonyms: 2-(diphenylmethoxy)-N,N-dimethylethylamine hydrochloride; diphenhydramine hydrochloride; Benadryl®, Unisom® Sleepgels, Dytuss®, Dramamine®.

Source: Available in capsules, tablets, chewable tablets, syrups, elixirs, topical, and injectable forms in a variety of prescription and over-the-counter medications. Products contain diphenhydramine alone or in combination with other drugs such as pseudoephedrine and acetaminophen. Diphenhydramine is also an ingredient in several Tylenol® (i.e., acetaminophen) preparations. Dimenhydrinate (Dramamine®) is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.

Drug Class: Antihistamine, antiemetic, sleep aid, sedative, CNS depressant.

Medical and Recreational Uses: Used as an antihistamine for the temporary relief of seasonal and perennial allergy symptoms. Diphenhydramine is also used as a sleep aid and a cough suppressant, and has been used as a centrally acting antitussive although the mechanism for this action is unclear. Dramamine is used as a prophylaxis against and for the treatment of motion sickness.

Potency, Purity and Dose: As an antihistamine, recommended doses for adults is 25-50 mg diphenhydramine every 6-8 hours, not to exceed 50-100 mg every 4-6 hours. For children, 12.5-25 mg three or four times daily is recommended. As a sleep aid the dose is 50 mg at bedtime. Adults can be given 10-50 mg intravenously or intramuscularly, up to a maximum daily dose of 400 mg.

Route of Administration: Oral, injected, and topical applications.

Pharmacodynamics: Diphenhydramine is a first generation antihistamine and is a H_1 receptor antagonist. Antagonism is achieved through blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most responses of smooth muscle to histamine and the vasoconstrictor effects of histamine. The antagonism may also produce anticholinergic effects, antiemetic effects, and significant sedative side effects.

Pharmacokinetics: Following oral administration diphenhydramine is well absorbed from the gastrointestinal tract, is widely distributed throughout the body, and is able to pass though the blood-brain barrier. The oral availability is 61%, and 78% is bound in plasma. Peak plasma concentrations are reached in 2-3 hours. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. The plasma half-life is 8.5±3.2 hours; shorter and longer

half-lives have been reported for children and elderly subjects, respectively. Urinary excretion of unchanged diphenhydramine is 1.9%.

Molecular Interactions / Receptor Chemistry: Diphenhydramine is metabolized via cytochrome P450 2D6 isoenzyme. Potential inhibitors of P450 2D6 could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination.

Blood to Plasma Concentration Ratio: 0.77 and 0.82 reported.

Interpretation of Blood Concentrations: Following a single oral dose of 50 mg, average peak plasma concentrations of 83 ng/mL diphenhydramine were detected at 3 hours, declining to 9 ng/mL by 24 hours. A single oral 100 mg dose resulted in average peak plasma concentrations of 112 ng/mL at 2 hours post dose. Effective antihistamine concentrations are greater than 25 ng/mL, drowsiness can be observed at 30-40 ng/mL, and mental impairment may be observed with concentrations above 60 ng/mL.

Interpretation of Urine Test Results: Less than 2% of an oral dose is excreted in the 24 hour urine as unchanged parent drug, while approximately 11% is eliminated as its glucuronide conjugate.

Effects: First generation H_1 antagonists can both stimulate and depress the CNS. Stimulation results in restlessness, nervousness and inability to sleep, while depressive effects include diminished alertness, slowed reaction time and somnolence. Diphenhydramine is particularly prone to cause marked sedation. Drowsiness, reduced wakefulness, altered mood, impaired cognitive and psychomotor performance may also be observed.

Side Effect Profile: Includes agitation, anticholinergic side effects such as dry mouth, confusion, dizziness, drowsiness, fatigue, disturbed coordination, irritability, paresthesia, blurred vision, and depression. In overdose, symptoms may include excitement, ataxia, tremor, sinus tachycardia, fever, hallucination, athetosis, convulsions or seizures, hypotension, deep coma, cardiorespiratory collapse, and death. Fixed and dilated pupils are also observed. Gastrointestinal symptoms are less with diphenhydramine than with other H_1 antagonists.

Duration of Effects: Dose-dependent, however, following oral administration of therapeutic doses, peak plasma concentrations are reached in 2-3 hours and effects usually last 4-6 hours.

Tolerance, Dependence and Withdrawal Effects: Some tolerance may develop to the sedative effects of diphenhydramine with repeated oral dosing. No reported dependence or withdrawal effects with doses recommended.

Drug Interactions: Effects of diphenhydramine are increased by the presence of alcohol, MAOI's, diazepam, hypnotics, sedatives, tranquilizers, and other CNS

depressants. Alcohol enhances such effects as drowsiness, sedation and decreased motor skills. These decrements in effect are more pronounced in the elderly.
MAOI's prolong and intensify the anticholinergic effects of diphenhydramine.

***Performance Effects*:** All first generation antihistamines, including diphenhydramine, have been demonstrated to diminish cognitive and psychomotor performance in healthy volunteers. Impairment might even be of greater clinical significance in patients when the allergic disorder per se adversely affects CNS function, as suggested in studies in which a reduction in cognitive functioning in patients was exacerbated by diphenhydramine. Laboratory studies have shown diphenhydramine to decrease alertness, decrease reaction time, induce somnolence, impair concentration, impair time estimation, impair tracking, decrease learning ability, and impair attention and memory within the first 2-3 hours post dose. Significant adverse effects on vigilance, divided attention, working memory, and psychomotor performance have been demonstrated. It is important to note that impairment has been shown to occur even in the absence of self-reported sleepiness or sedation. Concurrent use of diazepam and diphenhydramine caused significant performance decrements at 2 hours, and to some degree up to 4 hours.

***Effects on Driving*:** The drug manufacturer states that patients should be warned about engaging in activities requiring mental alertness such as driving a car. Diphenhydramine has repeatedly been shown to severely impair tracking and reaction time performance in actual on-the-road driving tests. Single doses of 50 mg have been shown to cause significant impairment during a 90 km highway test (measuring vehicle following, constant speed and lateral position). In contrast, single 25-100 mg doses caused no significant driving effects during a short 15 minute driving test. Using the Iowa Driving Simulator, Weiler et al, 2000 compared the effects of a single oral dose of 50 mg diphenhydramine to the effects corresponding to a blood alcohol concentration of 0.1 g/100 mL. Diphenhydramine caused significantly less coherence (ability to maintain a constant distance) and impaired lane keeping (steering instability and crossing center line) compared to alcohol. Overall driving performance was the poorest after taking diphenhydramine, and participants were most drowsy after taking diphenhydramine (before and after testing). The authors concluded that diphenhydramine clearly impairs driving performance, and may have an even greater impact than does alcohol on the complex task of operating a motor vehicle.

***DEC Category*:** CNS depressant

***DEC Profile*:** Data not available; however, the profile for a CNS depressant is: horizontal gaze nystagmus present; vertical gaze nystagmus present at high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate normal; blood pressure normal; body temperature normal. Diphenhydramine may produce dilated pupils.

Panel's Assessment of Driving Risks: Single therapeutic doses of diphenhydramine have been shown to significantly impair psychomotor performance during the first 4 hours, and may have a greater impact on driving performance than alcohol.

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Gamma-Hydroxybutyrate (GHB, GBL, and 1,4-BD)

GHB is a clear liquid, or a white powder with a soap-like texture. Precursor drugs such as gamma-butyrolactone (GBL) and 1,4 butanediol (1,4-BD) are clear liquids.

Synonyms:

GHB: Sodium oxybate, Xyrem® oral solution; liquid X, liquid XTC, salt water, scoop, soap, grievous bodily harm, georgia home boy, G, G-caps, easy lay, everclear, vita G, degreaser + lye, smart drug, gamma-OH, Somatomax.

GBL: 2(3)-furanone dihydro; Blue Nitro, G3, Invigorate, Jolt, ReActive, REMForce, RenewTrient, Rest-eze, Revivarant, Verve, V35.

1,4-BD: tetramethylene glycol; Amino Flex, Enliven, FX, GHRE, Inner G, NRG3, Pine Needle Extract, Revitalize, Serenity, SomatoPro, Thunder Nectar, Zen.

Source: GHB was first synthesized in 1960 as an experimental GABA analog, and was classified as a food and dietary supplement and sold in health food stores in early 1990. It was available in tablet, capsule and liquid forms. In late 1990, the FDA banned over-the-counter sales of GHB in the U. S. In 1999, the FDA issued warnings on the dangers of its precursor drugs GBL and 1,4-BD. In early 2000, GHB was federally reclassified as a Schedule 1 controlled substance. GBL and 1,4-BD are not scheduled, however, GBL is classified as a list 1 chemical and a controlled substance analog, while 1,4-BD is listed as a controlled substance analog. GHB can be clandestinely made and the ingredients are available in kit form over the internet. GHB is made from GBL and a base (e.g. lye/NaOH), the mixture is heated, and vinegar is added to reduce the pH. Acetone can then be added and the mixture dried, resulting in GHB powder. GBL and 1,4-BD are commercially available as industrial solvents and are used as ingredients in cleaners, solvents, paint removers, and engine degreasers. They are also sold as "natural supplements" over the internet, and in some health food stores and gymnasiums, and are marketed as natural, non-toxic dietary supplements.

Drug Class: CNS depressant, sedative, anesthetic.

Medical and Recreational Uses: In Europe, GHB is used as an anesthetic adjunct and hypnotic agent, used to treat narcolepsy, and used to suppress symptoms of alcohol-dependence and opiate withdrawal syndrome. In the U. S., medically formulated sodium oxybate (Xyrem®) has been approved as a Schedule III controlled substance for the treatment of cataplexy (sudden loss of muscle tone associated with narcolepsy). Recreationally, GHB is used for its intoxicating effects (euphoria, reduced inhibitions, sedation), and by bodybuilders as an alternative to anabolic steroids. GBL and 1,4-BD rapidly convert to GHB within the human body following oral administration and are taken as GHB substitutes. They are marketed as anti-aging drugs, for weight loss, to treat insomnia, anxiety and depression, and as mood enhancers and energizers.

Potency, Purity and Dose: Clinical doses for alcohol withdrawal syndrome are 25-50 mg/kg every 12 hours (1.7-3.5 g/70 kg); sleep induction 20-30 mg/kg (1.5-2.25 g/70 kg); prolonged deep sleep 75-100 mg/kg (5-7 g/70 kg); and anesthetic induction greater than 100 mg/kg (> 7 g/70 kg). Illicit manufacture often introduces impurities and wide

variations in potency. Recreational use of GHB often involves doses well in excess of one teaspoon (~2.5 g, or 35 mg/kg in a 70 kg adult) of the powder dissolved in water/alcohol, or one capful of liquid GHB, GBL, or 1,4-BD; such doses far exceed therapeutic doses. Chronic use can consist of dosing every few hours, around the clock, for months to years. Up to 100 g GHB has been reportedly used by an individual in one day. GHB and its precursor drugs are often used in combination with alcohol, MDMA, marijuana, methamphetamine, and cocaine.

Route of Administration: Oral, intravenous.

Pharmacodynamics: GHB is a naturally occurring compound present in both mammalian CNS and peripheral tissue. It is also a minor metabolite and precursor of the major inhibitory neurotransmitter GABA. GHB is also the pharmacologically active form of both GBL and 1,4-BD. GHB has weak agonist activity at $GABA_B$ receptors and there appears to be a distinct GHB receptor site in the brain. GHB dose-dependently alters dopaminergic activity; at sub-anesthetic doses there is an initial excitation of dopamine neurons producing elevated levels of synaptic dopamine; at anesthetic doses GHB blocks impulse flow from dopamine neurons resulting in a build-up of dopamine in the nerve terminals. GHB mimics natural physiological sleep, enhances REM sleep, and increases stage 3 and 4 of slow-wave sleep. GHB decreases alcohol consumption and intensity of withdrawals. Beyond the CNS effects, GHB has significant cardiovascular pharmacology, causing bradycardia and dysregulation of blood pressure (hyper- and hypotension). Interestingly, GHB causes a detectable increase in growth hormone and prolactin concentrations with doses as small as 3 g, and this is the basis for its use in body building despite there being no evidence of an actual increase in body mass.

Pharmacokinetics: Oral doses are rapidly absorbed from the gastrointestinal tract and exhibit first pass metabolism. Absorption is capacity limited (an increase in dose results in increased time to peak concentration). There is an increased rate of absorption of GHB on an empty stomach leading to a decreased time to peak concentration and an increased concentration. Accumulation is not known to occur following repeated doses. GHB readily crosses the blood-brain barrier and placental barrier, and is distributed in the brain, cerebrospinal fluid, vitreous, liver, and kidney. The dose-response curve is steep, and a large between and within subject variability is noted. GHB is rapidly eliminated and has a half-life of 27 minutes (range 20-53 minutes) which appears to increase with higher doses, a sign of zero order or saturation kinetics. GHB is metabolized to succinic semialdehyde (SSA) via GHB-dehydrogenase, then to succinic acid via SSA-dehydrogenase. GBL is metabolized to GHB via lactonase; while 1,4-BD is first metabolized to γ-hydroxybutyraldehyde via alcohol dehydrogenase, then to GHB via aldehyde dehydrogenase.

Molecular Interactions / Receptor Chemistry: Metabolism via cytochrome P450 isoenzymes has not been described.

Blood to Plasma Concentration Ratio: 1.2 (N=1)

Interpretation of Blood Concentrations: Peak plasma concentrations are observed at 20-45 minutes. Due to rapid elimination, GHB is undetectable in plasma or blood after 6-8 hours. Following single oral doses of 25 mg/kg GHB in 10 alcoholic dependant patients, mean peak plasma GHB concentrations were 54 mg/L (24-88 mg/L). Single oral doses of 12.5, 25, and 50 mg/kg in 8 healthy subjects produced mean peak plasma GHB concentrations of 23, 46 and 80 mg/L, respectively. Single oral doses of 26-52 mg/kg in 6 narcoleptic patients resulted in mean peak plasma GHB concentrations of 63 mg/L (30-102 mg/L). The same doses were administered to the same subjects 4 hours later, and the mean peak GHB concentrations obtained were 91 mg/L (47-125 mg/L). An intravenous dose of 50 mg/kg in an adult produced a peak blood GHB concentration of approximately 170 mg/L within 15 minutes. Patients presenting to an emergency department with GHB overdose/intoxication, had blood GHB concentrations ranging from 29-432 mg/L (mean 118 mg/L; N = 54).

Although GHB is naturally present in the human body, endogenous blood GHB concentrations are typically well below 1 mg/L in living subjects. In contrast, endogenous postmortem production of GHB can occur, and concentrations of up to 170 mg/L GHB have been reported in non-GHB using subjects. In postmortem analysis the analysis of multiple specimens such as vitreous and urine is recommended.

Interpretation of Urine Test Results: Peak urine concentrations are observed within 4 hours of administration and GHB is undetectable in urine after 10-12 hours. Endogenous concentrations of up to ~7 mg/L GHB have been detected in urine of non-GHB using subjects. It is suggested that a cut-off for urinary GHB be set at 10 mg/L. Similarly, in postmortem urine specimens from non-GHB using subjects, urine concentrations of GHB are typically below 10 mg/L.

Effects:
Psychological: At low doses, effects are similar to those seen with alcohol. Effects include relaxation, reduced inhibitions, euphoria, confusion, dizziness, drowsiness, sedation, inebriation, agitation, combativeness, and hallucinations.
Physiological: Nausea, vomiting, profuse sweating, somnolence, visual disturbances, nystagmus, loss of peripheral vision, short-term amnesia, uncontrolled shaking or seizures, bradycardia, hypothermia, suppression of gag reflex, respiratory depression, and transient or unarousable unconsciousness.

Side Effect Profile: Disorientation, sweating, vomiting, incontinence, apnea, severe ataxia, sinus bradycardia, twitching, seizure-like activity and hypothermia. In overdose, symptoms may include severe respiratory depression, mild acute respiratory acidosis, sinus bradycardia or sinus tachycardia, suppression of gag reflex, acute delirium, combativeness, unarousable unconsciousness, coma, and patients often need to be intubated. Deaths have been reported following overdose from GHB, GBL and 1,4-BD alone, and in combination with other drugs.

Duration of Effects: Onset of effects occurs within 10-20 minutes, peak plasma concentrations are achieved within 20-45 minutes, and effects generally last 2-5 hours. Complete recovery from GHB overdose can occur within 3-6 hours. Sleep induction time

is shortest with GBL and longest with 1,4-BD, as GBL is more lipophilic and is absorbed faster. There is a longer duration of effect following 1,4-BD ingestion as it metabolizes more slowly to GHB than does GBL.

***Tolerance, Dependence and Withdrawal Effects*:** Tolerance can develop to GHB with chronic abuse and even following chronic treatment. Subjects do not become tolerant to all the effects (e.g. tolerance does not develop to the enhanced sleep that GHB produces). Cross-tolerance exists between GHB and ethanol. Severe physical and psychological addiction occurs with chronic abuse. Clinical presentation of withdrawal may include mild clinical anxiety, confusion, agitation, tremor, muscular cramps, insomnia, combativeness, delirium, delusions, paranoia with hallucinations (auditory, tactile and visual), tachycardia, hypotension, and an occasional schizophrenic-like state. The withdrawal syndrome can start as early as 1-2 hours after the last dose in addicted individuals.

Drug Interactions: Potential additive effects between GHB and other sedating CNS depressants, including alcohol, antidepressants, antipsychotics, antihistamines and muscle relaxants. In rats, ethanol has significant synergistic effects on the sedative, behavioral and toxic effects of GHB, GBL and 1,4-BD. Ethanol also delays the conversion of 1,4-BD to GHB, because both 1,4-BD and ethanol utilize alcohol-dehydrogenase in their metabolic pathways. Several drugs have been shown to inhibit GHB-dehydrogenase and it is not known clinically what effects these drugs would have if administered concurrently. These drugs include valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram and cyanide.

Performance Effects: Oral GHB doses of 1-2 g have been shown not to deteriorate reactive, attentive and co-ordination skills related to driving, nor increase the effects of low dose alcohol. Similarly, oral doses of 12.5-25 mg/kg GHB had no effect on attention, vigilance, alertness, short-term memory or psychomotor coordination; although dizziness or dullness were experienced in 50-66% of subjects. It is important to note, however, that doses used in laboratory studies to date have been well below both recreational and abused doses of GHB.

Effects on Driving: Signs of behavioural effects and impaired performance have been reported in several driving case reports. In 13 driving under the influence cases where GHB was detected, the reported symptoms were generally those of a CNS depressant. The subjects were typically stopped because of erratic driving, such as weaving, ignoring road signs, and near-collisions. Common signs of impairment included confusion and disorientation, incoherent speech, short-term memory loss, dilated pupils, lack of balance and unsteady gait, poor coordination, poor performance of field sobriety tests, copious vomiting, unresponsiveness, somnolence, and loss of consciousness. GHB concentrations in blood specimens collected between 1-3.5 hours of the arrest ranged from 26-155 mg/L (median 95 mg/L). In another 11 cases of driving under the influence of GHB, concentrations of GHB in blood and urine specimens ranged from 81-360 mg/L and 780-2380 mg/L, respectively. Circumstances of their arrest, observed driving behavior and signs of impairment were similar to the previous study. Other reported symptoms have

included dizziness, drowsiness, agitation, loss of peripheral vision, slow responses, slow and slurred speech, and transient unconsciousness.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size generally dilated; reaction to light slow; pulse rate normal; blood pressure normal; body temperature generally down. Other characteristic indicators include vomiting, sweating, slurred speech, somnolence or transient unconsciousness, poor balance and coordination, and poor performance on field sobriety tests. Note that while pulse rate and blood pressure may decrease after GHB ingestion, both parameters may be elevated during drug withdrawal.

Panel's Assessment of Driving Risks: Given the ability of GHB to induce sleep and unconsciousness, recreational use of GHB or its precursor drugs have the potential to produce moderate to severe driving impairment.

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Ketamine

Ketamine is a white, crystalline powder or clear liquid.

***Synonyms*:** (+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone; Ketalar®, Ketaject®, Ketaset®, Vetalar®; K, Special K, Vitamin K, Lady K, Jet, Super Acid, Bump, Special LA Coke, KitKat, Cat Valium.

***Source*:** Available by prescription only, and is commercially available as a veterinary anesthetic. It is difficult to synthesize clandestinely and is usually stolen from veterinarian offices or diverted from legitimate pharmaceutical sources in liquid form. Ketamine is currently a schedule III controlled substance in the US.

***Drug Class*:** Dissociative anesthetic, hallucinogen, psychotomimetic.

***Medical and Recreational Uses*:** Primarily used in veterinary applications as a tranquilizer. Also used as an anesthetic induction agent for diagnostic and surgical procedures in humans, prior to the administration of general anesthetics. Occasionally used as a short-acting general anesthetic for children and elderly patients. Recreationally used as a psychedelic and for its dissociative effects.

***Potency, Purity and Dose*:** Ketamine is available as a racemic mixture with the S-(+)- isomer being more potent than the R-(-)- isomer. Commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. For induction of 5-10 minutes surgical anesthesia, a dose of 1.0-4.5 mg/kg is intravenously administered; 6.5-13 mg/kg is given intramuscularly for 12-25 minutes of surgical anesthesia. The liquid from injectable solutions can be gently heated to evaporate the water, leaving a white powder (ketamine hydrochloride) which can be snorted or orally ingested. Recreational doses are highly variable. Common doses are 25-50 mg intramuscularly, 30-75 mg snorting, and 75-300 mg oral. Snorting a small line ("bump", 30-50 mg) usually results in a dreamy effect. "K-hole" can be obtained following a dose of 60-125 mg intramuscularly, or by snorting 100-250 mg. Impurities are rarely seen, although ketamine hydrochloride itself can be used as a heroin adulterant.

***Route of Administration*:** Injected, snorted, orally ingested, and rectally administered. Similar to phencyclidine (PCP), ketamine can be added to tobacco or marijuana cigarettes and smoked.

***Pharmacodynamics*:** Involves analgesia, anesthetic and sympathomimetic effects that are mediated by different sites of action. Non-competitive NMDA receptor antagonism is associated with the analgesic effects; opiate receptors may contribute to analgesia and dysphoric reactions; and sympathomimetic properties may result from enhanced central and peripheral monoaminergic transmission. Ketamine blocks dopamine uptake and therefore elevates synaptic dopamine levels. Inhibition of central and peripheral cholinergic transmission could contribute to induction of the anesthetic state and hallucinations. Ketamine is structurally similar to PCP, but 10-50 times less potent in blocking NMDA effects.

Pharmacokinetics: Bioavailability following an intramuscular dose is 93%, intranasal dose 25-50%, and oral dose 20±7%. Ketamine is rapidly distributed into brain and other highly perfused tissues, and is 12% bound in plasma. The plasma half-life is 2.3 ± 0.5 hours. Oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydronorketamine. Ketamine and its metabolites undergo hydroxylation and conjugation. Norketamine produces effects similar to those of ketamine. There are no significant differences between the pharmacokinetic properties of the S-(+) and R-(-)-isomers.

***Molecular Interaction / Receptor Chemistry*:** Cytochrome P450 3A4 is the principal enzyme responsible for ketamine N-demethylation to norketamine, with minor contributions from CYP2B6 and CYP2C9 isoforms. Potential inhibitors of these isoenzymes could decrease the rate of ketamine elimination if administered concurrently, while potential inducers could increase the rate of elimination

***Blood to Plasma Concentration Ratio*:** Data not available.

***Interpretation of Blood Concentrations*:** There is no direct correlation between ketamine concentrations and behavior. Drowsiness, perceptual distortions and intoxication may be dose related in a concentration range of 50 to 200 ng/mL, and analgesia begins at plasma concentrations of about 100 ng/mL. During anesthesia, blood ketamine concentrations of 2000-3000 ng/mL are used, and patients may begin to awake from a surgical procedure when concentrations have been naturally reduced to 500-1000 ng/mL.

Interpretation of Urine Test Results: Urinary excretion of unchanged drug is 4±3%, and ketamine use can be detected in urine for about 3 days. Concentration ranges for ketamine in urine have been reported as low as 10 ng/mL and up to 25,000 ng/mL.

***Effects*:** Users have likened the physical effects of ketamine to those of PCP, and the visual effects to LSD.
Psychological: Decreased awareness of general environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, disorientation, and subjects are generally uncommunicative. Intense hallucinations, impaired thought processes, out-of-body experiences, and changes in perception about body, surroundings, time and sounds. Delirium and hallucinations can be experienced after awakening from anesthesia.
Physiological: Anesthesia, cataplexy, immobility, tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, profound insensitivity to pain, amnesia, slurred speech, and lack of coordination.

***Side Effect Profile*:** High incidence of adverse effects, including anxiety, chest pain, palpitations, agitation, rhabdomyolysis, flashbacks, delirium, dystonia, psychosis, schizophenic-like symptoms, dizziness, vomiting, seizures, and paranoia.

Duration of Effects: Onset of effects is within seconds if smoked, 1-5 minutes if injected, 5-10 minutes if snorted and 15-20 minutes if orally administered. Effects generally last 30-45 minutes if injected, 45-60 minutes if snorted, and 1-2 hours following oral ingestion. Ketamine is often readministered due to its relatively short duration of action. Some subjects may experience dreams 24 hours later. Marked dissociative effects, schizotypal symptoms and impaired semantic memory are found in some recreational users days after drug use.

Tolerance, Dependence and Withdrawal Effects: In long-term exposure, high tolerance, drug craving, and flashbacks are described. Little evidence of a physiological withdrawal syndrome unless abrupt discontinuation in chronic users.

Drug Interactions: Midazolam attenuates altered perception and thought processes. Lorazepam may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities, but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine.

***Performance Effects*:** Broad spectrum of cognitive impairments and marked dissociative effects. Increased distractibility and intensely visual or polysensual hallucinations. Impairment of immediate and delayed recall, and verbal declarative memory. Memory impairment is associated with encoding or retrieval processes, and not accounted for by decreased attention. Impaired language function, failure to form and use memory traces of task relevant information. Overall decreased awareness, increased reaction time, distorted perceptions of space, non-responsiveness, and blurred vision. The S-(+) isomer impairs psychomotor function 3-5 times more than the R-(-) isomer.

***Effects on Driving*:** The drug manufacturer suggests that patients should be cautioned that driving an automobile should not be undertaken for 24 hours or more following anesthesia. No driving studies have been performed.

***DEC Category*:** Phencyclidine.

***DEC Profile*:** Horizontal gaze nystagmus present; vertical gaze nystagmus present; lack of convergence present; pupil size normal; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include rigid muscles, cyclic behavior, and lack of response to painful stimuli.

***Panel's Assessment of Driving Risks*:** The use of ketamine is not conceivably compatible with the skills required for driving due to its moderate to severe psychomotor, cognitive, and residual effects.

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Lysergic acid diethylamide (LSD)

LSD is a white powder or a clear, colorless liquid.

Synonyms: *d*-lysergic acid diethylamide; acid, animal, barrels, beast, blotter, 'cid, dots, kool aid, LSD-25, lysergide, microdots, panes, sandoz, tabs, trips, white lightning, window panes.

***Source*:** LSD is manufactured from lysergic acid which occurs naturally in the ergot fungus that grows on wheat and rye. It is a Schedule I controlled substance, available in liquid, powder, tablet (microdots), and capsule form. The liquid is often applied to blotter paper squares (frequently with colorful designs), stickers, sugar cubes, candy, or soda crackers. LSD is also available in dropper bottles or in the form of gelatin sheets/shapes (window panes).

***Drug Class*:** Hallucinogen, psychedelic, psychotomimetic.

***Medical and Recreational Uses*:** No medicinal use. Recreationally used as a hallucinogen and for its ability to alter human perception and mood.

***Potency, Purity and Dose*:** The strength of illicit LSD nowadays ranges from 20 to 80 µg per dose, which is considerably less than doses reported during the 1960s and early 1970s, of 100-200 µg or higher per unit. Experienced users typically administer 100-200 µg for a "good high". The potency of liquid LSD in dropper bottles may vary because the liquid is water based.

***Route of Administration*:** Primarily oral administration, but can be inhaled, injected, and transdermally applied.

Pharmacodynamics: LSD is primarily a non-selective 5-HT agonist. LSD may exert its hallucinogenic effect by interacting with 5-HT_{2A} receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes. LSD mimics 5-HT at 5-HT_{1A} receptors, producing a marked slowing of the firing rate of serotonergic neurons.

Pharmacokinetics: LSD has a plasma half-life of 2.5-4 hours. Metabolites of LSD include N-desmethyl-LSD, hydroxy-LSD, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD. These metabolites are all inactive.

***Molecular Interactions / Receptor Chemistry*:** Metabolism via cytochrome P450 isoenzymes has not been described.

***Blood to Plasma Concentration Ratio*:** Data not available.

Interpretation of Blood Concentrations: Threshold toxic dose in humans has been reported with 100-200 µg with associated blood concentrations of 2-30 ng/mL. Intravenous doses of 1-2 µg /kg have been associated with blood concentrations of 1-5

ng/mL LSD. Single oral doses of 160 µg resulted in peak plasma concentrations of up to 9 ng/mL LSD.

Interpretation of Urine Test Results: LSD use can typically be detected in urine for periods of 2-5 days. In a reported case of LSD intoxication, a concentration of 11 ng/mL of LSD was detected in the urine. In subjects receiving 200-400 µg of LSD, concentrations in urine ranged from 1-55 ng/mL.

***Effects*:** Effects are unpredictable and will depend on the dose ingested, the user's personality and mood, expectations and the surroundings.
Psychological: Hallucinations, increased color perception, altered mental state, thought disorders, temporary psychosis, delusions, body image changes, and impaired depth, time and space perceptions. Users may feel several emotions at once or swing rapidly from one emotion to another. "Bad trips" may consist of severe, terrifying thoughts and feelings, fear of losing control, and despair.
Physiological: Tachycardia, hypertension, dilated pupils, sweating, loss of appetite, sleeplessness, dry mouth, tremors, speech difficulties, and piloerection.

***Side Effect Profile*:** Rhabdomyolysis, renal failure, prolonged mania, panic, impairment in color discrimination, and residual visual effects have been described. LSD users may manifest relatively long-lasting psychoses, such as schizophrenia or severe depression.

***Duration of Effects*:** Onset of effects is rapid following intravenous administration (10 minutes). Following oral ingestion, onset of the first effects are experienced in 20-30 minutes, peaking at 2-4 hours and gradually diminishing over 6-8 hours. Residual effects may last longer. Flashbacks may occur suddenly, often without warning, and may occur within a few days or more than a year after use.

***Tolerance, Dependence and Withdrawal Effects*:** Frequent, repeated doses of LSD are unusual and therefore tolerance is not commonly seen. Tolerance does develop to the behavioral effects after 3-4 daily doses, but no withdrawal syndrome has been described. LSD is not considered an addictive drug since it does not produce compulsive drug-seeking behavior.

***Drug Interactions*:** Cross-tolerance with mescaline and psilocybin has been demonstrated in animal models. LSD blocks subjective alcohol effects in many subjects. Possible seizures when concurrently taken with lithium or fluoxetine.

***Performance Effects*:** LSD produces significant psychedelic effects with doses as little as 25-50 µg. LSD impairs reaction time (auditory and visual), choice reaction time, and visual acuity for up to 4 hours. Impaired divided attention, ataxia, and grossly distorted perception have also been reported following LSD use.

***Effects on Driving*:** Epidemiology studies suggest the incidence of LSD in driving under the influence cases is extremely rare. In Denver, Colorado between Jan 1988 to June 1990, 242 drivers detained for driving while impaired were evaluated by drug

recognition examiners; only 1 case of LSD was confirmed following urine toxicology screens.

***DEC Category*:** Hallucinogen.

***DEC Profile*:** Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include extreme changes in behavior and mood, trance-like state, sweating, body tremors, piloerection, hallucinations, paranoia, and changes in sense of light, hearing, touch and smell.

***Panel's Assessment of Driving Risks*:** The use of LSD is not compatible with the skills required for driving due to its severe psychomotor, cognitive and residual effects.

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Methadone

Methadone hydrochloride is a white crystalline powder or colorless crystals. Available primarily in tablet or liquid form.

Synonyms: 6-dimethylamino-4.4-diphenyl-3-heptanone; Dolophine® Hydrochloride, Methadose®, Methadone Hydrochloride Intensol™.

Source: Methadone is a synthetic narcotic analgesic and is a schedule II controlled substance. Methadone is available by prescription as oral solutions (1-2 mg/mL strength), tablets (5-10 mg), dispersible tablets (40 mg), or injectable solutions (10 mg/mL).

Drug Class: Narcotic analgesic.

Medical and Recreational Uses: Methadone is an analgesic prescribed for the relief of moderate to severe pain, and is used in detoxification treatment of opioid dependence and maintenance in narcotic addiction. Compared to morphine, methadone has a much longer duration of action, suppressing opiate withdrawal symptoms and remaining efficacious for an extended period of time with repeated administration. Recreationally, methadone is abused for its sedative and analgesic effects.

Potency, Purity and Dose: Available as the racemic mixture, (R)- or *l*-methadone is 8-50 times more potent than the (S)- or *d*-isomer. For relief of severe acute pain the usual adult dose is 2.5-10 mg every 3-4 hours. For methadone maintenance the daily dose is generally 60-80 mg, but can vary from 30-120 mg. For detoxification treatment an initial oral dose of 15-20 mg is administered, with an additional dose if withdrawal symptoms are not suppressed; a stabilizing dose of 40 mg in single or divided dosages is prescribed for 2-3 weeks, then the dose is gradually decreased. Concurrent use of other prescription medication is common.

Route of Administration: Oral ingestion, intravenous, intramuscular or subcutaneous injection.

Pharmacodynamics: Methadone is a long acting μ opioid receptor agonist with potent central analgesic, sedative, and antitussive actions. Methadone inhibits ascending pain pathways, alters perception of and response to pain (dissociative effect), and produces generalized CNS depression. Respiratory depression also occurs due to complete blockade of respiratory centers to pCO_2. (S)-Methadone lacks significant respiratory depressive action and addiction liability.

Pharmacokinetics: When administered orally, methadone is rapidly absorbed from the gastrointestinal tract and can be detected in the blood within 30 minutes. Oral bioavailability varies from 41-99% and plasma protein binding is 60-90%. After repeated administration there is gradual accumulation in tissues. As for most lipid soluble drugs, a large between and within subject variability is observed. The half-life of (R,S)-methadone is 15-60 hours, and 10-40 hours for (R)-methadone. Methadone undergoes extensive biotransformation in the liver primarily to two inactive metabolites,

2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP), through N-demethylation and cyclization. These are eliminated by the kidney and excreted through the bile. In total, nine metabolites have been identified including two minor active metabolites, methadol and normethadol.

Molecular Interactions / Receptor Chemistry: Methadone is metabolized to EDDP via the cytochrome P450 CYP3A4 isoform. Potential inhibitors of this isoform could decrease the rate of methadone elimination if administered concurrently, while potential inducers could increase the rate of elimination. Methadone itself inhibits cytochrome P450 2D6 isoform.

Blood to Plasma Concentration Ratio: 0.75 and 0.77 reported.

Interpretation of Blood Concentrations: Methadone can be detected in plasma within 30 minutes following oral ingestion, reaching a peak concentration at ~4 hours. Mean EDDP concentration are ~15% that of methadone. There is often a large overlap between reported therapeutic (0.03-0.56 mg/L) and fatal concentrations (0.06-3.1 mg/L). Peak serum concentrations following a single oral dose of 15 mg were 0.075 mg/L, 0.86 mg/L for 100 mg, and 0.83 mg/L for 120 mg; all at 4 hours. Chronic oral administration of 100-200 mg to tolerant subjects produced average peak plasma concentrations of 0.83 mg/L at 4 hours, decreasing to 0.46 mg/L at 24 hours. Peak plasma methadone concentrations of 0.034 mg/L were obtained at 50 minutes following intramuscular injection of 10 mg, while intravenous administration of 10 mg produced concentrations of 0.096 mg/L at 34 minutes. Concentrations greater than 0.10 mg/L are required for prevention of opiate withdrawal symptoms. In cancer patients treated for pain relief and sedation, methadone concentrations were 0.35 ± 0.18 mg/L.

Interpretation of Urine Test Results: The percentage of a dose excreted in the urine as unchanged methadone and EDDP will vary with the pH of the urine. Urinary excretion of unchanged parent drug is 5-50% and EDDP 3-25%. It may be possible to use excretion data to monitor individuals' compliance in a methadone program after establishing their intraindividual variation in excretion patterns through long-term monitoring.

Effects:
Psychological: Drowsiness, sedation, dizziness, lightheadedness, mood swings (euphoria to dysphoria), depressed reflexes, altered sensory perception, stupor, and coma.
Physiological: Strong analgesia, headache, dry mouth, facial flushing, nausea, constipation, respiratory depression, muscle flaccidity, pupil constriction, and decreased heart rate.

Duration of Effects: Onset of analgesia occurs 10-20 minutes following parenteral administration and 30-60 minutes after oral administration. Oral administration results in a delay in onset, lower peak concentration and longer duration of action. Following single oral doses effects may last 6-8 hours, increasing to 22-48 hours in cases of chronic administration.

Side Effect Profile: Sedation, alteration in cognitive and sensory efficiency, respiratory depression, nausea, vomiting, headache, constipation, urinary retention, sweating, sleep disorders, and concentration disorders. Infrequent side effects include urticaria, hypersensitivity reaction, shock, and pulmonary edema. Overdose can include slow, shallow breathing, respiratory depression, clammy skin, convulsions, extreme somnolence, apnea, circulatory collapse, cardiac arrest, coma, and possible death.

Tolerance, Dependence and Withdrawal Effects: Upon repeated administration, tolerance may develop to the nauseant, miotic, sedative, respiratory depressant, and cardiovascular effects of methadone. Tolerance develops more slowly to methadone than to morphine in some patients. Methadone can produce physiological and psychological drug dependence of the morphine type, and has the potential for being abused. Withdrawal symptoms are similar to those of other opioids but are less severe, slower in onset, and last longer. Symptoms include watery eyes, runny nose, nausea, loss of appetite, diarrhea, cramps, muscle aches, dysphoria, restlessness, irritability, anxiety, pupillary dilation, piloerection, tremors, chills, sweating, increased sensitivity to pain, insomnia, and tachycardia.

Drug Interactions: There is additive CNS depressive effects with concurrent use of sedatives, hypnotics, tranquilizers, other narcotic analgesics, tricyclic antidepressants, alcohol and other CNS depressant drugs, resulting in exaggerated respiratory depression and sedation. Methadone can potentiate the deleterious effects of alcohol. Pentazocine, nalbuphine, butorphanol and buprenorphine are partial agonists and will behave as antagonists in the presence of methadone, resulting in the precipitation of withdrawal symptoms. Rifampin reduces blood concentrations of methadone and may lead to withdrawal. Blood levels of desipramine have increased with concurrent methadone therapy.

Performance Effects: In general, laboratory studies have shown that non-tolerant individuals receiving single doses of methadone have produced dose-dependent reductions in reaction time, visual acuity, information processing, and sedation. Significant psychomotor impairments are seldom evident when tolerant subjects have been tested, including performance deficits in reaction time, attention, and peripheral vision. In the majority of experimental clinical trials, psychophysical performance tests have yielded the same results for methadone substitution patients as for control groups. However, variable results have been observed. Attention and perception tasks have been impaired in methadone maintenance patients, but sociodemographic factors may have played a role. In patients receiving 35-85 mg methadone daily, significant impairment was measured on attention, perception and learning tasks but there was no reaction time deficit. In patients receiving a daily average of 63 mg methadone, significant impairment in distance perception, attention span and time perception was observed. No significant adverse effects were measured with addicts stabilized for at least 1 year on daily oral doses of methadone.

Effects on Driving: The drug manufacturer cautions that methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous

tasks, and that the sedative effects of the drug may be enhanced by concurrent use of other CNS depressants, including alcohol. In healthy, non-methadone using volunteers, single doses of methadone will impair driving ability. Numerous European studies of long-term methadone maintenance patients have shown that appropriately administered methadone does not cause significant psychomotor or cognitive impairment when administered regularly and when the subject abstains from all other drugs. However, in the majority of cases, patients did not exhibit stable abstinence from drug use and had an increased occurrence of simultaneous psychiatric/neurotic disorders or personality disturbances which, by themselves, could be a reason to doubt their driving ability. In Germany, the Joint Advisory Council for Traffic Medicine at the Federal Ministry of Transport, Building and Housing and the Federal Ministry for Health issued the following recommendation: Heroin addicts treated with methadone are generally not fit to drive; however, these patients may be considered fit to drive if they show a period of methadone substitution for more than a year; stable psychosocial integration; no evidence of the consumption of additional psychotropic substances; evidence of a subject's readiness to feel responsible for himself/herself; therapy compliance; and no evidence of serious personality defects.

DEC Category: Narcotic Analgesic.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size constricted; little to no reaction to light; pulse rate down; blood pressure down; body temperature down. Other characteristic indicators may include muscle tone flaccidity, droopy eyelids, drowsiness, depressed reflexes, and dry mouth.

Panel's Assessment of Driving Risks: Moderate to severely impairing in naïve or non-tolerant individuals, causing dose-dependent reductions in reaction time, visual acuity and information processing. Significant psychomotor impairment is not expected in tolerant individuals. Driving ability and driving fitness are nevertheless often limited because of consumption of additional psychotropic substances and psychopathological findings.

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Methamphetamine (and Amphetamine)

Methamphetamine hydrochloride is a white to light brown crystalline powder, or clear chunky crystals resembling ice. Methamphetamine base is a liquid.

Synonyms: *Methamphetamine*: chalk, chrissy, crank, crystal, glass, go, hydro, ice, meth, rock candy, speed, whiz; Desoxyn®; *Amphetamine*: dextroamphetamine; Dexedrine®, Adderall®, Benzedrine®, DextroStat®, Biphetamine®, Gradumet®.

Source: The majority of street methamphetamine is produced in clandestine laboratories (e.g. reduction of *l*-ephedrine or *d*-pseudoephedrine over red phosphorus with hydroiodic acid, or reduction with sodium or lithium in condensed liquid ammonia). Methamphetamine remains concentrated in western U. S. states and some rural areas elsewhere. *d*-Methamphetamine is a schedule II controlled substance (Desoxyn®) available in 5 mg white, 10 mg pink, and 15 mg yellow strength tablets. Amphetamine is also a Schedule II controlled substance and is usually supplied as the sulfate salt of the *d*-isomer (Dexedrine®), or as the racemic mixture (Benzedrine®), or a mixture of the two (Adderall®). Dexedrine® is available in 5, 10, and 15 mg strength, orange/black capsules, or 5 mg tablets. Adderall® is available in 5, 7.5, 10, 12.5, 20, and 30 mg strength, blue or orange tablets.

Drug Class: CNS stimulant, sympathomimetic, appetite suppressant.

Medical and Recreational Uses: Medicinally, methamphetamine is used in the treatment of narcolepsy, attention deficit disorder (ADD), and attention deficit hyperactivity disorder (ADHD). Typical doses are 10 mg/day or up to 40 mg daily, and a course of greater than six weeks is not recommended. Methamphetamine is infrequently used in the treatment of obesity, overeating disorders, and weight loss due to its abuse potential. Amphetamine is also used in ADD, narcolepsy, and weight control. Recreationally, methamphetamine is abused to increase alertness, relieve fatigue, control weight, treat mild depression, and for its intense euphoric effects.

Potency, Purity and Dose: Purity of methamphetamine is currently very high, at 60-90%, and is predominantly *d*-methamphetamine which has greater CNS potency than the *l*-isomer or the racemic mixture. Common abused doses are 100-1000 mg/day, and up to 5000 mg/day in chronic binge use. Therapeutic doses of Desoxyn® are 2.5-10 mg daily, with dosing not exceed 60 mg/day. To treat narcolepsy, 5-60 mg/day of amphetamine is ingested in divided doses; and in ADD and ADHD doses of 2.5-10 mg/day is administered, depending on age.

Route of Administration: Methamphetamine users often begin with intranasal or oral use and progress to intravenous use, and occasionally smoking. In contrast to cocaine, the hydrochloride salt of methamphetamine can itself be smoked. Methamphetamine is used sometimes with alcohol or marijuana, particularly during the withdrawal phase.

Pharmacodynamics: Methamphetamine increases synaptic levels of the neurotransmitters dopamine, serotonin (5-HT) and norepinephrine, and has α and β

adrenergic agonist effects. Norepinephrine is responsible for methamphetamine's alerting, anorectic, locomotor and sympathomimetic effects; dopamine stimulates locomotor effects, psychosis, and perception disturbances; and 5HT is responsible for delusions and psychosis. Methamphetamine's effects are similar to cocaine but its onset is slower and the duration is longer. Racemic amphetamine and d-amphetamine have similar chemical properties and actions to methamphetamine but are less potent.

Pharmacokinetics: Following oral administration, peak methamphetamine concentrations are seen in 2.6-3.6 hours and the mean elimination half-life is 10.1 hours (range 6.4-15 hours). The amphetamine metabolite peaks at 12 hours. Following intravenous injection, the mean elimination half-life is slightly longer (12.2 hours). Methamphetamine is metabolized to amphetamine (active), p-OH-amphetamine and norephedrine (both inactive). Several other drugs are metabolized to amphetamine and methamphetamine and include benzphetamine, selegeline, and famprofazone.

Molecular Interactions / Receptor Chemistry: Methamphetamine is metabolized to amphetamine via cytochrome P450 2D6. Potential inhibitors of the 2D6 isoenzyme could decrease the rate of methamphetamine elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.65 (N=1).

Interpretation of Blood Concentrations: Blood concentrations can generally be used to distinguish therapeutic use from abuse. Concentrations of 0.02-0.05 mg/L are typical for therapeutic use, and up to 0.2 mg/L have been documented. Concentrations greater than this represent abuse. Concentrations do not disclose phase of use. Normal concentrations in recreational use are 0.01 to 2.5 mg/L (median 0.6 mg/L). Concentrations above this range will likely be associated with severe, possibly life threatening, toxicity. There is no evidence for improved performance in any task or test following use of doses greater than 40 mg (or concentrations greater than 0.2 mg/L).

Peak blood methamphetamine concentrations occur shortly after injection, a few minutes after smoking, and around 3 hours after oral dosing. Peak plasma amphetamine concentrations occur around 10 hours after methamphetamine use.

Interpretation of Urine Test Results: Positive results generally indicate use within 1-4 days but could be up to a week following heavy chronic use. Rate of excretion into the urine is heavily influenced by urinary pH. Between 30-54% of an oral dose is excreted in urine as unchanged methamphetamine and 10-23% as unchanged amphetamine. Following an intravenous dose, 45% is excreted as unchanged parent drug and 7% amphetamine.

Effects: Methamphetamine effects are less intense after oral ingestion than following smoked or intravenous use.
Early phase – Psychological: Euphoria, excitation, exhilaration, rapid flight of ideas, increased libido, rapid speech, motor restlessness, hallucinations, delusions, psychosis, insomnia, reduced fatigue or drowsiness, increased alertness, heightened sense of well

being, stereotypes behavior, feelings of increased physical strength, and poor impulse control.
Early phase – Physiological: Increased heart rate, increased blood pressure, increased respiration rate, elevated temperature, palpitations, irregular heartbeat, dry mouth, abdominal cramps, appetite suppressed, twitching, pallor, dilated pupils, HGN at high doses, faster reaction time, increased strength, and more efficient glucose utilization.
Late phase – Psychological: Dysphoria, residual stimulation, restlessness, agitation, nervousness, paranoia, violence, aggression, lack of coordination, pseudo-hallucinations, delusions, psychosis, and drug craving.
Late phase – Physiological: Fatigue, sleepiness with sudden starts, itching/picking/scratching, normal heart rate, and normal to small pupils which are reactive to light.

Binge use of methamphetamine can be broken down into the following phases: Rush – (5 minutes) intense euphoria, rapid flight of ideas, sexual stimulation, high energy, obsessive/compulsive activity, thought blending, dilated pupils; Shoulder – (1 hour) less intense euphoria, hyperactivity, rapid flight of ideas, obsessive/compulsive activity, thought blending, dilated pupils; Binge use – (1-5 days) the drug is frequently readministered in an attempt to regain or maintain euphoria; Tweaking – (4-24 hours) dysphoria, scattered and disorganized thought, intense craving, paranoia, anxiety and irritability, hypervigilance, auditory and tactile hallucinations, delusions, and normal pupils; Crash – (1-3 days) intense fatigue, uncontrollable sleepiness and catnapping, continuing stimulation, drug craving; Normal – (2-7 days) apparent return to "normalcy" although drug craving may appear; Withdrawal – anergia, anhedonia, waves of intense craving, depression, hypersomnolence, exhaustion, extreme fatigue.

Side Effect Profile: Light sensitivity, irritability, insomnia, nervousness, headache, tremors, anxiety, suspiciousness, paranoia, aggressiveness, delusions, hallucinations, irrational behavior, and violence. In overdose, symptoms may include hyperthermia, tachycardia, severe hypertension, convulsions, chest pains, stroke, cardiovascular collapse, and possible death. Other common side effects following abuse of amphetamines include viral hepatitis, Sexually Transmitted Diseases (STDs), HIV, septicemia, abscesses, collapsed blood vessels, and malnutrition. Chronic abuse generally produces a psychosis that resembles schizophrenia and is characterized by paranoia, picking at the skin, preoccupation with one's own thoughts, and auditory and visual hallucinations. Violent and erratic behavior is frequently seen among chronic abusers. Over time, methamphetamine appears to cause reduced levels of dopamine, which can result in symptoms like those of Parkinson's disease.

Duration of Effects: Onset of effects is rapid following intravenous use and smoking, while effects onset more slowly following oral use. Overall effects typically last 4-8 hours; residual effects can last up to 12 hours.

Tolerance, Dependence and Withdrawal Effect: Methamphetamine has a high potential for abuse and dependence. Tolerance may develop and users may quickly become addicted and use it with increasing frequency and in increasing doses. Abrupt

discontinuation of use can produce extreme fatigue, mental depression, apathy, long periods of sleep, irritability, and disorientation.

Drug Interactions: Phenobarbital, propoxyphene, phenytoin and MAOI's slow the metabolism of amphetamines and increases their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings. Amphetamines may counteract sedative effects of antihistamines. Methamphetamine may restore ethanol induced impairment in simple repetitive tasks of short duration, however, there is no restoration of ethanol-induced deficits of balance and steadiness. In general, high doses of amphetamines are likely to increase the impairing effects of alcohol. Chlorpromazine and haloperidol block dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines. Amphetamine potentiates the analgesic effect of meperidine.

Performance Effects: Laboratory studies have been limited to much lower doses than those used by methamphetamine abusers. Doses of 10-30 mg methamphetamine have shown to improve reaction time, relief fatigue, improve cognitive function testing, increase subjective feelings of alertness, increase time estimation, and increase euphoria. However, subjects were willing to make more high-risk choices. The majority of laboratory tests were administered 1 hour post dose. Expected performance effects following higher doses may include agitation, inability to focus attention on divided attention tasks, inattention, restlessness, motor excitation, increased reaction time, and time distortion, depressed reflexes, poor balance and coordination, and inability to follow directions.

***Effects on Driving*:** The drug manufacturer states that patients should be informed that methamphetamine and amphetamine may impair the ability to engage in potentially hazardous activities such as driving a motor vehicle. In epidemiology studies drive-off-the-road type accidents, high speed, failing to stop, diminished divided attention, inattentive driving, impatience, and high risk driving have been reported. Significant impairment of driving performance would also be expected during drug withdrawal. In a recent review of 101 driving under the influence cases, where methamphetamine was the only drug detected, blood concentrations ranged from <0.05-2.36 mg/L (mean 0.35 mg/L, median 0.23 mg/L). Driving and driver behaviors included speeding, lane travel, erratic driving, accidents, nervousness, rapid and non-stop speech, unintelligible speech, disorientation, agitation, staggering and awkward movements, irrational or violent behavior, and unconsciousness. Impairment was attributed to distraction, disorientation, motor excitation, hyperactive reflexes, general cognitive impairment, or withdrawal, fatigue and hypersomnolence.

DEC Category: CNS stimulant.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature normal to down. Other

characteristic indicators may include restlessness, body tremors, talkativeness, exaggerated reflexes, anxiety, and track marks or recent injection sites.

Panel's Assessment of Driving Risks: At lower dose, amphetamines have few effects on cognitive functioning and may result in an enhancement of some psychomotor tasks, but risk-taking increases at higher doses and responses become inappropriate. Drug withdrawal could also lead to the impairment of psychomotor skills required for safe driving.

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Methylenedioxymethamphetamine (MDMA, Ecstasy)

MDMA is a white, tan or brown powder. Available primarily in tablet form.

Synonyms: 3,4-methylenedioxymethamphetamine; ecstasy, ADAM, candy canes, disco biscuit, doves, E, eckie, essence, hug drug, love drug, M&M, rolls, white doves, X, XTC.

Source: MDMA is the methylenedioxy derivative of methamphetamine. Starting materials in its illicit manufacture include isosafrole (Leuckart reaction) and safrole (Merck patent). MDMA is most commonly found in tablet forms of various colors, carrying distinctive markings on one side such as a dove, E, yin/yang symbol, Mitsubishi symbol, etc. MDMA is a Schedule I controlled substance.

Drug Class: Mild CNS stimulant, empathogen, entactogen, mild hallucinogen and psychedelic, appetite suppressant.

Medical and Recreational Uses: Originally patented as an appetite suppressant and used as a possible adjunct to psychotherapy, there is currently no legitimate medical use in the U. S. MDMA is recreationally used as a party, rave or dance drug for its stimulant, mild hallucinogenic, and empathogenic properties.

Potency, Purity and Dose: MDMA exists as a racemic mixture, with the S-(+)-enantiomer having greater CNS potency compared to the R-(-)-enantiomer. Potency of street samples is highly variable, and tablets sold as 'ecstasy' may in fact contain little or no MDMA, but may contain caffeine, ephedrine, phenylpropanolamine, paramethoxyamphetamine (PMA), methylenedioxyamphetamine (MDA), dextromethorphan, amphetamine, methamphetamine, and ketamine. Some tablets have been reported to contain LSD or heroin. Typical doses in a series of pills can range between 10–150 mg of MDMA. User surveys report a range of doses between 50-700 mg in a session, with an average of 120 mg. Most common pattern of use is binge consumption at all night rave or dance parties. MDMA is frequently taken with other recreational drugs such as ethanol, marijuana, cocaine, methamphetamine, nitrous oxide, and GHB.

Route of Administration: Primarily oral administration, although MDMA could conceivably be dissolved and injected, or crushed and snorted.

Pharmacodynamics: MDMA is a phenylethylamine that has stimulant as well as psychedelic effects. MDMA is related in structure and effects to methamphetamine, however, it has significantly less CNS stimulant properties than methamphetamine. MDMA has a high affinity for 5-HT_2 receptors. Both S- and R- enantiomers of MDMA cause acute depletion of presynaptic serotonin (5-HT), depression of 5-HT synthesis by tryptophan hydroxylase, and retrograde destruction of 5-HT neurons following high doses. MDMA also increases levels of norepinephrine and dopamine. The MDMA metabolite, S-(+)- MDA, elicits more stereotypic behavior and is an even more potent

neurotoxin than the parent drug. MDA destroys serotonin-producing neurons which play a direct role in regulating aggression, mood, sexual activity, sleep, and sensitivity to pain.

Pharmacokinetics: MDMA is rapidly absorbed and the half-life of MDMA is ~ 7 hours, although non-linear pharmacokinetics have been observed due to stereoselective pharmacokinetics of the enantiomers. MDMA is metabolized to MDA which is the only metabolite reported in blood and plasma. S-(+)- MDA accumulates in blood due to stereoselective metabolism of S-(+)-MDMA. MDA is further metabolized to its 3-hydroxy-4-methoxy and 3,4-dihydroxy derivatives (HMA and HHA). Additional MDMA metabolites include 3-hydroxy-4-methoxymethamphetamine (HMMA) and 3,4-dihydroxymethamphetamine (HHMA). These polar hydroxylated metabolites are conjugated prior to their excretion in urine.

Molecular Interaction / Receptor Chemistry: The majority of MDMA N-demethylation to MDA is via the cytochrome P450 2D6 isoenzyme, with minor contributions by the 1A2 isoform. Potential inhibitors of these isoenzymes could decrease the rate of MDMA elimination if administered concurrently, while potential inducers could increase the rate of elimination. Both extensive and poor MDMA metabolizers have been identified.

Blood to Plasma Concentration Ratio: Data not available.

Interpretation of Blood Concentrations: No clear correlation exists between MDMA blood concentrations and effects. MDMA and MDA are the analytes detected in blood, with MDA concentrations typically only 5-10% of the corresponding MDMA concentrations. Higher MDA:MDMA ratios may indicate co-administration of MDA. Plasma concentrations following single oral doses of 50, 75, 100, 125 and 150 mg of MDMA were 0.02-0.08 mg/L, 0.13 mg/L, 0.19-0.21 mg/L, 0.24 mg/L, and 0.44 mg/L, respectively. Peak concentrations of MDMA and MDA are observed at 1.5-2 hours and 4 hours, respectively.

Interpretation of Urine Test Results: MDMA, MDA, HMMA, HHMA, HMA and HHA are typically found in urine following their hydrolysis. MDA and HMMA concentrations in urine are typically 10-15% of the corresponding MDMA concentrations.

Effects:
Psychological: Low to moderate doses (50-200 mg) produce mild intoxication, relaxation, euphoria, an excited calm or peace, feelings of well-being, increase in physical and emotional energy, increased sociability and closeness, heightened sensitivity, increased responsiveness to touch, changes in perception, and empathy. At higher doses, agitation, panic attacks, and illusory or hallucinatory experiences may occur.
Physiological: Low to moderate doses (50-200 mg) produce mild visual disturbances (blurred or double vision, increased light sensitivity), dilated pupils, dry mouth, sweating, ataxia, muscle tension, and involuntary jaw clenching.

Side Effect Profile: Impairment of cognitive, perception, and mental associations. Psychological difficulties include confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia. Subjects may experience fatigue, uncoordinated gait, decreased fine motor skills, attentional dysfunction (difficulty to maintain attention during complex tasks), preoccupation, hyperthermia, tachycardia, hyperthermia, hyponatremia, convulsions, and catatonic stupor. Prolonged cognitive and behavioral effects may occur including poor memory recall, flashbacks, panic attacks, psychosis, and depersonalization due to serotonergic neuron damage and decreased serotonin production as a result of long-term use.

Duration of Effects: Following oral administration, effects onset in 20-30 minutes and desired effects may last only an hour or more, depending on dose. Other general effects last for approximately 2-3 hours. LSD is sometimes used in combination with MDMA to increase its duration of effects. Residual and unwanted effects are generally gone within 24 hours although confusion, depression and anxiety may last several weeks.

Tolerance, Dependence and Withdrawal Effect: Drug stacking refers to the ingestion of single doses consecutively as effects begin to wane, similar to cocaine or methamphetamine binges. Such extensive or binge use usually occurs over weekends, and can result in exhaustion, apathy, depression, irritability, insomnia and muscle tension early the next week (often referred to as "terrible Tuesdays"). Tolerance does develop, however, the occurrence of physical and/or psychological dependence is unknown. Persistent neurological deficits may occur, including serotonergic neuron damage which leads to less production of serotonin.

Drug Interactions: The dopamine D_2 receptor antagonist, haloperidol, attenuates psychological effects of MDMA but has no effect on physiological effects.

Performance Effects: MDMA can enhance impulsivity and make it difficult for a person to maintain attention during complex tasks (selective attention, divided and sustained attention, and complex attention tasks). Laboratory studies have demonstrated changes in cognitive, perception and mental associations, instability, uncoordinated gait, and poor memory recall. Distortion of perception, thinking, and memory, impaired tracking ability, disorientation to time and place, and slow reactions are also known performance effects. Single oral doses of MDMA causes subjective excitability, anxiety, perceptual changes, and thought disorders 1-3 hours post dose.

Effects on Driving: In an advanced driving simulator study, subjects were given a mean single dose of 56 mg MDMA. Compared to a sober state, moderate effects on vehicle control, acceptance of higher levels of risk, acute changes in cognitive performance, and impaired information processing ability were observed. In six subjects arrested for driving under the influence, MDMA was the only drug detected at blood concentrations ranging from <0.05-0.58 mg/L. The subjects were cooperative and laid back, and experienced muscle twitching, body tremors, perspiring, dilated pupils, slow reaction to light, and poor performance on field sobriety tests. The following concentrations of MDMA have also been measured in other retrospective studies; serum

MDMA concentrations ranging from 0.001-0.514 mg/L (mean 0.076 mg/L) in 18 cases of driving impairment; blood MDMA concentrations ranging from 0.04-0.38 mg/L (mean 0.18±0.14 mg/L; median 0.19 mg/L) in 9 impaired driving cases; blood MDMA concentrations of 0.12, 0.08, and 0.14 mg/L in 3 impaired driving cases; and a blood MDMA concentration of 2.14 mg/L and urine 118.8 mg/L in one driving fatality case. Another study reported the occurrence of speeding, jumping red lights, hallucinations/delusions, and a sense of detachment in five impaired driving cases, however, no MDMA concentrations were mentioned.

DEC Category: Hallucinogen; (with many characteristics similar to a CNS stimulant)

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size dilated; reaction to light slow; pulse rate elevated; blood pressure normal to elevated; body temperature normal to elevated. Other characteristic indicators may include profuse sweating, muscle twitching, body tremors, and poor performance in field sobriety tests. Subjects are usually described as very cooperative and "laid-back". Note that elevated blood pressure and body temperature are not always observed.

Panel's Assessment of Driving Risks: Low to moderate single doses of MDMA can cause acute changes in cognitive performance and impair information processing, which in turn would impair driving ability. Basic vehicle control is only moderately affected, however, subjects may accept higher levels of risk.

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Morphine (and Heroin)

Morphine and heroin are white, crystalline powders. Illicit heroin may vary in color from white to dark brown due to impurities, or may appear as a black tar-like material.

Synonyms: *Morphine*: Astramorph®, Duramorph®, Infumorph®, Kadian®, Morphine Sulfate®, MSIR®, MS-Contin®, Oramorph SR®, Roxanol®. *Heroin*: diacetylmorphine, diamorphine; Mexican brown or Mexican black tar heroin; bags, blue-steel, China white, H, horse, junk, no-name, silk, skag, smack. Scramble (cut heroin), bone (uncut heroin for smoking), chippers (occasional users).

Source: Morphine is a naturally occurring substance extracted from the seedpod of the poppy plant, *Papavar somniferum*. The milky resin that seeps from incisions made in the unripe seedpod is dried and powdered to make opium, which contains a number of alkaloids including morphine. Morphine concentration in opium can range from 4-21%. An alternate method of harvesting morphine is by the industrial poppy straw process of extracting alkaloids from the mature dried plant, which produces a fine brownish powder. Morphine is a schedule II controlled substance and is available in a variety of prescription forms: injectables (0.5-25 mg/mL strength); oral solutions (2-20 mg/mL); immediate and controlled release tablets and capsules (15-200 mg); and suppositories (5-30 mg). Heroin is a schedule I controlled substance and is produced from morphine by acetylation at the 3 and 6 positions. The majority of heroin sold in the U. S. originates from Southeast Asia, South America (Columbia) and Mexico. Low purity Mexican black tar heroin is most common on the West coast, while high purity Columbian heroin dominates in the East and most mid-western states.

Drug Class: Narcotic analgesic.

Medical and Recreational Uses: Morphine is used medicinally for the relief of moderate to severe pain in both acute and chronic management. It can also be used to sedate a patient pre-operatively and to facilitate the induction of anesthesia. Heroin has no currently accepted medical uses in the U.S., however, it is an analgesic and antitussive.

Potency, Purity and Dose: The dosage of morphine is patient-dependent. A usual adult oral dose of morphine is 60-120 mg daily in divided doses, or up to 400 mg daily in opioid tolerant patients. Recreationally, daily heroin doses of 5-1500 mg have been reported, with an average daily dose of 300-500 mg. Addicts may inject heroin 2-4 times per day. Depending on the demographic region, the street purity of heroin can range from 11-72% (average U.S. purity is ~38%). Heroin may be cut with inert or toxic adulterants such as sugars, starch, powdered milk, quinine, and ketamine. Heroin is often mixed with methamphetamine or cocaine (“speedball”) and injected; or co-administered with alprazolam, MDMA (Ecstasy), crack cocaine, or diphenhydramine.

Route of Administration: *Morphine*: oral, intramuscular, intravenous, rectal, epidural, and intrathecal administration. Morphine tablets may be crushed and injected, while opium can be smoked. *Heroin*: smoked, snorted, intravenous (“mainlining”), and

subcutaneous ("skin popping") administration. Black tar heroin is typically dissolved, diluted and injected, while higher purity heroin is often snorted or smoked.

Pharmacodynamics: Morphine produces its major effects on the CNS primarily through μ-receptors, and also at κ- and δ-receptors. μ_1-receptors are involved in pain modulation, analgesia, respiratory depression, miosis, euphoria, and decreased gastrointestinal activity; μ_2-receptors are involved in respiratory depression, drowsiness, nausea, and mental clouding; κ-receptors are involved in analgesia, diuresis, sedation, dysphoria, mild respiratory depression, and miosis; and δ-receptors are involved in analgesia, dysphoria, delusions, and hallucinations. Heroin has little affinity for opiate receptors and most of its pharmacology resides in its metabolism to active metabolites, namely 6-acetylmorphine, morphine, and morphine-6-glucuronide.

Pharmacokinetics: The oral bioavailability of morphine is 20-40%, and 35% is bound in plasma. Morphine has a short half-life of 1.5 - 7 hours and is primarily glucuroconjugated at positions 3 and 6, to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively. A small amount (5%) is demethylated to normorphine. M6G is an active metabolite with a higher potency than morphine, and can accumulate following chronic administration or in renally impaired individuals. The half-life of M6G is 4 +/- 1.5 hours. Close to 90% of a single morphine dose is eliminated in the 72 hours urine, with 75% present as M3G and less than 10% as unchanged morphine. Heroin has an extremely rapid half-life of 2-6 minutes, and is metabolized to 6-acetylmorphine and morphine. The half-life of 6-acetylmorphine is 6-25 minutes. Both heroin and 6-acetylmorphine are more lipid soluble than morphine and enter the brain more readily.

Molecular Interactions / Receptor Chemistry: The uridine 5'-diphosphate-glucuronosyltransferase (UGT) 2B7 isoform is primarily involved in the metabolism of morphine. Potential inhibitors of this UGT isoform could decrease the rate of morphine elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Morphine 1.02; M6G 0.57; M3G 0.59

Interpretation of Blood Concentrations: Tolerance makes interpretation of blood or plasma morphine concentrations extremely difficult. Peak plasma morphine concentrations occur within an hour of oral administration, and within 5 minutes following intravenous injection. Average plasma concentrations of 0.065 mg/L are necessary for adequate therapeutic analgesia in ambulatory patients. Anesthetic concentrations can reach beyond 2 mg/L in surgical patients. Following oral doses of 10-80 mg, corresponding peak morphine concentrations in serum were 0.05-0.26 mg/L. Following an intravenous dose of 8.75g/70 kg, a peak serum concentration of 0.44 mg/L was reached. In 10 intravenous drug fatalities, where morphine was the only drug detected, postmortem whole blood morphine concentrations averaged 0.70 mg/L (range 0.20-2.3 mg/L). Following a single 12 mg intravenous mg dose of heroin, a peak heroin concentration of 0.141 mg/L was obtained at 2 minutes, while the 6-acetylmorphine and

morphine concentrations were 0.151 and 0.044, respectively. A single 5 mg intravenous dose of heroin produced a peak plasma morphine concentration of 0.035 mg/L at 25 minutes, while intravenous doses of 150-200 mg have produced plasma morphine concentrations of up to 0.3 mg/L. Intranasal administration of 12 mg heroin in 6 subjects produced average peak concentrations of 0.016 mg/L heroin in plasma within 5 minutes; 0.014 mg/L of 6-acetylmorphine at 0.08-0.17 hours; and 0.019 mg/L of morphine at 0.08-1.5 hours.

Interpretation of Urine Test Results: Positive morphine urine results generally indicate use within the last two to three days, or longer after prolonged use. Detection of 6-acetylmorphine in the urine is indicative of heroin use. High concentrations may indicate chronic use of the drug. It is important to hydrolyze urine specimens to assess a urine morphine concentration.

Effects: Depends heavily on the dose of morphine or heroin, the route of administration, and previous exposure. Following an intravenous dose of heroin, the user generally feels an intense surge of euphoria ("rush") accompanied by a warm flushing of the skin, dry mouth, and heavy extremities. The user then alternates between a wakeful and drowsy state ("on the nod").
Psychological: Euphoria, feeling of well-being, relaxation, drowsiness, sedation, lethargy, disconnectedness, self-absorption, mental clouding, and delirium.
Physiological: Analgesia, depressed heart rate, respiratory depression, CNS depression, nausea and vomiting, reduced gastrointestinal motility, constipation, flushing of face and neck due to dilatation of subcutaneous blood vessels, cramping, sweating, pupils fixed and constricted, diminished reflexes, and depressed consciousness.

Side Effect Profile: Drowsiness, inability to concentrate, apathy, lessened physical activity, constipation, urinary retention, nausea, vomiting, tremors, itching, bradycardia, severe respiratory depression, and pulmonary complications such as pneumonia. Medical complications among abusers arise primarily from adulterants found in street drugs and in non-sterile injecting practices, and may include skin, lung and brain abscesses, collapsed veins, endocarditis, hepatitis and HIV/AIDS. Overdose can include slow, shallow breathing, clammy skin, convulsions, extreme somnolence, severe respiratory depression, apnea, circulatory collapse, cardiac arrest, coma, and death.

Duration of Effects: Depending on the morphine dose and the route of administration, onset of effects is within 15-60 minutes and effects may last 4-6 hours. The duration of analgesia increases progressively with age although the degree of analgesia remains unchanged. Following heroin use, the intense euphoria lasts from 45 seconds to several minutes, peak effects last 1-2 hours, and the overall effects wear off in 3-5 hours, depending on dose.

Tolerance, Dependence and Withdrawal Effects: Both morphine and heroin have high physical and psychological dependence. With regular use, tolerance develops early to the duration and intensity of euphoria and analgesia. Withdrawal symptoms may occur if use is abruptly stopped or reduced. Withdrawal can begin within 6-12 hours after the last

dose and may last 5-10 days. Early symptoms include watery eyes, runny nose, yawning and sweating. Major withdrawal symptoms peak between 48-72 hours after the last dose and include drug craving, restlessness, irritability, dysphoria, loss of appetite, tremors, severe sneezing, diarrhea, nausea and vomiting, elevated heart rate and blood pressure, chills alternating with flushing and excessive sweating, goose-flesh, abdominal cramps, body aches, muscle and bone pain, muscle spasms, insomnia, and severe depression.

Drug Interactions: Alcohol increases the CNS effects of morphine such as sedation, drowsiness, and decreased motor skills. There is a higher risk of respiratory depression, hypotension and profound sedation or coma with concurrent treatment or use of other CNS depressant drugs such as barbiturates, benzodiazepines, hypnotics, tricyclic antidepressants, general anesthetics, MAO inhibitors, and antihistamines. Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Small doses of amphetamine substantially increase the analgesia and euphoriant effects of morphine and may decrease its sedative effects. Antidepressants may enhance morphine's analgesia. Partial agonists such as buprenorphine, nalbuphine, butorphanol, and pentazocine will precipitate morphine withdrawal.

Performance Effects: Laboratory studies have shown that morphine may cause sedation and significant psychomotor impairment for up to 4 hours following a single dose in normal individuals. Early effects may include slowed reaction time, depressed consciousness, sleepiness, and poor performance on divided attention and psychomotor tasks. Late effects may include inattentiveness, slowed reaction time, greater error rate in tests, poor concentration, distractibility, fatigue, and poor performance in psychomotor tests. Subjective feelings of sedation, sluggishness, fatigue, intoxication, and body sway have also been reported. Significant tolerance may develop making effects less pronounced in long-term users for the same dose. In a laboratory setting, heroin produced subjective feelings of sedation for up to 5-6 hours and slowed reaction times up to 4 hours, in former narcotic addicts. Euphoria and elation could also play a role on perception of risks and alteration of behaviors.

Effects on Driving: The drug manufacturer states that morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car, and patients must be cautioned accordingly. Driving ability in cancer patients receiving long-term morphine analgesia (mean 209 mg daily) was considered not to be impaired by the sedative effects of morphine to an extent that accidents might occur. There were no significant differences between the morphine treated cancer patients and a control group in vigilance, concentration, motor reactions, or divided attention. A small but significant slowing of reaction time was observed at 3 hours. In several driving under the influence case reports, where the subjects tested positive for morphine and/or 6-acetylmorphine, observations included slow driving, weaving, poor vehicle control, poor coordination, slow response to stimuli, delayed reactions, difficultly in following instructions, and falling asleep at the wheel.

DEC Category: Narcotic Analgesic.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size constricted; little or no reaction to light; pulse rate down; blood pressure down; body temperature down. Other characteristic indicators may include presence of fresh injection marks, track marks, flaccid muscle tone, droopy eyelids, drowsiness or "on-the-nod", and low raspy slow speech.

Panel's Assessment of Driving Risks: Classification of risk depends on tolerance, dose, time of exposure, acute or chronic use, presence or absence of underlying pain, physiological status of individual, and the presence of other drugs. Moderately to severely impairing in non-tolerant individuals. Mild to moderately impairing if morphine is used as medication on a regular basis for chronic pain. Severely impairing in acute situations if used orally, or as an intravenous medication, or if either drug is taken illicitly.

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Phencyclidine (PCP)

PCP is a white, crystalline powder (contaminants may cause tan to brown color), or a clear, yellowish liquid.

***Synonyms*:** 1-phenylcyclohexylpiperidine; amp, angel dust, animal tranquilizer, dips, dust, elephant, embalming fluid, formaldehyde, fry, hog, ozone, peace pill, rocket fuel, Sernyl, Sernylan, super kools, TicTac, tranq, water, wet.

***Source*:** Synthetic chemical made in clandestine laboratories, or diverted from veterinary sources. PCP is currently a Schedule II controlled substance. In illicit synthesis, piperidine is reacted with cyanide and cyclohexanone to make piperidinocyclohexanecarbonitrile (PCC), which is then reacted with phenylmagnesium bromide to make PCP. PCP can be mixed with dyes and sold in a variety of tablets, capsules and colored powders. PCP is also sold as a liquid in small shaker bottles. PCP analogs are also available: cyclohexamine (PCE), phenylcyclohexylpyrrolidine (PHP), phenylcyclopentylpiperidine (PCPP), and thienylcyclohexylpiperidine (TCP).

***Drug Class*:** Hallucinogen, dissociative anesthetic, psychotomimetic, sedative-hypnotic.

***Medical and Recreational Uses*:** Formerly used as a surgical anesthetic, however, there is no current legitimate medical use in humans. Used as a veterinary anesthetic or tranquilizer. Recreationally used as a psychedelic and hallucinogen.

***Potency, Purity and Dose*:** A light dose typically consists of 3-5 mg; a common dose is 5-10 mg; while a strong dose is greater than 10 mg. Lighter doses are usually smoked, intravenously or intranasally administered, while heavier doses are commonly ingested orally. The liquid can be sprinkled on tobacco or marijuana then smoked, or the cigarettes or joints themselves can be dipped in PCP solution; the resulting PCP dose can therefore vary widely. Due to difficulty of synthesis, street preparations have highly variable concentrations of PCP and byproducts. PCC, the PCP precursor, is found in approximately 20% of illicit samples and is more toxic than PCP as it releases cyanide. Abuse of PCP precursors or analog chemicals leads to similar or more devastating pharmacological effects than PCP. PCP is often administered or mixed with other drugs such as crack cocaine (“beam me up”), cocaine hydrochloride (“lovelies”), and marijuana (“crystal supergrass”, “donk”, “killer joints”, “sherms”, “wacky weed”, “wicky stick”).

***Route of Administration*:** Smoked, intravenous injection, snorted, added as eye drops, oral ingestion, and transdermal absorption.

Pharmacodynamics: Dopaminergic, anticholinergic and opiate-like activities exist. PCP is a non-competitive NMDA-receptor antagonist, and blocks dopamine reuptake and elevates synaptic dopamine levels. It has high affinity to sites in the cortex and limbic structures.

Pharmacokinetics: Well absorbed following all routes of administration, although ~ 50% of PCP in cigarette smoke is converted to an inactive thermal degradation product.

PCP is highly lipid soluble and is stored in fat and brain tissue. The plasma binding of PCP is 65% and its half-life ranges from 7-46 hours (average 21 hours). PCP is extensively metabolized to inactive metabolites by a variety of metabolic routes.

***Molecular Interaction / Receptor Chemistry*:** The cytochrome P450 3A isoenzyme plays a major role in PCP biotransformation. Potential inhibitors of this isoenzyme could decrease the rate of PCP elimination if administered concurrently, while potential inducers could increase the rate of elimination. PCP itself may inhibit 2B1 and 2C11 isoforms.

***Blood to Plasma Concentration Ratio*:** 0.94 and 1.0 reported.

***Interpretation of Blood Concentrations*:** There is no direct correlation between PCP concentration and behavioral or physical findings. Blood levels peak 1-4 hours after ingestion. Average peak plasma concentrations of 2.7 and 2.9 ng/mL were achieved after a 1 mg oral and intravenous dose, respectively. PCP concentrations ranged from 0.3 to 143 ng/mL in 63 patients presenting at a psychiatric hospital emergency room and were associated with a wide variety of psychotic clinical pictures resembling mania, depression or schizophrenia. All these patients had at least one manifestation of toxic psychosis and/or acute delirium, in addition to other symptoms. Similarly, plasma PCP concentrations ranged up to 812 ng/mL in 22 patients with nonfatal PCP intoxication. The most common physical findings were combativeness-agitation (64%), depressed level of consciousness (50%), hypertension (43%), miosis (43%) and tachycardia (43%). Blood PCP concentrations ranged from 12 to 118 ng/mL in 26 individuals arrested for public intoxication.

***Interpretation of Urine Test Results*:** Elimination of PCP in 72 hours urine ranges from 4 to 19% for unchanged drug and 25 to 30% for conjugated metabolites. Approximately 97% of a dose is excreted in 10 days, and PCP use can be detected in urine by immunoassay up to a week following a high dose. Urine PCP concentrations ranged from 0.4-340 mg/L in 19 intoxicated patients.

***Effects*:**
Psychological: Effects are usually dose dependent, and include euphoria, calmness, feelings of strength and invulnerability, lethargy, disorientation, loss of coordination, distinct changes in body awareness, distorted sensory perceptions, impaired concentration, disordered thinking, illusions and hallucinations, agitation, combativeness or violence, memory loss, bizarre behavior, sedation, and stupor.
Physiological: Rise in blood pressure and heart rate, flushing, profuse sweating, generalized numbness of extremities, blurred vision, grimacing facial expression, speech difficulties, ataxia, muscular incoordination, marked analgesia, nystagmus, and anesthesia. In the anesthetized state, the patient remains conscious with a staring gaze and rigid muscles.

***Side Effect Profile*:** Excessive salivation, nausea, vomiting, amnesia, combativeness, severe anxiety, paranoia, flashbacks, seizures, coma, and death. PCP can simulate

schizophrenic-like symptomatology such as flattened affect, dissociative thought disorder, depersonalization and catatonic states. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, weight loss, liver function abnormalities, and rhabdomyolysis.

Duration of Effects: Onset of effects is very rapid when smoked or injected (1-5 minutes) and are delayed when snorted or orally ingested (30 minutes), with a gradual decline of major effects over 4-6 hours. A return to 'normal' may take up to 24 hours. Consciousness is regained within 10-60 minutes following intravenous administration, with a prolonged recovery period of 3-18 hours. Long-term psychological effects are possible and PCP may precipitate a psychotic reaction lasting a month or more that clinically appears like schizophrenia.

Tolerance, Dependence and Withdrawal Effects: Most PCP users administer the drug intermittently, although daily use has been reported and tolerance may develop. There is evidence of tolerance to behavioral effects of PCP in animals. PCP can be addicting and use can lead to psychological dependence, craving and drug seeking behavior. There has been no demonstration of physical dependency in humans. Upon abrupt discontinuation, physical distress, lack of energy, and depression are reported. Long periods of use may lead to memory loss, difficulties with speech and thinking, depression, and weight loss. These can last up to a year after cessation of use.

Drug Interactions: Benzodiazepines can decrease hypertensive effects and reverse seizure activity of PCP. Chlorpromazine and PCP use can cause severe hypotension. PCP may enhance effects of other CNS depressants like barbiturates and alcohol.

***Performance Effects*:** Laboratory studies have shown that PCP causes disorientation, drowsiness, dizziness, ataxia, double or blurred vision, body image changes, disorganization of thoughts, combativeness, impairment of eye-hand coordination, memory impairment, paresthesia, slowed reaction time, distorted perceptions of space. Effects generally occur within 1 hour post dose. Subjective sensation of intoxication has been reported up to 8 hours and slowed reaction time up to 14 hours.

***Effects on Driving*:** Fifty-six (56) subjects were arrested for erratic driving and were evaluated by a drug recognition examiner. All subjects were judged to be driving under the influence of PCP, and blood PCP concentrations ranged from 12 to 188 ng/mL (mean 51 ng/mL). Similarly, blood PCP concentrations ranged from 10 to 180 ng/mL (mean 73 ng/mL) in 50 subjects arrested for driving under the influence of PCP.

***DEC Category*:** Phencyclidine.

***DEC Profile*:** Horizontal gaze nystagmus present; vertical gaze nystagmus present; lack of convergence present; pupil size normal; reaction to light normal; pulse rate elevated; blood pressure elevated; body temperature elevated. Other characteristic indicators may include rigid muscles, cyclic behavior, sudden turn to violence, lack of response to

painful stimuli, trance-like state or blank stare, sweating, incomplete or delayed verbal responses.

***Panel's Assessment of Driving Risks*:** The use of PCP is not compatible with skills required for safe driving. Severe impairment of mental and physical abilities can occur following single doses.

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Toluene

Toluene is a colorless, flammable liquid with a sweet pungent odor.

***Synonyms*:** Toluol, methylbenzene, methyl benzol, and phenylmethane.

***Source*:** Toluene is an aromatic hydrocarbon, occurring naturally in crude oil and in the tolu tree. It is produced during the process of making gasoline and other fuels from crude oil, in making coke from coal, and as a by-product in the manufacture of styrene. Toluene has numerous commercial and industrial applications and is a solvent in paints, lacquers, thinners, glues, correction fluid and nail polish remover, and is used in the printing and leather tanning processes. Due to its easy accessibility, low cost and ease of concealment, some U.S. states have placed restrictions on the sale of these products to minors.

***Drug Class*:** Volatile solvent, CNS depressant.

***Medical and Recreational Uses*:** No approved medical use of toluene. It is frequently abused for its intoxicating effects. Recreational use is most common among younger adolescents primarily because it is readily available, inexpensive and legal.

***Potency, Purity and Dose*:** Solvents in many commercial and industrial products are often mixed and the solvent "sniffer" is often exposed to other solvents in addition to toluene. Acute and chronic accidental exposure to toluene can also occur, particularly in work environments. Regulatory Limits: OSHA recommends a maximum of 200 ppm toluene in workplace air for an 8-hour work day, 40-hour work week; NIOSH recommends an exposure limit of 100 ppm toluene in workplace air; and ACGIH recommends an exposure limit of 50 ppm in workplace air.

***Route of Administration*:** Inhalation of vapor. May be sniffed directly from on open container, or "huffed" from a rag soaked in the substance and held to the face. Alternatively, the open container or soaked rag can be placed in a bag where the vapors can concentrate before being inhaled. Exposure can also occur by ingesting the liquid or via skin contact.

***Pharmacodynamics*:** Solvents have three proposed mechanisms of action: they may alter the structure of membrane phospholipid bi-layers, impairing various ion channels; they may alternatively alter membrane bound enzymes or receptor-site specificity for endogenous substrates; or they may produce toxic metabolites modifying the hepatic microsomal system and possibly adducting RNA and DNA molecules. Toluene depresses neuronal activity and reversibly enhances $GABA_A$ receptor-mediated synaptic currents and α_1-glycine receptor-activated ion channel function. Toluene also inhibits glutamatergic neurotransmission via NMDA receptors and alters dopaminergic transmission.

***Pharmacokinetics*:** Toluene is well-absorbed following oral ingestion and rapidly absorbed following inhalation. Toluene is detectable in the arterial blood within

10 seconds of inhalation exposure. It is highly lipid soluble and accumulates in adipose tissue, tissues with high fat content, and highly vascularized tissues. Highest concentrations are found in the liver, kidney, brain and blood. The initial half-life in whole blood averages 4.5 hours, (range of 3-6 hours), with a terminal phase half-life of 72 hours. The half-life in adipose tissue ranges from 0.5-2.7 days, increasing with amounts of body fat. Approximately 80% of a dose is metabolized in the liver. Side-chain hydroxylation to benzyl alcohol is followed by oxidation to benzaldehyde by alcohol dehydrogenase, oxidation to benzoic acid by aldehyde dehydrogenase and conjugation with glycine to hippuric acid or reaction with glucuronic acid to form benzoyl glucuronide. Ring hydroxylation to o- and p-cresol is a minor (~1%) metabolic pathway. 4%-20% is excreted unchanged by the lungs and <0.1% is excreted unchanged in the urine. 60%-70% is excreted in urine as hippuric acid (glycine conjugate), and 10%-20% as benzoic acid glucuronide conjugate.

Molecular Interactions / Receptor Chemistry: Toluene is metabolized to benzyl alcohol via the cytochrome P450 2E1 isoform, and to a lesser extent to benzyl alcohol, o-cresol, and p-cresol by 2B6, 2C8, 1A2 and 1A1 isoforms. Potential inhibitors of these isoenzymes could decrease the rate of toluene elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Breath Concentration Ratio: Ranges from 7 to 15

***Interpretation of Blood Concentrations*:** In non-exposed individuals, average toluene concentrations have been measured at 0.47 µg/L (non-smokers) and 1.14 µg/L (smokers). Toluene is detectable in arterial blood within 10 seconds of inhalation exposure. Exposure to 38 ppm for 8 hours resulted in blood toluene concentrations of 0.59 mg/L. Similarly, exposure to 34 ppm for 8 hours resulted in blood toluene concentrations of 0.457 mg/L, decreasing to 0.038 mg/L after 16 hours. Exposure to 100 ppm for 30 minutes produced 0.4 mg/L of blood toluene in resting individuals and 1.2 mg/L after exercise. In 136 toluene abusers hospitalized or arrested while intoxicated, blood toluene concentrations ranged from 0.3-30 mg/L. Three fatalities from acute toluene inhalation had blood concentrations of 50, 60, and 79 mg/L. In 8 fatal cases of accidental or intentional acute exposure of toluene, blood concentrations ranged from 10-48 mg/L (mean 22 mg/L).

In 53 toluene abusers, blood concentrations of less than 1.0 mg/L corresponded to an odor of "chemical" on the subject's breath; some signs of impairment were observed at concentrations of 1.0-2.5 mg/L; 50% of subjects with concentrations of 2.5-10 mg/L were hospitalized with marked intoxication including hallucinations; and unconsciousness or death were reported at concentrations of 10 mg/L or greater. In 6 subjects with blood toluene concentrations ranging from 9.8-31 mg/L, slurred speech, slow movements, and an inability to concentrate were observed within minutes of cessation of use.

***Interpretation of Urine Test Results*:** In 136 toluene abusers hospitalized or arrested while intoxicated, urine toluene concentrations ranged from 0-5 mg/L. In 120 glue sniffers, concentrations of toluene in the urine ranged from 0.1-40.3 mg/L. Urinary o-

cresol and hippuric acid concentrations may have a high correlation with blood toluene concentrations. Hippuric acid excretion increases during the first 4 hours of exposure to up to 4 times the background level, then decreases rapidly to background levels within 6 hours. O-cresol excretion peaks during the last hour of chronic exposure or in the period immediately after acute exposure. Exercise increases the rate of both hippuric acid and o-cresol excretion. Hippuric acid concentrations (not corrected for creatinine) in non-exposed persons averaged 800 mg/L (range 400-1400); daily exposure to 50 ppm averaged 1920 mg/L (range 1260-2930); 100 ppm ranged from 2800-3500 mg/L; and 200 ppm averaged 5970 mg/L (range 4120-8650). O-cresol is not normally detected in the urine of non-exposed persons, while exposure to 200 ppm results in concentrations of 1-3 mg/L.

***Effects*:**
Psychological: Dizziness, euphoria, grandiosity, floating sensation, drowsiness, reduced ability to concentrate, slowed reaction time, distorted perception of time and distance, confusion, weakness, fatigue, memory loss, delusions, and hallucinations.
Physiological: Irritation to the nose, throat, and eyes, headache, nystagmus, slurred speech, ataxia, staggering, impaired color vision, vigilance, nausea, vomiting, respiratory depression, convulsions, severe organ damage, coma, and death.
Mild exposure (100-1500 ppm) dose-dependently results in euphoria, dizziness, reduced inhibitions, feelings of inebriation similar to alcohol intoxication, headache, nausea, lethargy, slow thought and speech, impairment of coordination, loss of memory, slowed reaction time, fatigue, sedation, confusion, impaired cognition function, impaired visual perception, staggering gait, muscular fatigue, and insomnia. More severe intoxication (10,000-30,000 ppm) will lead to tremors, arrhythmias, paralysis, unconsciousness, coma, and death. Chronic exposure may result in paranoid psychosis, temporal lobe epilepsy, mental retardation, and visual impairment.

***Side Effect Profile*:** Toluene can cause brain, liver and kidney damage, hearing loss, memory impairment, and attention deficits. Death can result from heart failure, asphyxiation or aspiration. Toluene also owes its pharmacology to a mucosal irritant effect from an exothermic reaction with water. This results in vomiting, lacrimation and ocular burning, cough, chest pain, wheezing and possible interstitial edema, and kidney toxicity with tubular acidosis. Toluene exposure is also associated with a transient liver injury.

Duration of Effects: Once inhaled, the extensive capillary surface of the lungs allows rapid absorption of toluene and blood levels peak rapidly. Entry into the brain is extremely fast and onset of effects is almost immediate. Toluene effects generally last several hours.

Tolerance, Dependence and Withdrawal Effects: Tolerance to the effects of toluene has been shown in rats. Toluene has the potential to produce physical and psychological dependence, and its abuse liability is significant. Signs of physical dependence are observed on withdrawal.

Drug Interactions: There is a likely synergy or potentiation of effects with other solvents and CNS depressants. Acute consumption of ethanol inhibits toluene elimination resulting in increased blood toluene concentrations and tissue exposure. This is probably due to competition for alcohol dehydrogenase.

Performance Effects: Most analyses on performance have been on subjects exposed to 50-200 ppm over a 6-8 hour work period. Marked impairment in neurological and neuropsychological test performance have been observed, including impaired working memory and executive cognitive functions, impairment of visual-vigilance tasks, loss in color vision and visual perception, inability to concentrate, slow movements, and decreased response time to simple brief tests.

***Effects on Driving*:** No driving or simulator studies exist for toluene. Blood toluene concentrations were above ~1.0 mg/L in 114 drivers arrested on suspicion of driving while intoxicated in Norway between 1983-1987. In 29 of these cases toluene was the only detected drug, with mean blood concentrations of 10 mg/L (range 1-29.3 mg/L). The authors stated there was no simple relation between blood toluene concentrations and degree of impairment, however, almost all drivers with blood toluene concentrations greater than 9.2 mg/L were considered impaired or highly probably impaired. No driving observations were documented.

DEC Category: Inhalant

DEC Profile: Horizontal gaze nystagmus present in high doses; vertical gaze nystagmus present in high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate elevated; blood pressure elevated; body temperature normal. Other characteristic indicators may include strong odor of solvent or chemical on breath or clothes, residue of substance around nose, mouth or hands, slurred speech, and general intoxication.

Panel's Assessment of Driving Risks: Acute and chronic exposure to toluene can result in severe impairment.

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Zolpidem (and Zaleplon, Zopiclone)

Zolpidem is a white to off-white crystalline powder.

Synonyms: N,N, 6-trimethyl-2-p-tolyl imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate; zolpidem tartrate; Ambien®.

Source: Zolpidem is available by prescription and is a Schedule IV controlled substance. Ambien® is available in strengths of 5 mg and 10 mg (white and pink oval tablets, respectively). Sonata® contains zaleplon. Imovane® contains zopiclone.

Drug Class: Non-benzodiazepine sedative-hypnotic, CNS depressant, sleep aid.

Medical and Recreational Uses: Zolpidem is a non-benzodiazepine hypnotic used in short-term treatment (up to 4 weeks) of insomnia. Zaleplon and zopiclone also are indicated for the treatment of insomnia.

Potency, Purity and Dose: Recommended zolpidem dose is 10 mg immediately before bedtime (5 mg in the elderly). Recommended nighttime zaleplon and zopiclone doses are 5-20 mg and 7.5 mg, respectively. Patients treated with zolpidem often concurrently use other medications such as antidepressants, narcotic analgesics, and muscle relaxants

Route of Administration: Oral.

Pharmacodynamics: While zolpidem has a chemical structure unrelated to benzodiazepines, it is a $GABA_A$ receptor agonist and shares some of the pharmacological properties of benzodiazepines. Zolpidem preferentially binds to receptors containing an $\alpha 1$ subunit (also known as BZ1- or $\omega 1$-receptor subtypes). Zolpidem shortens sleep latency and prolongs total sleep time in patients with insomnia, but has little effect on the stages of sleep in normal subjects. It also has weak anticonvulsant properties. Zaleplon binds preferentially to BZ-1, but also to BZ-2 and BZ-3; while zopiclone binds equally to BZ-1 and BZ-2.

Pharmacokinetics: Zolpidem is absorbed readily from the gastrointestinal tract. First-pass hepatic metabolism results in an oral bioavailability of 67%, and 92% is bound in plasma. Zolpidem has a short elimination half-life (2.2 + 0.4 hours), which is reduced in children (~ 1.4 hours) and increased in the elderly (~ 2.8 hours) and patients with hepatic cirrhosis (~ 9.9 hours). Peak plasma concentrations are detected at 1.5-2.5 hours. Peak concentrations are decreased with food and increased in patients with hepatic insufficiency. Zaleplon has a bioavailability of 30% and has a shorter half-life (1.1 hours) compared to zolpidem.

Molecular Interactions / Receptor Chemistry: Zolpidem is converted to hydroxylated metabolites principally by cytochrome P450 3A4 isoenzymes, with minor contributions by 1A2 and 2C9 isoforms. Potential inhibitors of these isoenzymes could decrease the

rate of zolpidem elimination if administered concurrently, while potential inducers could increase the rate of elimination

***Blood to Plasma Concentration Ratio*:** Data not available.

Interpretation of Blood Concentrations: Single doses of 5 mg zolpidem resulted in average peak concentrations of 0.06 mg/L at 1.6 hours; 10 mg produced 0.12 mg/L at 1.6 hours; 15 mg produced 0.20 mg/L at 1.5 hours; and 20 mg produced 0.23 mg/L at 2.1 hours.

Interpretation of Urine Test Results: Urinary excretion of unchanged zolpidem is less than 1%.

Effects:
Psychological: Sleep induction, drowsiness, dizziness, lightheadedness, amnesia, confusion, concentration difficulties, and memory impairment.
Physiological: Nausea, ataxia, slow and slurred speech, slow reflexes, and difficulty with coordination.

Side Effect Profile: Somnolence, lightheadedness, vertigo, headache, nausea, fatigue, cognitive deficits, and impairment of consciousness ranging from somnolence to light coma. Infrequently reported side effects include agitation, depressive syndrome, detachment, nightmares, hallucination, leg cramp, paresthesia, speech disorder, double vision, dry mouth, and diarrhea. Hangover effects are unlikely with zolpidem, although morning-after anterograde amnesia may occur. In overdose, patients mainly suffer somnolence and drowsiness, pinpoint pupils, respiratory depression, and in extreme cases, coma and respiratory failure.

Duration of Effects: Following 10-20 mg oral doses of zolpidem, effects can last up to 4-5 hours (dose-dependent). There are generally no residual effects the morning after a nighttime dose of zolpidem. Sedation may extend for 8-16 hours following intoxication. Zaleplon has a more rapid onset and shorter duration of effects compared to zolpidem, while zopiclone has longer duration of effects.

Tolerance, Dependence and Withdrawal Effects: Tolerance and dependency are not typically detected after 4 weeks of therapeutic use; however, tolerance may develop with chronic use. There is some evidence of tolerance and physical dependency observed with chronic administration of zolpidem in animal models. Withdrawal following abrupt discontinuation may include mild dysphoria and insomnia, abdominal and muscle cramps, vomiting, sweating, tremors, convulsions, fatigue, flushing, lightheadedness, nervousness, and panic attacks.

Drug Interactions: Imipramine has an additive effect of decreased alertness; chlorpromazine has an additive effect of decreased alertness and decreased psychomotor performance; ritonavir decreases clearance though inhibiting CYP3A hydroxylation; ketoconazol also decreases clearance; and flumazenil is an effective and therapeutic

pharmacodynamic antagonist. Alcohol increases the sedation and decreases psychomotor performance produced by zolpidem. Other CNS depressant drugs may potentiate the effects of zolpidem. Zopiclone has additional performance decrements when concurrently taken with alcohol, carbamazepine, and diazepam.

Performance Effects: Unsteady gait, confusion, disorientation, and significant cognitive and psychomotor impairment can be observed within 1-5 hours following zolpidem doses of 10-20 mg. Memory impairment (learning, recall and recognition of words, pictures, and numbers) psychomotor slowing (digit symbol substitution task, circular light tasks), reduced attentional capacity (impaired divided and sustained attention), impaired balance (ataxia, dizziness), visual disturbances (double vision), and impaired time estimation have been recorded. Psychomotor impairment can be found up to 5 hours after a single 15 mg oral dose and up to 8.25 hours after a 20 mg dose. Memory and learning impairment can be found up to 8.25 hours following a 10-20 mg dose. There has been no significant residual effect on memory or actual driving when subjects have been tested the morning after a single 10 mg dose.

Following a single 10-20 mg dose of zaleplon, studies have shown no residual effects on actual driving (5-10 hours) or on body sway, reasoning, retrieval and spatial memory (4-9 hours); however, significant impairment has been reported within 1-3 hours of dosing. Minor impairment of delayed free recall has occurred 4 hours after 20 mg dose of zaleplon. For zopiclone, a single 7.5 mg dose can cause severe residual effects on actual driving at 5 and 10 hours, severe residual effects on body sway and memory at 4 hours, and minor impairment of delayed free recall 9 hours after dosing.

Effects on Driving: The drug manufacturer states that patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as driving a motor vehicle. Within the first 4-5 hours, zolpidem can produce significantly impaired coordinative, reactive and cognitive skills following single oral doses of 10-20 mg. However, no significant adverse effects were observed during a 1.5 hour driving test on a rural road, 10-12 hours after drug administration. In five reported cases of driving impairment in which zolpidem was the only drug detected, blood concentrations of zolpidem ranged from 0.08 to 1.4 mg/L (mean 0.65 mg/L). Symptoms and observed behavior included erratic driving (weaving, lane travel), slow and slurred speech, slow reflexes, dazed appearance, disorientation, confusion, loss of balance and coordination, loss of short-term memory, blacking out, somnolence, dilated pupils, double vision, poor performance on field sobriety tests, poor attention, and an inability to stand or walk unassisted. In another six reported cases of driving under the influence of zolpidem, blood concentrations ranged from 0.1 to 0.73 mg/L (mean 0.31 mg/L). The subjects were involved in automobile accidents or were seen to drive erratically, and symptoms included slow and slurred speech, ataxia, unsteady gait, confusion and disorientation.

DEC Category: CNS depressant

DEC Profile: Horizontal gaze nystagmus present; vertical gaze nystagmus present for high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse

rate down; blood pressure down; body temperature normal. Other characteristic indicators may include slow and slurred speech, somnolence, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: Zolpidem causes significant effects when driving within 5 hours of use (10 mg dose). Zaleplon causes significant impairment within 3 hours of use (10 mg), but no significant impairment after 4 hours (10 mg) and 5 hours (20 mg). Zolpidem and zaleplon are relatively free of residual morning-after effects. Zopiclone causes severe impairment 1-5 hours after dosing (7.5 mg), with residual hangover effects up to 10-11 hours.

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Biographical Sketches of Lead Authors and Main Contributors

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Fiona Couper, Ph.D.

Dr. Fiona J. Couper received her B.Sc. (Honors) degree in Pharmacology/Toxicology and her Ph.D. degree in Forensic Medicine/Toxicology from Monash University, Melbourne, Australia. During this period, Dr. Couper also worked as a forensic toxicologist at the Victorian Institute of Forensic Medicine (VIFM) in Melbourne. From 1997-1998, Dr. Couper held a postdoctoral fellowship position at the National Institute of Forensic Sciences and the VIFM, and in late 1998 became a senior research fellow at the University of Washington and the Washington State Toxicology Laboratory, in Seattle, U.S.A. Dr. Couper is now the Chief Toxicologist at the Office of the Chief Medical Examiner, Washington D.C. Dr. Couper's research has focused on the effects of prescription and illicit drugs on driving impairment, the use of drugs to facilitate sexual assaults, GHB and drug overdoses in the emergency room, and the prevalence of drug use in various community groups. Dr. Couper is also an active member of the Society of Forensic Toxicologists (SOFT), the American Academy of Forensic Sciences (AAFS), and the International Association of Forensic Toxicologists. Additionally, she is the chair of the Joint AAFS/SOFT Drugs and Driving Committee.

Barry Logan, Ph.D.

Dr. Barry K. Logan was born in Bearsden, Scotland, and earned his bachelor's degree in chemistry and Ph.D. in forensic toxicology from the University of Glasgow. In 1986 he accepted a research position in the Department of Toxicology and Chemical Pathology at the University of Tennessee in Memphis. In 1990 he joined the faculty of the University of Washington (UW) in the Department of Laboratory Medicine and was appointed Washington State Toxicologist. In 1999 the Washington State Toxicology Laboratory merged with the Washington State Patrol, and Dr. Logan was named Director of the newly created Forensic Laboratory Services Bureau. In addition to his duties as State Toxicologist and Clinical Assistant Professor at UW, he oversees operations of the State Patrol Crime Laboratories, Breath Test Section, and Implied Consent Section. Dr. Logan has more than 70 publications in the field of forensic toxicology and drug analysis, and is Board Certified by the American Board of Forensic Toxicology. He has been elected to the National Safety Council's Committee on Alcohol and Other Drugs and to the International Council on Alcohol, Drugs, and Traffic Safety, and has served as a consultant to the National Institute of Justice, the United Nations Drug Control Program, and numerous state agencies. He is a Fellow of the American Academy of Forensic Sciences, an active member of the Society of Forensic Toxicologists, and serves on the editorial boards of the Journal of Forensic Sciences and the Journal of Analytical Toxicology. His current research interests include stimulant use and driving impairment, drug interactions and postmortem toxicology, and drug facilitated sexual assault.

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Dr. Michael R. Corbett received his B.Sc., M.Sc. and Ph.D. degrees in chemistry from the University of Toronto, the last being conferred in 1989. He is also the coordinator, and an instructor, in the forensic science courses offered through the School of Continuing Studies at the University of Toronto, and has supervised undergraduate students in research projects at the Department of Pharmacology. Dr. Corbett received the prestigious "Excellence in Teaching Award" for overall cumulative achievement in 2001. Dr. Michael Corbett is currently a senior forensic toxicologist in the Province of Ontario in Canada. In the area of alcohol, other drugs, and the operation of motor vehicles, Dr. Corbett has been directly involved in over 2500 cases. He is a designated analyst pursuant to the Criminal Code of Canada. He has provided educational programs on alcohol screening devices and instruments, including human subject testing, to police, lawyers, judges, media, and university students. Dr. Corbett serves as a member of the editorial board of the Journal of Analytical Toxicology. He belongs to numerous professional peer organizations including the AAFS, SOFT and The International Association of Forensic Toxicologists (TIAFT). He also participates in committees including the Committee on Alcohol and Other Drugs of the Highway Traffic Safety Division of the National Safety Council and the Joint AAFS/SOFT Drugs and Driving Committee. Dr. Corbett is certified as a Diplomat in Forensic Toxicology by the American Board of Forensic Toxicology (D-ABFT).

Laurel Farrell, M.S.

Ms. Laurel J. Farrell received her B.A. in Chemistry from the University of Northern Colorado in 1979. Ms. Farrell then worked for the Colorado Department of Public Health and Environment for over twenty-one years serving in a variety of capacities in the drug and alcohol analytical laboratories. For the last half of her employment she served as the staff authority in the toxicology laboratory routinely providing expert testimony in Colorado courts and in US District Court on the effects of alcohol and other drugs on human performance. For the last two and half years, Ms. Farrell has been assigned to the Colorado Bureau of Investigation's Denver Laboratory. She is a member of several professional organizations. As an active member of the Society of Forensic Toxicologists, she has just finished seven years as an officer/director serving as President in 2002. She is a Fellow of the American Academy of Forensic Sciences and served as Chair of the Joint AAFS/SOFT Drugs and Driving Committee from 2000-2002 and as a member on this committee from 1995 to the present. Over that time period, Ms. Farrell has assisted in coordinating a number of continuing education workshops in the area of drug impaired driving and has recently served a guest editor for two volumes of Forensic Science Review focusing on the Effects of Drugs on Human Performance and Behavior. She is also an elected member of the National Safety Council's Committee on Alcohol and Other Drugs and the International Council on Alcohol, Drugs, and Traffic Safety.

Marilyn Huestis, Ph.D.

Dr. Marilyn A. Huestis is the Acting Chief, Chemistry and Drug Metabolism Section (CDM), Clinical Pharmacology and Therapeutics Research Branch, Intramural Research Program (IRP), National Institute on Drug Abuse (NIDA), NIH. Dr. Huestis conducts controlled drug administration studies and directs the core chemistry laboratory of the IRP, NIDA. She has worked in the fields of clinical and emergency toxicology, therapeutic drug monitoring, urine drug testing, and forensic toxicology, which have provided a unique background and the knowledge and experience necessary for drug abuse research. Her research focuses on the pharmacodynamics and pharmacokinetics of drugs of abuse. Special areas of interest include cannabinoids, alternate matrices for drug analysis, correlations of blood levels of drugs with performance effects, medication development projects including the buprenorphine as a pharmacotherapeutic agent in opioid dependence, and in utero drug exposure. Pregnant opiate addicts receiving buprenorphine or methadone as part of their treatment program have provided a unique opportunity to study the disposition of drugs in the mother and fetus, and the relationship between drug concentrations in a wide variety of biological specimens and maternal and neonatal outcome measures. Dr. Huestis hopes to develop a better understanding of drug abuse in women and the consequent drug exposure of neonates and children. Dr. Huestis is the principal investigator of several phase I clinical studies evaluating the effects of the cannabinoid receptor antagonist, SR 141716 in cannabis users. Dr. Huestis received a bachelor's degree in biochemistry from Mount Holyoke, a master's degree in clinical chemistry from the University of New Mexico, and a doctoral degree in toxicology from the University of Maryland in Baltimore. Dr. Huestis has been working in the fields of forensic and analytical toxicology, and clinical chemistry for more than thirty years and is recognized nationally and internationally for her contributions to the field. She has published extensively in these fields and serves on the Editorial Board of the Journal of Analytical Toxicology. She is an Adjunct Associate Professor in the Toxicology program of the University of Maryland at Baltimore and directs graduate and post-graduate student research. Dr. Huestis is currently President of the International Association of Forensic Toxicologists, past president of the Society of Forensic Toxicologists (SOFT) and past Chair of the Toxicology Section of the American Academy of Forensic Sciences. Dr. Huestis is also a member of the International Cannabinoid Research Society, American Association for Clinical Chemistry, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, the California Association of Toxicologists, Society of Hair Testing, and the United States Anti-Doping Agency Research Advisory Board.

Wayne Jeffrey, M.S.

Mr. Wayne K. Jeffery received his B.Sc (Pharmacy) degree in 1968 and M.Sc. (Pharmaceutical Chemistry) degree in 1971, from the University of Alberta, Edmonton, Alberta, Canada. He has been the Toxicology Section Head, Royal Canadian Mounted Police, Forensic Laboratory, Vancouver, since 1976. Mr. Jeffery is a member of 7 professional associations, including the Alberta Pharmaceutical Association and the Canadian Pharmaceutical Association. He has been a member of the Canadian Society of

Forensic Sciences, Drugs and Driving Committee since 1986 and has been chairman since 1994. He is the co-coordinator of the DRE/SFST Program in British Columbia and is the DRE coordinator for Canada. Mr. Jeffery has 19 scientific publications dealing with all aspects of Forensic Alcohol and Toxicology including 3 chapters in published books. He has given training on drug identification and identifying the drug user to Police forces in Asia, Caribbean, Central and South America and Europe; and is a lecturer on the following Police courses: Drug Identification, Drug Undercover Investigative Techniques, Clandestine laboratory Investigations and Chemical Safety and Drug Awareness Training.

Jan Raemakers, Ph.D.

Dr Jan Ramaekers obtained his Ph.D. in psychopharmacology from Maastricht University, on behavioral toxicity of medicinal drugs. Dr Ramaekers spent 8 years of research at the Institute for Human Psychopharmacology at Maastricht University. During these years he conducted a large number of experimental studies on the effects of medicinal drugs, such as antidepressants, antipsychotics, anxiolytics, anticonvulsants and antihistamines on cognition, psychomotor function and actual driving performance of healthy volunteers and patients. In 1995, the Institute for Human Psychopharmacology received the Widmark Award (International Counsel of Alcohol, Drugs and Traffic Safety), “for numerous contributions to the advancement of the cause of alcohol, drugs and traffic safety and sustained contributions to the support in this field”. In 1998, Dr Ramaekers accepted a position as Assistant Professor at the Faculty of Psychology at Maastricht University. He has been a co-organizer of courses in the field of Human Psychopharmacology, Biological Psychology and Traffic & Aviation Psychology. Dr Ramaekers is currently involved in research on the effects of illicit drugs, i.e. marijuana and MDMA, on driving. He is a member of the British Association of Psychopharmacology (BAP), the Collegium Internationale Neuro-Psychopharmacologicum (CINP) and the International Counsel of Alcohol, Drugs and Traffic Safety (ICADTS).

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