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Exhibit I

In re the Investigation by ERIC T. SCHNEIDERMAN,
Attorney General of the State of New York,
of the Sale of Unlabeled, Misbranded and
Misleadingly Labeled Designer Drugs.

AFFIDAVIT

STATE OF NEW YORK)
COUNTY OF JEFFERSON) ss:

Maja Lundborg-Gray, M.D., FAAEM, FACEP, being duly sworn deposes and says as follows:

1. I am a physician licensed to practice medicine in the State of New York. I am board certified in emergency medicine since 1999 (recertified in 2009), a Fellow of the American Academy of Emergency Medicine, and a Fellow of the American College of Emergency Physicians. I am the president of North Country Emergency Medicine Consultants, P.C., and oversee the Emergency Department practice at Samaritan Medical Center, Watertown, New York. (Annexed hereto as Ex. A is a copy of my professional *curriculum vitae*.) Samaritan Medical Center's Emergency Department evaluates over 50,000 patients per year. See Professional *curriculum vitae* annexed hereto. In addition to these roles, I am the Emergency Medical Services Medical Director for Jefferson County, a Medical Director for the Regional Emergency Medicine Advisory Committee (REMAC) and I have directory oversight of an emergency first response company, Guilfoyle Ambulance Service, Inc., as their Medical Director.

2. This affidavit is submitted in support of Attorney General Eric T. Schneiderman's investigation of unlabeled, misbranded and misleadingly labeled so-called "designer drugs" sold from store shelves in New York State. Designer drugs are intended to stimulate, sedate or cause hallucinations or euphoria when ingested or

inhaled. Designer drugs used to refer to synthetic marijuana and bath salts, but the field of products is growing rapidly beyond these general categories. For example, products such as salvia, kratom, fly agaric mushrooms, geranium extract, blue lotus, and other "botanicals" are now readily available in retail outlets known as "head shops."

3. Recently the medical profession has been combating the public health challenge resulting from the use of these unlabeled, misbranded and misleadingly labeled designer drugs sold by headshops and other vendors. They pose an unreasonable risk of physical harm to the consuming public, and create an extremely dangerous situation both to the consumer, as well as to first responders. Poison Control numbers in New York State show a dramatic increase in calls related to all classes of these drugs over just the last three years.

4. Generally, synthetic marijuana products consist of plant material that has been laced with chemicals (synthetic cannabinoids) that mimic the ingredients in marijuana, but without THC. These products are marketed toward young people as a "legal" high and are consumed under the belief they are safe, legal and have no ill side effects. However, users are unaware that these products may be coated with chemicals that typically cause extreme anxiety, seizures, and convulsions when ingested. Further addiction and severe withdrawal symptoms are other hazards which in some instances are life-threatening.

5. "Bath salts" contain stimulant compounds that mimic the high of cocaine, methamphetamines, and ecstasy, but are extremely dangerous to consume. Patients are presenting with severe and sometimes deadly health effects from using these products, commonly including agitation, tachycardia (rapid heartbeat), elevated blood pressure,

hallucinations, seizures, extreme paranoia, panic, vomiting, mood swings, intense cravings to redose, and suicidal or homicidal thoughts. In extreme but increasingly common circumstances, these patients are being diagnosed with end stage organ failure, i.e. cardiac (heart), renal (kidney), liver failure which may lead to death and long term disability.

6. Patients who have taken bath salts are also frequently violent and assaultive on first presentation and present a definite danger, not only to the public, but to first responders, police, and the Emergency Department staff who care for these patients. These individuals often demonstrate extreme strength, with totally irrational behavior and responses.

7. There is a completely new level of violence and unpredictability associated with these patients. In some instances, hospital staff have been diverted from helping other patients in order to assist in securing and stabilizing designer drug users.

8. As set forth above, the designer drug problem is not limited to synthetic products. Increasingly, other street drug alternatives including "botanic" products such as salvia, kratom, fly-agaric mushrooms, geranium extract, blue lotus and others are being offered for a "legal high" or drug effect.

9. According to the U.S. Department of Justice Drug Enforcement Administration, salvia divinorum is an herb in the mint family native to certain areas of the Sierra Mazateca region of Oaxaca, Mexico. Salvia divinorum products are "abused for their ability to evoke hallucinogenic effects, which, in general, are similar to those of other scheduled hallucinogenic substances." Salvinorin-A is believed to be the active ingredient responsible for the hallucinogenic effects. Neither salvia divinorum nor

Salvinorin-A, have any approved medical uses in the United States. See Exhibit B. Side effects also include losing coordination, dizziness and slurred speech. I have reviewed the DEA fact sheet annexed hereto as Exhibit B, and agree with its statements on how and why salvia divinorum products are abused, their side effects and their lack of any licit medical use.

10. According to the Drug Enforcement Agency, kratom is a tropical tree native Southeast Asia. Like psychostimulant drugs, consumption of kratom leaves or extracts produces both stimulant effects in low doses and sedative effects in high doses and can lead to addiction. Several cases of psychosis resulting from use of kratom have been reported, where individuals addicted to kratom exhibited psychotic symptoms, including hallucinations, delusion, and confusion. Withdrawal effects include symptoms of hostility, aggression, mood swings, runny nose, achy muscles and bones, and jerky movement of the limbs. There is no legitimate medical use for kratom in the United States. I have reviewed the DEA fact sheet annexed hereto as Exhibit C, and agree with its statements on the effects of kratom, the possible psychosis that may result from ingesting kratom, the withdrawal effects and its lack of any licit medical use.

11. The Food and Drug Administration has identified fly agaric mushrooms (*amanita muscaria*) as a poison, and I concur. As set forth by the FDA, fly agaric mushrooms produce ibotenic acid and muscimol. Both substances produce the same effects, but muscimol is approximately five times more potent than ibotenic acid. Symptoms of poisoning generally occur within 1 to 2 hours after the mushrooms are ingested. Abdominal discomfort may be present or absent initially, but the chief symptoms are drowsiness and dizziness (sometimes accompanied by sleep), followed by

a period of hyperactivity, excitability, derangement of the senses, manic behavior, and delirium. Periods of drowsiness may alternate with periods of excitement, but symptoms generally fade within a few hours. According to the FDA report, fatalities rarely occur in adults, but in children, accidentally consuming large quantities of these mushrooms may result in convulsions, coma, or other neurologic problems for up to 12 hours. Ex. D.

12. It is my understanding that "geranium extract" is also appearing in designer drug products. I understand it to be the common name for 1,3-dimethylamylamine, a stimulant. DMAA is known to narrow the blood vessels and arteries, which can elevate blood pressure and may lead to cardiovascular events ranging from shortness of breath and tightening in the chest to heart attack. I understand that there has been a warning letter issued by the FDA regarding the sale of this compound as a "dietary supplement," and I concur with the substance of that warning. Ex. E.

13. Another "botanic," blue lotus (*Nymphaea caerulea*), contains nuciferine, an alkaloid with a profile of action associated with dopamine receptor blockade. It induces catalepsy, it inhibits spontaneous motor activity, conditioned avoidance response, amphetamine toxicity and stereotypy. It also contains aporphine, one of a class of quinoline alkaloids. Ex. F (S.K. Bhattacharya, et al., "Psychopharmacological Studies on Nuciferine and its Hofman Degradation Product Atherosperminine," *Psychopharmacology*, v. 59, pp. 29-33 [1978]). The net effect of ingesting these chemicals would likely be significant sedation.

14. These and other synthetics and botanic "extracts," can hide in designer drugs and cause serious health effects in the users.

15. I am also concerned about the use of nitrous oxide by the public for the purpose of inebriation and intoxication. According to a Nitrous Oxide Alert Bulletin issued by the Massachusetts Department of Public Health, Bureau of Substance Abuse Services, annexed hereto as Exhibit G,

The painkilling and numbing qualities of nitrous oxide begin to take effect when the gas is at concentrations of 10 percent. At higher concentrations, approaching 50%, a sense of well-being or euphoria is experienced. A person experiencing the effects of nitrous oxide may:

- Have slurred speech
- Have difficulty in maintaining his or her balance or walking
- Be slow to respond to questions
- Be immune to any stimulus such as pain, loud noise, and speech
- Lapse into unconsciousness (at higher concentrations)

If a person remains conscious and stops breathing the nitrous oxide, recovery can occur within minutes. A person who is rendered unconscious by nitrous oxide is likely to stop breathing within a few seconds as a result of a depressed central nervous system--brain, brain stem, and spinal cord. This depression is caused by a combination of the effects of nitrous oxide and the lowered oxygen content that occurs as pure N₂O displaces oxygen from the lungs with each succeeding inhalation of the gas. The end result is that the person can be asphyxiated. Death usually occurs when abusers, in their attempt to achieve a higher state of euphoria, breathe pure N₂O in a confined space -- in a small room or an automobile, or by placing their head inside a plastic bag. Tragedy can occur very quickly. Prolonged exposure to high concentrations of N₂O without supplemental oxygen, or a series of inhalations (without breathing clean air between inhalations) can result in death. This can happen in seconds. Since the narcotic effect of a single breath of nitrous oxide is very brief (lasting for only seconds), abusers tend to repeatedly inhale in order to stay "high," increasing the danger. With N₂O, there is no sensation of choking or gasping for air to warn the abuser that asphyxiation is imminent. A person who loses consciousness, and continues to inhale the pure gas, will die.

I agree with this Bulletin with respect to the effects of nitrous oxide and the danger it poses to users.

16. One problem remains consistent: No one knows for certain what the ingredients are in the toxic compounds without extensive, specialized toxicological

testing. Further, this testing is currently "send out testing" for most hospitals and is not available on the day of Emergency Department evaluation of the patient.

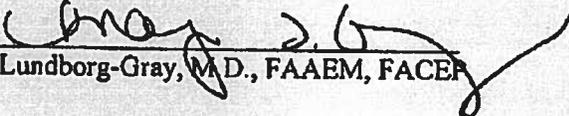
17. Perhaps the most important information physicians and medical personnel need when responding to a medical emergency is the identity of the drugs or substances that were recently ingested by the patient. This information is critical in determining an effective course of emergency treatment. In addition, this information is critically important to the safety of first responders in order for them to judge the hazards of a situation and is equally critically important to the medical and nursing staff in Emergency Departments while they evaluate and stabilize patients intoxicated with these drugs. Patients using these drugs put the community at large, police, first responders, hospital staff and other Emergency Department patients and their families at true risk due to the unknown effects of the intoxicants.

18. Unlike many illegal "street" drugs which our patients can commonly identify, victims of these designer drugs typically do not know the ingredients of the products they have purchased and consumed. Furthermore, even if the product name is known and disclosed, they are often labeled "not for human consumption" and provide no information as to possible health effects.

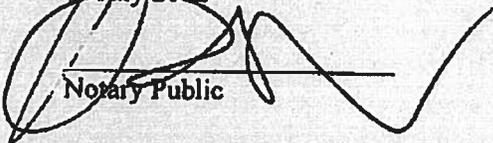
19. For many of the presenting patients, it is difficult to differentiate between a true psychiatric episode and the effects of these new, undisclosed intoxicants. Although many patients are treated and released, some experience severe outcomes, including organ failure or death. Additionally, due to the long half lives of the drugs being consumed, some patients are unknowingly being admitted to a psychiatric bed with a new

diagnosis of psychosis. The inability to pinpoint a toxin delays appropriate and necessary medical treatment.

20. The use of unidentified "designer drugs" continues to present challenges and dangers to the public and taxes the resources and safety of police, first responders, emergency personnel and the community at large.


Maja Lundborg-Gray, M.D., FAAEM, FACEP

Sworn to me this 5th day
of July 2012


Notary Public

DEANNA R. NELSON
Notary Public, State of New York
Registration No. 02NE5028585

Exp. 5/31/17

Exhibit I-A



**Maja Lisa Lundborg-Gray, MD, FAAEM,
FACEP**

30 Washington Street
Watertown, NY 13601
315-786-4813

MLGRAY@SHSNY.COM

Board Status

Board Certified in Emergency Medicine, ABEM, 1999, recertified 2009
Fellow, ACEP; Fellow, AAEM

Professional Experiences

- 1999 – present North Country Emergency Medicine Consultants, P.C., President
Own and operate a group of 12 plus physicians, 7 plus midlevel providers, and
administrative assistant. Our group is contracted to serve the Emergency
Department patients at Samaritan Medical Center evaluating over 50,000 patients
a year. Active participant in the Press Ganey initiative.
- May 2002 – 2008 Chairperson, Samaritan Medical Center, Emergency Department.
Oversight of 45,000 plus ED visits a year during this period.
Development/implementation of Quality Assurance practices. Development of
Emergency Department Performance Improvement Plan which is updated yearly
and reported to the Board and the Medical Executive Committee. Emergency
Department liaison to virtually all hospital departments, to administration at
Samaritan Medical Center, to local and county EMS, to Fort Drum MEDDAC
division, and to local community interests (NYS Living Museum at Thompson
Park, Business Fair, etc).
- 1998 – 1999 Emergency Medicine Consultants, P.C., employee
Samaritan Medical Center, Watertown, NY
- 1989 – 1990 High School Teacher: Chemistry, Advanced Placement Chemistry.
Dorm mother to group of Junior and Senior women (25 women).
Field Hockey and Tennis coach.
Miss Porter's School, Farmington, CT.

Education

- 1995 – 1998 **Allegheny University Hospital, Medical College of PA Division,**
Philadelphia, PA. Emergency Medicine Resident.
- 1991 – 1995 **New York Medical College,** Valhalla, NY. Doctor of Medicine, June 1995.
- 1990 – 1991 **New York Medical College,** Valhalla, NY. Graduate school.
- 1985 – 1989 **Trinity College,** Hartford, CT. Bachelor of Science, Biochemistry, June 1989.

Appointments

- 2001 – 2004 Adjunct Clinical Assistant Professor of Emergency Medicine
New York College of Osteopathic Medicine
- 2004 – present Clinical Assistant Professor of Family Medicine
University of New England College of Osteopathic Medicine

Activities/Interests

- Committees/Boards**
- Herring College Trust Board, Vice President, 2005 – 2007; Secretary 2008 – present; member 2002 to present
 - Thompson Park Conservancy Board, 2007 to present
 - Medical Staff Peer Review Committee, 2011 to present
 - Physician Development Committee, 2011 to present
 - Medical Executive Committee, SMC, 2002 – 2008
 - Strategic Planning Oversight Committee, SMC, 2005
 - Bioterrorism Preparedness Steering Committee, Internal and External, SMC, 2002 – 2008
 - Medical Staff Peer Review Task Force, SMC, 2005
 - ICU/Special Care Unit Committee, 2003 – present
 - CPR Committee, SMC, 2003 – 2006
 - Transition Team Committee, SMC, 2003 – 2004
 - Credentialing Committee, SMC, 2000 – 2004
 - Pharmacy and Therapeutic Committee, SMC, 1999 – 2001
 - Education Committee, SMC, 1999 – 2001
- EMS**
- REMAC Physician, 1999 – present, volunteer
 - Jefferson County EMS Medical Director, 2005 – present
 - Medical Director, Guilfoyle Ambulance, 2004 – present
 - Medical Director, Evans Mills Ambulance, 2008 – present, volunteer
 - Medical Director, Watertown Fire Dept, 1999 – present, volunteer
 - Medical Director, Brownville Rescue Squad, 2004 – present, volunteer
 - Medical Director, Black River Ambulance Squad, 2000
 - Medical Director, Felts Mills Fire Dept, Public Access Defibrillation, 2012-present
 - Medical Director, Sackets Harbor Ambulance, 2009
 - Medical Director, Henderson Fire Dept,
 - Medical Director, Harrisville Rescue Squad,
 - Medical Director, Town of Watertown Ambulance Squad, 2007
 - Medical Director, Glen Park Volunteer Fire Dept BLSFR,
 - Medical Director, Northpole Fire Dept BLSFR,
 - Medical Director, Bernier and Carr, Public Access Debrillator, 2012-present

Medical Director, EVAC Air Ambulance, 1999 – 2001, volunteer
Medical Director, Mannsville Manor Rescue, 1999 – 2004, volunteer,
EMS squad no longer in existence
Medical Director, Ellisburg Rescue Squad, 2003 – 2005, volunteer
Interim Medical Director, Jefferson Community College Paramedic
Program, 2004 – 2005

SMC Emergency Department Projects

ED Consulting Project, Clinical Leader, 2012 to present,
Emergency Excellence

Emergency Department Performance Improvement Plan and Report.
Encompasses collection/analysis/presentation of audit data (Audits –
Cardiac Arrest, Thrombolytic for Acute Myocardial Infarctions/CVA,
Trauma 1 and 2, HIV Postexposure Prophylaxis, Xray Discrepancies, ECG
Discrepancies, Left Without Being Seen/Left Against Medical Advice,
Suspected Domestic Abuse, Suspected Child Abuse, Length of Stay, Case
Reviews, 48 Hour Return analysis/Excell worksheet development/use,
Patient Complaints, NYPORT/DOH cases, Medical Record Compliance,
etc)

Development of and Update of SMC Emergency Department Mission
Statement and Core Values, summer 2005

Let's Not Meet By Accident Program: one of several developers of this
program at SMC. Collaboration between NYS Police, SMC ED and staff,
SUNY Trauma Center, Guilfoyle Ambulance. Driver's Education
students are shown in a 2 hour session the consequences of bad decision
making while behind the wheel. NYS Police and an ED physician discuss
the legal and medical consequences. The students rotate through the
morgue, organ donating session, ambulance bay. The session culminates in
observing and partaking in a Level 1 trauma simulation.

Development of Children and Fever Clinical Pathways, 2005.

Yearly Chairman review and update of Emergency Department polices.
Create new polices as needed – ex. Guidelines for Treatment of
Envenomations - NYS Living Museum at the Thompson Park.

Yearly Chairman review of HIV/Postexposure Prophylaxis for Sexual
Assault, Occupational/Nonoccupational Exposures with Infectious Disease
Specialist at SMC and SUNY

New York Medical College, Valhalla, NY

Student Senator, 1991 – 1995; Vice President, 1994 – 1995
Chairperson, Student Liaison Program for Clinical Years, 1993 – 1994
Chairperson, Alumni Student Phonathon, 1991 – 1993
Chairperson, Improve Student Life Committee, 1991 – 1992
Committee to form Policy for Student Harassment, 1992 – 1993
Emergency Medicine Club, 1993 – 1995

Trinity College, Hartford, CT

Alumni Interviewer, 1989 – present

Chemistry Society, 1985 – 1989, Vice President 1988 - 1989

Biology Club, 1985 – 1989

Junior Varsity Field Hockey, 1985 – 1986

Publications

Lundborg M, Heeren JK. Semi-microscale preparation on n-butyl bromide. Microscale Newsletter, Bowdoin College, 1988.

Lundborg M, Wang J, Xu X, Ochoa M, Schustek M, Zeballos G, Hintze TH. Mechanism of nitro-L-arginine induced hypertension in conscious dogs: reflexes, endothelin, and distributing of blood flow. Am J Phys, submitted for publication.

Lundborg M, Wang J, Hintze TH. Mechanisms of nitro-L-arginine induced hypertension in conscious dogs. The FASEB Journal, vol. 7, no. 4, February 1993: 4313A.

Hintze TH, Shen W, Wang J, Lundborg M. Role of EDRF/shear rate in the control of blood flow during exercise. JACC, vol. 21, no. 2, February 1993: 432A.

Shen W, Lundborg M, Wang J, Xu X, Hintze TH. An endothelium-derived relaxing factor-mediated mechanism buffers renal and splanchnic vasoconstriction during acute exercise in conscious dogs. Circulation, vol. 88, no. 4, Part 2, October 1993: 2019A.

Shen W, Lundborg M, Wang J, Stewart J, Xu X, Ochoa M, Hintze TH. The role of EDRF in the regulation of regional blood flow and vascular resistance at rest and during exercise in conscious dogs. J of Appl Phys, vol. 77, no. 2, July 1994: 165 – 172.

Awards

Emergency Medicine Physician of Excellence Award,
Jefferson County EMS, May 2000

Residency, 1998 Toxicology Award

New York Medical College, 1995

Walter Redisch MD Memorial Research Award

Bessie Morais MD Memorial Research Award

Parents Council Service Award

Cor et Manus Award

Educational Activities

1998 – present Active participant in medical education of osteopathic and allopathic interns/residents/students rotating through SMC

1998 – 2004 New York Osteopathic Medicine, Faculty

2004 – present University of New England College of Osteopathic Medicine, Clinical
Asst Professor of Family Medicine (Emergency Medicine)

March 1998 Chief Resident, Emergency Medicine Residency Program

1997 – 2000 ACLS Instructor

1995 – 1998 Clinical Instructor, Clinical Skills Course, Allegheny University School of
Medicine, Philadelphia, PA

1995 – 1998 Volunteer, Doctor-Lawyer Drug Abuse Prevention Project, elementary
school, Philadelphia, PA

1989 – 1990 High School Teacher (Chemistry, AP Chemistry) and Coach, Miss
Porter's School, Farmington, CT

1988 – 1989 Teaching Assistant: Physical Chemistry, Physical Biochemistry, Organic
Chemistry I and II, Trinity College, Hartford, CT

Professional Organizations

American Academy of Emergency Medicine, 1994 – present

American College of Emergency Physicians, 1994 – present

References Upon Request

Exhibit I-B



SALVIA DIVINORUM AND SALVINORIN A **(Street Names: Maria Pastora, Sage of the Seers, Diviner's Sage, Salvia, Sally-D, Magic Mint)**

November 2008
DEA/OD/ODE

Introduction:

Salvia divinorum is a perennial herb in the mint family native to certain areas of the Sierra Mazateca region of Oaxaca, Mexico. The plant, which can grow to over three feet in height, has large green leaves, hollow square stems and white flowers with purple calyces, can also be grown successfully outside of this region. *Salvia divinorum* has been used by the Mazatec Indians for its ritual divination and healing. The active constituent of *Salvia divinorum* has been identified as salvinorin A. Currently, neither *Salvia divinorum* nor any of its constituents, including salvinorin A, are controlled under the federal Controlled Substances Act (CSA).

Licit Uses:

Neither *Salvia divinorum* nor its active constituent salvinorin A has an approved medical use in the U.S.

Chemistry and Pharmacology:

Salvinorin A, also called Divinorin A, is believed to be the ingredient responsible for the hallucinogenic effects of *Salvia divinorum*. Chemically, it is a neoclerodane diterpene found primarily in the leaves, and to a lesser extent in the stems. Although several other substances have been isolated from the plant, none have been shown to be psychoactive.

In the U.S., plant material is typically either chewed or smoked. When chewed, the leaf mass and juice are maintained within the cheek area with absorption occurring across the lining of the oral mucosa (buccal). Effects first appear within 5 to 10 minutes. Dried leaves, as well as extract-enhanced leaves purported to be enriched with salvinorin A, are also smoked. Smoking pure salvinorin A, at a dose of 200-500 micrograms, results in effects within 30 seconds and lasts about 30 minutes.

A limited number of studies have reported the effects of using either plant material or salvinorin A. Psychic effects include perceptions of bright lights, vivid colors and shapes, as well as body movements and body or object distortions.

Other effects include dysphoria, uncontrolled laughter, a sense of loss of body, overlapping realities, and hallucinations (seeing objects that are not present). Adverse physical effects may include incoordination, dizziness, and slurred speech.

Scientific studies show that salvinorin A is a potent and selective kappa opioid receptor agonist. Other drugs that act at the kappa opioid receptor also produce hallucinogenic effects and dysphoria similar to that produced by salvinorin A. Salvinorin A does not activate the serotonin 2A receptor, which mediates the effects of other schedule I hallucinogens.

Illicit Uses:

Salvinorin A and *Salvia divinorum* products are abused for their ability to evoke hallucinogenic effects, which, in general, are similar to those of other scheduled hallucinogenic substances.

User Population:

According to a National Survey on Drug Use and Health Report published by SAMHSA in February 2008, it is estimated that 1.8 million persons aged 12 or older used *Salvia divinorum* in their lifetime, a approximately 750,000 did so in the past year. Use was more common among young adults (18 to 25 years old) as opposed to older adults (>26 years of age). Young adults were 3 times more likely than youths aged 12 to 17 to have used *Salvia divinorum* in the past year. Use is more common in males than females.

Illicit Distribution:

Salvia divinorum is grown domestically and imported from Mexico and Central and South America. The Internet is used for the promotion and distribution of *Salvia divinorum*. It is sold as seeds, plant cuttings, whole plants, fresh and dried leaves, extract-enhanced leaves of various strengths (e.g., 5x, 10x, 20x, 30x), and liquid extracts purported to contain salvinorin A. These products are also sold at local shops (e.g., head shops and tobacco shops).

Control Status:

Salvia divinorum and salvinorin A are not currently controlled under the CSA. However, a number of states have placed controls on *Salvia divinorum* and/or salvinorin A. As of November 2008, thirteen states have enacted legislation placing regulatory controls on *Salvia divinorum* and/or salvinorin A. Delaware, Florida, Illinois, Kansas, Mississippi, Missouri, North Dakota, Oklahoma, and Virginia have placed *Salvia divinorum* and/or salvinorin A into schedule I of state law. California, Louisiana, Maine and Tennessee enacted other forms of legislation restricting the distribution of the plant. States in which legislative bills proposing regulatory controls died are Alabama, Alaska, Hawaii, Indiana, Iowa, Minnesota, Nebraska, Oregon, South Carolina, and Utah. Legislative bills proposing regulatory controls are pending in Michigan, New Jersey, New York, Ohio, Pennsylvania, Texas and Wisconsin.

Salvinorin A and/or *Salvia divinorum* have been placed under regulatory controls in Australia, Belgium, Denmark, Estonia, Finland, Italy, Japan, Spain, and Sweden.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section, FAX 202-353-1263 or telephone 202-307-7183.

Exhibit I-C



Drug Fact Sheet

Kratom

Overview

Kratom is a tropical tree native to Thailand, Malaysia, Burma, and other areas of Southeast Asia. Consumption of its leaves produces both stimulant effects (in low doses) and sedative effects (in high doses) and can lead to addiction. The leaves from Kratom trees are widely available on the internet and sold as crushed leaves that can be smoked or steeped for tea and as gel caps.

Street names

Thang, Kakuam, Thom, Ketum, Biak

Looks like

The kratom tree can reach heights of 50 feet with a spread of more than 15 feet. Forms available through the Internet include leaves (whole or crushed), powder, extract, encapsulated powder, and resin "pies," (pellets made from reduced extract).

Methods of abuse

Kratom is mainly abused orally as a tea. Chewing kratom leaves is another method of abuse.

Affect on mind

At low doses, kratom produces stimulant effects with users reporting increased alertness, physical energy, talkativeness, and sociable behavior. At high doses, users experience sedative effects. Effects occur within 5 to 10 minutes of ingestion and last for 2 to 5 hours. Kratom consumption can lead to addiction. Several cases of psychosis resulting from use of kratom have been reported, where individuals addicted to kratom exhibited psychotic symptoms, including hallucinations, delusion, and confusion. Withdrawal effects include symptoms of hostility, aggression, mood swings, runny nose, achy muscles and bones, and jerky movement of the limbs.

Affect on body

Kratom's effects on the body include nausea, itching, sweating, dry mouth, constipation, increased urination, and loss of appetite. Long-term users of kratom have experienced anorexia, weight loss, insomnia, skin darkening, dry mouth, frequent urination, and constipation.

Drugs causing similar effects

The dominant effects of kratom are similar to those of psychostimulant drugs.

Overdose effects

Kratom has been abused as a recreational drug around the world. In low doses, Kratom works as a stimulant and in high doses as a sedative. In low doses (10 grams) kratom induces mild euphoria and reduces fatigue, and generally does not interfere with ordinary activities. With strong doses (20-50 grams) the effects are said to be profoundly euphoric and immensely pleasurable.

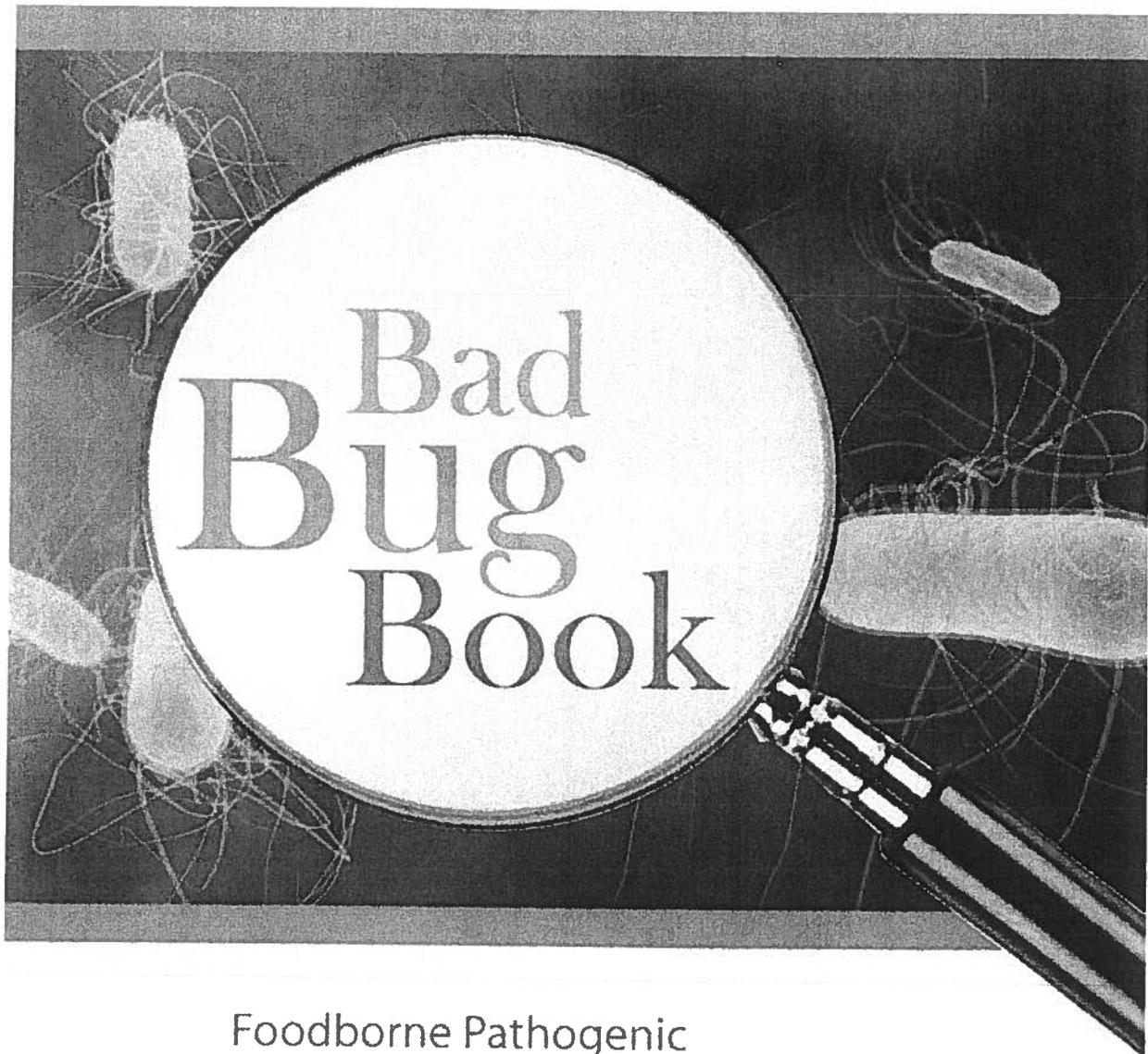
Legal status in the United States

Kratom is not controlled under the Controlled Substances Act. There is no legitimate medical use for Kratom in the United States. However, it is marketed on the internet as "alternative medicine" for use as a pain killer, medicine for diarrhea, and other ailments and for the treatment of opiate addiction. Kratom is legal in the United States but is on the DEA list of Drugs and Chemicals of Concern.

Common places of origin

The kratom tree grows in areas of Southeast Asia, but various forms of kratom are widely available on the Internet.

Exhibit I-D



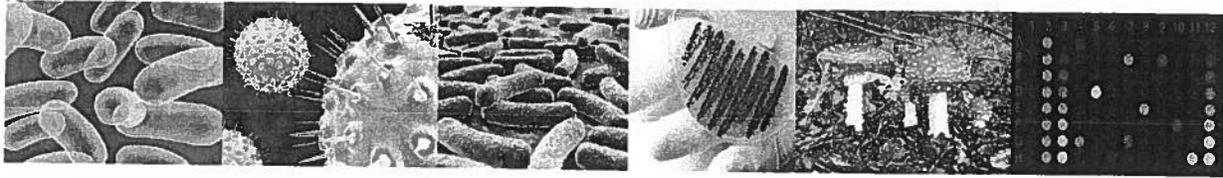
Foodborne Pathogenic
Microorganisms and Natural
Toxins Handbook



EXCERPTED

Bad Bug Book

Handbook of Foodborne Pathogenic Microorganisms and Natural Toxins



Introduction

Food safety is a complex issue that has an impact on all segments of society, from the general public to government, industry, and academia. The second edition of the Bad Bug Book, published by the Center for Food Safety and Applied Nutrition, of the Food and Drug Administration (FDA), U.S. Department of Health and Human Services, provides current information about the major known agents that cause foodborne illness. The information provided in this handbook is abbreviated and general in nature, and is intended for practical use. It is not intended to be a comprehensive scientific or clinical reference.

Under the laws administered by FDA, a food is adulterated if it contains (1) a poisonous or otherwise harmful substance that is not an inherent natural constituent of the food itself, in an amount that poses *a reasonable possibility* of injury to health, or (2) a substance that is an inherent natural constituent of the food itself; is not the result of environmental, agricultural, industrial, or other contamination; and is present in an amount that *ordinarily* renders the food injurious to health. The first includes, for example, a toxin produced by a fungus that has contaminated a food, or a pathogenic bacterium or virus, if the amount present in the food *may be* injurious to health. An example of the second is the tetrodotoxin that occurs naturally in some organs of some types of pufferfish and that *ordinarily* will make the fish injurious to health. In either case, foods adulterated with these agents are prohibited from being introduced, or offered for introduction, into interstate commerce.

Our scientific understanding of pathogenic microorganisms and their toxins is continually advancing. When scientific evidence shows that a particular microorganism or its toxins can cause foodborne illness, the FDA may consider that microorganism to be capable of causing a food to be adulterated. Our knowledge may advance so rapidly that, in some cases, an organism found to be capable of adulterating food might not yet be listed in this handbook. In those situations, the FDA still can take regulatory action against the adulterated food.

The agents described in this book range from live pathogenic organisms, such as bacteria, protozoa, worms, and fungi, to non-living entities, such as viruses, prions, and natural toxins. Included in the chapters are descriptions of the agents' characteristics, habitats and food sources, infective doses, and general disease symptoms and complications. Also included are examples of outbreaks, if applicable; the frequency with which the agent causes illness in the U.S.; and susceptible populations. In addition, the chapters contain brief overviews of the analytical methods used to detect, isolate, and/or identify the pathogens or toxins.

However, while some general survival and inactivation characteristics are included, it is beyond the scope of this book to provide data, such as D and z values, that are used to establish processes for the elimination of pathogenic bacteria and fungi in foods. One reason is that inactivation parameters for a given organism may vary somewhat, depending on a number of factors at the time of measurement. For more information on this topic, readers may wish to consult other resources. One example is the International Commission on Microbiological Specifications for Foods, the source of a comprehensive book (*Microorganisms in Foods 5. Characteristics of Microbial Pathogens*) on the heat resistance (D and z values) of foodborne pathogens in various food matrices, as well as data on survival and growth in many foods, including data on water activity and pH.

The Bad Bug Book chapters about pathogenic bacteria are divided into two main groups, based on the structure of the microbes' cell wall: Gram negative and Gram positive. A few new chapters have been added, reflecting increased interest in certain microorganisms as foodborne pathogens or as potential sources of toxins.

Another new feature is the brief section for consumers that appears in each chapter and is set apart from the main text. These sections provide highlights of information, about the microbe or toxin, that will be of interest to consumers, as well as information and links regarding safe food-handling practices. A glossary for consumers is included at the end of the book, separately from the technical glossary.

Various chapters link readers to Federal agencies with an interest in food safety, including the FDA, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture Food Safety Inspection Service. These are the primary agencies that collaborate to investigate outbreaks of foodborne illness, prevent foodborne illness, and advance the field of food safety, to protect the public's health. In addition, some technical terms have been linked to the National Library of Medicine's Entrez glossary.

Links to recent articles from the CDC's Morbidity and Mortality Weekly Reports are provided in selected chapters, to provide readers with current information about outbreaks or incidents of foodborne disease. At the end of selected chapters about pathogenic microorganisms, hypertext links are included to relevant Entrez abstracts and GenBank genetic loci.

Introduction for Consumers: A Snapshot

Each chapter in this book is about a pathogen – a bacterium, virus, or parasite – or a natural toxin that can contaminate food and cause illness. The book was prepared by the Food and Drug Administration (FDA) and contains scientific and technical information about the major pathogens that cause these kinds of illnesses. A separate “consumer box” in each chapter provides non-technical information, in everyday language. The boxes describe plainly what can make you sick and, more important, how to prevent it.

Most foodborne illnesses, while unpleasant, go away by themselves and don't have lasting effects. But you'll read about some pathogens that can be more serious, have long-lasting effects, or cause death. To put these pathogens in perspective, think about how many different foods and how many times you eat each day, all year, without getting sick from the food. The FDA and other Federal agencies work together and with the food industry to make the U.S. food supply one of the safest in the world.

You also play a part in the safety of what you eat. When you read the consumer boxes, you'll see that different pathogens can be risky in different ways, and that a safety step that's effective against one might not be as effective against another. So what should you do? The answer is to follow some simple steps that, together, lower the risk from most pathogens.

Washing your hands before and after handling food, and in between handling different foods, is one of the most important steps you can take. Do the same with equipment, utensils, and countertops.

Wash raw fruits and vegetables under running water. These nutritious foods usually are safe, as you probably know from the many times you've eaten them, but wash them just in case they've somehow become contaminated. For the most part, the less of a pathogen on a food – if any – the less chance that it can make you sick.

Cooking food to proper temperatures kills most bacteria, including Salmonella, Listeria, and the kinds of E. coli that cause illness, and parasites.

Keep any pathogens that could be on raw, unwashed foods from spreading by keeping raw and cooked foods separate. Keep them in different containers, and don't use the same equipment on them, unless the equipment is washed properly in between. Treat countertops the same way.

Refrigerate food at 40°F as soon as possible after it's cooked. Remember, the less of a pathogen there is in a food, the less chance that it can make you sick. Proper refrigeration keeps most types of bacteria from growing to numbers that can cause illness (although if a food already has high numbers of bacteria when it's put in the refrigerator, it could still cause illness).

Here are a few examples of why following all of these steps is important. Some types of bacteria form spores that aren't killed by cooking. Spores are a survival mode in which those bacteria make an inactive form that can live without nutrition and that develops very tough protection against the outside world. After cooking, the spores may change and grow into bacteria, when the food cools down. If any bacteria were present, refrigerating food quickly after cooking would help keep them from growing. On the other hand, cooking does kill most harmful

bacteria. Cooking is especially important when a pathogen is hard to wash off of a particular kind of food, or if a bacterium can grow at refrigerator temperatures, as is true of *Listeria monocytogenes* and *Yersinia enterocolitica*.

As you read about the differences among the pathogens, remember that there's a common theme: following all of the safety steps above can help protect you. The exceptions are toxins, such as the poisons in some mushrooms and a few kinds of fish and shellfish. Cooking, freezing, and washing won't necessarily destroy toxins. Avoiding them is your best protection, as you'll see when you read the chapters.

Table 1. Symptomatic diagnoses of mushroom poisonings

Onset Rapid (15 minutes to 2 hours after ingestion)		
Symptoms	Cause	Prognosis
Nausea and abdominal discomfort, sometimes with diarrhea and vomiting	Unknown toxins from numerous genera	Generally, rapid and complete recovery; serious cases may last 2 to 3 days and require fluid replacement
Profuse, prolonged sweating, tearing (lacrimation), salivation beginning 15-30 min after ingestion	Muscarine from <i>Clitocybe</i> or <i>Inocybe</i> spp.	Generally, complete recovery within approximately 2 h
Inebriation or hallucinations without drowsiness or sleep	Psilocybin from <i>Psilocybe</i> , <i>Panaeolus</i> , <i>Gymnopilus</i> , <i>Conocybe</i> , or <i>Pluteus</i> spp.	Generally, complete and spontaneous recovery within 5-10 h; may take up to 24 h, with large doses
Delirium with sleepiness or coma developing within 1 or 2h after ingestion	Ibotenic acid/muscimol from <i>Amanita muscaria</i> or <i>A. pantherina</i>	Generally, alternating periods of drowsiness and excitement for several h, followed by total recovery
Onset Delayed (6 hours to 3 days after ingestion)		
Symptoms	Cause	Prognosis
Persistent and violent vomiting, abdominal pain, profuse, watery diarrhea beginning around 12 h after ingestion	alpha-, beta-, and gamma-amanitins from <i>Amanita phalloides</i> and its relatives; <i>Galerina autumnalis</i> and its relatives; or <i>Lepiota josserandii</i> and its relatives	Generally, apparent recovery a few hours after onset of symptoms, followed by a symptom-free period of 3 to 5 days, which precedes a period of jaundice, loss of strength, coma, and, often, death
Feeling of abdominal fullness and severe headache about 6 h after ingestion, vomiting, no diarrhea	Gyromitrin and related hydrazines from <i>Gyromitra esculenta</i> and its relatives	Generally, complete recovery within 2 to 6 days; may require correction of metabolic acidosis; some deaths have occurred, due to liver failure

symptoms may be followed by abdominal pain, severe nausea, diarrhea, blurred vision, and labored breathing. Intoxication generally subsides within 2 hours.

Deaths are rare, but may result from cardiac or respiratory failure, in severe cases.

Ibotenic Acid/Muscimol Poisoning: [CDC/MMWR](#), [NIH/PubMed](#), [Agricola](#)

The Fly Agaric (*Amanita muscaria*) and Panthercap (*Amanita pantherina*) mushrooms both produce ibotenic acid and muscimol. Both substances produce the same effects, but muscimol is approximately five times more potent than ibotenic acid.

Symptoms of poisoning generally occur within 1 to 2 hours after the mushrooms are ingested. Abdominal discomfort may be present or absent initially, but the chief symptoms are drowsiness and dizziness (sometimes accompanied by sleep), followed by a period of hyperactivity, excitability, derangement of the senses, manic behavior, and delirium. Periods of drowsiness may alternate with periods of excitement, but symptoms generally fade within a few hours.

Fatalities rarely occur in adults, but in children, accidentally consuming large quantities of these mushrooms may result in convulsions, coma, or other neurologic problems for up to 12 hours.

Psilocybin Poisoning: [CDC/MMWR](#), [NIH/PubMed](#), [Agricola](#)

A number of mushrooms belonging to the genera *Psilocybe*, *Panaeolus*, *Copelandia*, *Gymnopilus*, *Conocybe*, and *Pluteus* which, when ingested, produce a syndrome similar to alcohol intoxication (sometimes accompanied by hallucinations). Several of these mushrooms (e.g., *Psilocybe cubensis*, *P. mexicana*, *Conocybe cyanopus*) are eaten for their psychotropic effects in religious ceremonies of certain native American tribes, a practice that dates to the pre-Columbian era.

The toxic effects are caused by psilocin and psilocybin. Onset of symptoms is usually rapid, and the effects generally subside within 2 hours. Poisonings by these mushrooms rarely are fatal in adults and may be distinguished from ibotenic acid poisoning by the absence of drowsiness or coma.

The most severe cases of psilocybin poisoning occur in small children, in whom large doses may cause hallucinations accompanied by fever, convulsions, coma, and death. These mushrooms are generally small, brown, nondescript, and not particularly fleshy; they are seldom mistaken for food fungi by innocent hunters of wild mushrooms.

Poisonings caused by intentional ingestion (other than that associated with religious tribal ceremonies) may involve overdoses or intoxications caused by a combination of the mushroom and some added psychotropic substance (such as PCP).

- Gastrointestinal Irritants

[Agricola](#)

- Psychotropic mushrooms more easily confused with edible mushrooms include the Showy Flamecap or Big Laughing Mushroom (*Gymnopilus spectabilis*), which has been mistaken for Chanterelles (*Cantharellus* spp.) and for *Gymnopilus ventricosus* found growing on wood of conifers in western North America.
- The Fly Agaric (*Amanita muscaria*) and Panthercap (*Amanita pantherina*) mushrooms are large, fleshy, and colorful. Yellowish cap colors on some varieties of the Fly Agaric and the Panthercap are similar to the edible Caesar's Mushroom (*Amanita caesarea*), which is considered a delicacy in Italy.
- Another edible yellow-capped mushroom occasionally confused with yellow *A. muscaria* and *A. pantherina* varieties is the Yellow Blusher (*Amanita flavorubens*). Orange to yellow-orange *A. muscaria* and *A. pantherina* may also be confused with the Blusher (*Amanita rubescens*) and the Honey Mushroom (*Armillariella mellea*).
- White to pale forms of *A. muscaria* may be confused with edible field mushrooms (*Agaricus* spp.).
- Young (button stage) specimens of *A. muscaria* also have been confused with puffballs.

5. Diagnosis

In the case of poisoning by the deadly Amanitas, important laboratory indicators of liver damage (elevated LDH, SGOT, and bilirubin levels) and kidney damage (elevated uric acid, creatinine, and BUN levels) will be present. Unfortunately, in the absence of dietary history, these signs could be mistaken for symptoms of liver or kidney impairment as the result of other causes (e.g., viral hepatitis). It is important that this distinction be made as quickly as possible, because the delayed onset of symptoms generally will mean that organ damage already has occurred.

A clinical testing procedure is currently available only for the most serious types of mushroom toxins, the amanitins. The commercially available method uses a 3H-radioimmunoassay (RIA) test kit and can detect sub-nanogram levels of toxin in urine and plasma. Unfortunately, it requires a 2-hour incubation period, and this is an excruciating delay in a type of poisoning that the clinician generally does not see until a day or two has passed. Amatoxins are eliminated in the urine, vomitus, and feces. They can be detected by chromatography, radioimmunoassay, and ELISA methods from bodily fluids and hepatorenal biopsies (Diaz 2005 b).

Since most clinical laboratories in this country do not use even the older RIA technique, diagnosis is based entirely on symptoms and recent dietary history. Despite the fact that cases of mushroom poisoning may be broken down into a relatively small number of categories based on symptomatology, positive botanical identification of the mushroom species consumed remains the only means of unequivocally determining the particular type of intoxication involved, and it is still vitally important to obtain such accurate identification as quickly as possible. Cases involving ingestion of more than one toxic species, in which one set of symptoms masks or mimics another set, are among many reasons for needing this information.

Unfortunately, a number of factors (not discussed here) often make identification of the causative mushroom impossible. In such cases, diagnosis must be based on symptoms alone. To rule out other types of food poisoning and to conclude that the mushrooms eaten were the cause of the

analysis is made on the basis of toxin chemistry. The exact chemical natures of most of the toxins that produce milder symptoms are unknown.

Chromatographic techniques (TLC, GLC, HPLC) exist for the amanitins, orellanine, muscimol/ibotenic acid, psilocybin, muscarine, and the gyromitrins. The amanitins may also be determined by commercially available 3H-RIA kits or ELISA test kits.

The most reliable means of diagnosing a mushroom poisoning remains botanical identification of the fungus that was eaten. Correctly identifying the mushrooms before they are eaten will prevent accidental poisonings. Accurate post-ingestion analyses for specific toxins, when no botanical identification is possible, may be essential only in cases of suspected poisoning by the deadly *Amanitas*, since prompt and aggressive therapy (including lavage, activated charcoal, and plasmapheresis) can greatly reduce the mortality rate.

8. Examples of Outbreaks

For more information about recent outbreaks, see the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Reports.

9. Other Resources

- Loci index for genomes *A. arvensis* | *L. sulphureus* | *V. bohemica* | *G. esculenta* | *I. geophylla* | *C. dealbata* | *A. muscaria* | *A. pantherina* | *Psilocybe spp.* | *C. rickenii* | *P. acuminatus* | *Pluteus spp.* | *C. molybdites* | *T. pardinum* | *O. illudens* | *P. involutus* | *A. virosa* | *Cortinarius spp.* | *C. atramentarius*
- GenBank Taxonomy database

10. Molecular Structures

Amanitin

Orellanine

Muscarine

Ibotenic Acid

Muscimol

Psilocybin

Gyromitrin

Coprine

3-5 days	Diarrhea, fever, vomiting abdominal pain, respiratory symptoms.	Enteric viruses
1-6 weeks	Diarrhea, often exceptionally foul-smelling; fatty stools; abdominal pain; weight loss.	<i>Giardia lamblia</i>
1 to several weeks	Abdominal pain, diarrhea, constipation, headache, drowsiness, ulcers, variable; often asymptomatic.	<i>Entamoeba histolytica</i>
3-6 months	Nervousness, insomnia, hunger pangs, anorexia, weight loss, abdominal pain, sometimes gastroenteritis.	<i>Taenia saginata</i> , <i>T. solium</i>
Neurological symptoms occur (visual disturbances, vertigo, tingling, paralysis)		
Less than 1 h	*** SEE GASTROINTESTINAL AND/OR NEUROLOGICAL SYMPTOMS (Shellfish Toxins) (this Appendix)	Shellfish toxin
	Gastroenteritis, nervousness, blurred vision, chest pain, cyanosis, twitching, convulsions.	Organic phosphate
	Excessive salivation, perspiration, gastroenteritis, irregular pulse, pupils constricted, asthmatic breathing.	Muscaria-type mushrooms
	Tingling and numbness, dizziness, pallor, gastric hemorrhage, desquamation of skin, fixed eyes, loss of reflexes, twitching, paralysis.	Tetradon (tetrodotoxin) toxins
1-6 h	Tingling and numbness, gastroenteritis, dizziness, dry mouth, muscular aches, dilated pupils, blurred vision, paralysis.	Ciguatera toxin
	Nausea, vomiting, tingling, dizziness, weakness, anorexia, weight loss, confusion.	Chlorinated hydrocarbons
2 h to 6 days, usually 12-36 h	Vertigo, double or blurred vision, loss of reflex to light, difficulty in swallowing, speaking, and breathing, dry mouth, weakness, respiratory paralysis.	<i>Clostridium botulinum</i> and its neurotoxins
More than 72 h	Numbness, weakness of legs, spastic paralysis, impairment of vision, blindness, coma.	Organic mercury

Exhibit I-E

U.S. Food & Drug Administration

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FDA NEWS RELEASE

For Immediate Release: April 27, 2012

Media Inquiries: Tamara Ward, 301-796-7567, tamara.ward@fda.hhs.gov

Trade Press Inquiries: Sebastian Cianci, 240-402-2291, sebastian.cianci@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA challenges marketing of DMAA products for lack of safety evidence

Agency cites ten companies in warning letters

The U.S. Food and Drug Administration today issued warning letters to ten manufacturers and distributors of dietary supplements containing dimethylamylamine, more popularly known as DMAA, for marketing products for which evidence of the safety of the product had not been submitted to FDA.

Also referred to as 1,3-dimethylamylamine, methylhexanamine, or geranium extract, the ingredient is in dietary supplements and is often touted as a "natural" stimulant.

The companies receiving warning letters and their product names are:

Company	Product(s)
Exclusive Supplements ¹	Biorhythm SSIN Juice
Fahrenheit Nutrition ²	Lean Efx
Gaspari Nutrition ³	Spirodex
iSatori Global Technologies, LLC ⁴	PWR
Muscle Warfare, Inc. ⁵	Napalm
MuscleMeds Performance Technologies ⁶	Code Red
Nutrex Research ⁷	Hemo Rage Black
	Lipo-6 Black Ultra Concentrate
	Lipo-6 Black
	Lipo-6 Black Hers Ultra Concentrate
	Lipo-6 Black Hers
SEI Pharmaceuticals ⁸	MethylHex 4,2
SNI LLC ⁹	Nitric Blast
USP Labs, LLC ¹⁰	Oxy Elite Pro
	Jack3D

"Before marketing products containing DMAA, manufacturers and distributors have a responsibility under the law to provide evidence of the safety of their products. They haven't done that and that makes the products adulterated," said Daniel Fabricant, Ph.D., Director of FDA's Dietary Supplement Program.

Specifically, the warning letters cite the companies for marketing products for which a notification had not been submitted for the use of DMAA as a New Dietary Ingredient (NDI). Under current law, dietary supplement manufacturers or distributors who use certain dietary ingredients not marketed in a dietary supplement prior to October 15, 1994, are responsible for notifying the FDA of evidence to support their conclusion that their dietary supplements containing NDIs are safe. Manufacturers or distributors must submit notification at least 75 days before marketing their products. The companies warned today were marketing products for which this requirement had not been met.

The FDA warning letters also advised the companies that the agency is not aware of evidence or history of use to indicate that DMAA is safe. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA),

manufacturers, marketers and distributors of dietary supplements are responsible for ensuring that they are marketing a safe product.

The FDA letters noted that DMAA is known to narrow the blood vessels and arteries, which can elevate blood pressure and may lead to cardiovascular events ranging from shortness of breath and tightening in the chest to heart attack. The agency has received 42 adverse event reports on products containing DMAA. While the complaints do not establish that DMAA was the cause of the incidents, some of the reports have included cardiac disorders, nervous system disorders, psychiatric disorders, and death.

The agency additionally warned the companies that synthetically-produced DMAA is not a "dietary ingredient" and, therefore, is not eligible to be used as an active ingredient in a dietary supplement. DSHEA defines a dietary ingredient as a vitamin, mineral, amino acid, herb or other botanical, a dietary substance for use by man to supplement the diet, or a concentrate, metabolite, constituent, extract, or combination of these substances.

The companies have 15 business days to respond to the FDA with the specific steps they will take to address the issues in the warning letters.

For more information:

[How dietary supplements are regulated](#)¹¹

[Dietary Supplement Health and Education Act of 1994](#)¹²

[New Dietary Ingredient notification process](#)¹³

[Reporting adverse events associated with FDA regulated products](#)¹⁴

#

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Exhibit I-F

Psychopharmacological Studies on (–)-Nuciferine and Its Hofmann Degradation Product Atherosperminine

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Abstract. (–)-Nuciferine and its Hofmann degradation product atherosperminine showed divergent psychopharmacological effects. Because nuciferine has been reported to be a neuroleptic and atherosperminine has some chemical resemblance to dopamine, they were investigated for their dopamine-receptor activities. Nuciferine had a pharmacologic profile of action associated with dopamine-receptor blockade; i.e., it induced catalepsy, inhibited spontaneous motor activity, conditioned avoidance response, amphetamine toxicity and stereotypy. On the other hand, atherosperminine produced effects associated with dopamine receptor stimulation, i.e., stereotypy, increase in spontaneous motor activity and amphetamine toxicity, reversal of haloperidol-induced catalepsy and inhibition of conditioned avoidance response, inhibition of morphine analgesia, and potentiation of the anticonvulsant action of diphenylhydantoin. The results are discussed on the basis of the chemical configuration of the two compounds.

Key words: Aporphine alkaloid and derived aryl-ethylamine – Nuciferine – Neuroleptic – Atherosperminine – Dopamine-receptor agonist/antagonist

(–)-Nuciferine, an aporphine alkaloid isolated from *Nelumbo nucifera* Gaertn., the Asiatic lotus, has been reported to exhibit a chlorpromazine-like pharmacologic profile of activity, although they are structurally unrelated (Macko et al., 1972). We were also interested in the pharmacologic actions of (–)-nuciferine because of the reported use of the plant in the traditional Indian system of medicine, Ayurveda, for a number of clinical conditions, including mental diseases (Kirtikar and Basu, 1935; Nadkarni, 1954; Chopra et al., 1956, 1958).

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While investigating the central effects of nuciferine and its Hofmann degradation product atherosperminine, we were intrigued by the widely divergent pharmacologic actions of the two drugs. It was therefore considered worthwhile to investigate the action of these two compounds on experimental parameters known to be associated with brain dopamine-(DA-)receptor activity, particularly because a neuroleptic like nuciferine is expected to produce at least some of its effects through DA-receptor blockade (Janssen, 1965; Van Rossum, 1966; Fog et al., 1968, 1971; Fog, 1972; Randrup et al., 1973) and because atherosperminine exhibited some pharmacological effects usually associated with DA-receptor stimulation (Fog, 1972).

Materials and Methods

Nuciferine (see Fig. 1), the major alkaloid of Indian lotus (*Nelumbo nucifera* Gaertn.), was isolated from the leaves of this aquatic plant by conventional method, as reported earlier (Tripathi et al., 1974). Treatment of nuciferine with methyl iodide gave a crystalline methiodide, m. p. 174°, which underwent a clean Hofmann elimination on refluxing with ethanolic sodium hydroxide (1 N) and yielded exclusively the phenanthrene derivative (see Fig. 1), a naturally occurring alkaloid of *Atherosperma moschatum* Labill (Bick et al., 1965). This compound was characterised from spectral evidence as well as by direct comparison with authentic atherosperminine (Tripathi et al., 1974).

Psychopharmacological experiments with nuciferine and the phenanthrene derivative were conducted on adult albino rats (100–200 g) and albino mice (20–30 g) of both sexes, at an ambient temperature of 25–29° C. Ten animals were used in each experimental group, unless otherwise mentioned. All drugs were administered i.p. and the pretreatment time was uniformly kept at 30 min.

Observational Test for General Behaviour and Toxicity in Albino Rats and Mice. Graded doses of the test drugs were administered to groups of animals, which were then observed for a period of 4 h and again after 24 h, for gross behavioural changes and acute toxicity (Turner, 1965). LD₅₀ was calculated in mice by the method of Miller and Tainter (1944).

Effect on Hexobarbitone (100 mg/kg, i.p.) Sleeping Time in Mice. Sleeping time was recorded as the interval between losing and regaining righting reflex.

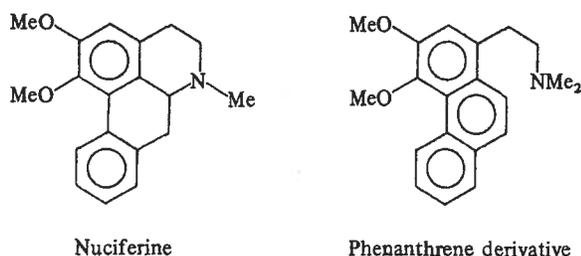


Fig. 1. Chemical structures of nuciferine and its phenanthrene derivative

Effect on Spontaneous Motor Activity (SMA) in Mice. SMA was recorded in groups of five unacclimatised mice each, using an actophotometer, and a 1-h cumulative record was taken for purpose of statistical evaluation. The methods were those of Dews (1953).

Effect on Amphetamine Toxicity in Aggregated Mice. Two doses of amphetamine were used, one (30 mg/kg, i.p.) producing 100% mortality and the other (10 mg/kg, i.p.) producing 20% mortality within 6 h. The methods were those of Trepanier et al. (1969).

Effect on Conditioned Avoidance Response (CAR) in Trained Rats. The pole-climbing apparatus (Cook and Weidley, 1957) was used. In some experiments the effect of one of the test drugs was noted on haloperidol- (0.5 mg/kg, i.p.) induced inhibition (100%) of CAR.

Effect on Haloperidol- (2 mg/kg, i.p.) Induced Catalepsy in Rats. The ring test of Pertwee (1972), with some modifications to make it suitable for rats (Bhattacharya and Bose, 1976), was used.

Effect on Amphetamine- (10 mg/kg, s.c.) Induced Stereotypy in Rats. Effect was measured according to Fog (1972).

Effect on Morphine Analgesia in Rats. The rat tail-hot wire technique of Davies et al. (1946) was used. Morphine was used in two doses, one (7.5 mg/kg, i.p.) showing significant analgesic effect and the other (2.0 mg/kg, i.p.) showing an insignificant analgesic action. The latent period of the tail-flick response was noted as the index of analgesia and the peak effect, which generally appeared 15 min after morphine, has been taken into account for data presentation and statistical analysis.

Effect on the Anticonvulsant Effect of Diphenylhydantoin Against Maximal Electroshock-Induced Seizures in Rats. Diphenylhydantoin was used in a dose (2.5 mg/kg, i.p.) that had no anticonvulsant effect per se. The methods were those of Toman et al. (1946).

Results

General Behaviour. Nuciferine (25–50 mg/kg, i.p.) produced moderate to marked sedation, hypothermia, ptosis, and diminished motility and grooming behaviour. Reflexes were intact and the animals responded to external stimuli. In higher doses (100–150 mg/kg, i.p.) rats exhibited catalepsy and maintained the awkward postures they were kept in. On the other hand, atherosperminine (25–50 mg/kg, i.p.) produced signs of central stimulation characterised by piloerection, increased motility, restlessness, tremors, and an abnormal twisting movement of the body. In higher doses (100 mg/kg, i.p.) rats exhibited stereotypy characterised by continuous licking and biting of the wire cages, gnawing, and occasional spurts of backward locomotion. A few rats exhibited clonic convulsions.

Effect on Hexobarbitone Sleep. Nuciferine markedly potentiated hexobarbitone sleep, whereas atherosperminine had practically no effect (Table 1).

Effect on SMA. Nuciferine significantly reduced SMA, whereas atherosperminine enhanced SMA (Table 2).

Effect on Amphetamine Toxicity. Nuciferine (25 mg/kg, i.p.) significantly inhibited amphetamine- (30 mg/kg, i.p.) induced lethal effect in aggregated mice, whereas atherosperminine (50 mg/kg, i.p.) potentiated the toxic effect of a lower dose (10 mg/kg, i.p.) of amphetamine (Table 3).

Effect on CAR- and Haloperidol- (0.5 mg/kg, i.p.) Induced Inhibition of CAR. Nuciferine (25 mg/kg, i.p.) totally blocked CAR in trained rats without affecting the response to unconditioned stimulus. Atherosperminine (100 mg/kg, i.p.) had no effect on CAR, but it reversed the blockade of CAR by haloperidol (Table 4).

Effect on Haloperidol- (2.0 mg/kg, i.p.) Induced Catalepsy. Pretreatment with atherosperminine (50 mg/kg, i.p.) markedly inhibited haloperidol-induced catalepsy.

Effect on Amphetamine- (10 mg/kg, s.c.) Induced Stereotypy. Nuciferine (25 mg/kg, i.p.) totally inhibited (100%) amphetamine-induced stereotyped response.

Effect on Morphine Analgesia. Nuciferine markedly potentiated the analgesic effect of a subanalgesic dose (2.0 mg/kg, i.p.) of morphine, whereas atherosperminine (50 mg/kg, i.p.) significantly inhibited morphine analgesia (7.5 mg/kg, i.p.) (Table 5).

Effect on Anticonvulsant Action of Diphenylhydantoin. Both nuciferine and atherosperminine potentiated the anticonvulsant effect of a sub-anticonvulsant dose (2.5 mg/kg, i.p.) of diphenylhydantoin by 50% and 70%, respectively (Table 6).

Acute Toxicity. LD₅₀ of nuciferine and atherosperminine, after i.p. administration in mice, was 289 mg/kg (220–360) and 356 mg/kg (250–430), respectively.

Discussion

The observations made with nuciferine in the present study confirm its chlorpromazine-like neuroleptic activity reported earlier (Macko et al., 1972). Thus the behavioural effects produced by the drug, including catalepsy, potentiation of hexobarbitone hypnosis, morphine analgesia, and anticonvulsant action of diphenylhydantoin, together with inhibition of amphetamine toxicity and stereotypy and blockade of CAR, all suggest possible neuroleptic activity (Brucke et al., 1966). We, however, failed to reproduce the analgesic

Table 1

Drugs (mg/kg, i.p.)	Sleeping time (min)		P
	Mean	SEM	
Hexobarbitone (100)	32.6	5.9	—
Nuciferine (25)			
+ hexobarbitone (100)	69.8	7.5	< 0.01
Atherosperminine (50)			
+ hexobarbitone (100)	28.9	3.7	> 0.05

P = Statistical significance in relation to control hexobarbitone group (*t*-test)

Table 2

Drugs (mg/kg, i.p.)	SMA (1-h cumulative record)		P
	Mean	SEM	
Normal saline	684	82	—
Nuciferine (25)	196	56	< 0.001
Atherosperminine (50)	1024	112	< 0.05

P = Statistical significance in relation to normal saline group (*t*-test)

effect of nuciferine reported by Macko et al. (1972), although it did potentiate morphine analgesia.

The Hofmann degradation product of nuciferine, atherosperminine, showed a quite dissimilar profile of activity, as compared to its parent compound. It produced excitation and stereotypy, had no effect on hexobarbitone hypnosis or CAR, inhibited morphine analgesia, potentiated amphetamine toxicity, and reversed haloperidol-induced catalepsy and blockade of CAR. However, both compounds potentiated the anticonvulsant action of diphenylhydantoin. This remarkable qualitative difference in the action of nuciferine and atherosperminine, prompted us to analyse the data on the basis of probable receptor activity of the two drugs. The inability of atherosperminine to potentiate hexobarbitone hypnosis and to inhibit CAR (Courvoisier et al., 1953), together with its other pharmacologic actions, discussed below, shows that it lacks the neuroleptic action of its parent drug, nuciferine.

It is generally conceded that stereotyped behaviour in rats is mediated by activation of dopamine (DA) receptors (Fog, 1972; Randrup et al., 1973, 1975; Randrup and Munkvad, 1974). Neuroleptics inhibit drug-induced stereotypy by producing DA-receptor blockade (Fog, 1972; Randrup et al., 1973). Similarly, catalepsy induced by neuroleptics, like haloperidol, is known to be due to DA-receptor blockade (Janssen, 1965; Fog, 1972). Hence it is conceivable that nuciferine and atherosperminine produced catalepsy and stereotypy by blocking and stimulating DA receptors,

Table 3

Drugs (mg/kg, i.p.)	Percent mortality	P
Amphetamine (30)	100	—
Nuciferine (25)		
+ Amphetamine (30)	30	< 0.01
Amphetamine (10)	20	—
Atherosperminine (50)		
+ Amphetamine (10)	70	< 0.05

N = 10; P = Statistical significance in relation to respective amphetamine groups (χ^2 test)

Table 4

Drugs (mg/kg, i.p.)	Inhibition of CAR (%)	P
Normal saline	0	—
Nuciferine (25)	100	< 0.001*
Atherosperminine (100)	0	—
Haloperidol (0.5)	100	< 0.001*
Atherosperminine (100)		
+ haloperidol (0.5)	0	< 0.001**

* Statistical significance in relation to normal saline group

** Statistical significance in relation to haloperidol group (χ^2 test)

Table 5

Drugs (mg/kg, i.p.)	Latent period of tail-flick response (s)		P
	Mean	SEM	
Morphine (2)	2.6	0.3	—
Nuciferine (25)	1.7	0.6	—
Nuciferine (25)			
+ morphine (2)	14.2	1.1	< 0.001
Morphine (7.5)	17.6	1.6	—
Atherosperminine (50)	0.9	0.1	—
Atherosperminine (50)			
+ morphine (7.5)	9.2	1.3	< 0.01**

* Statistical significance in relation to morphine (2) group

** Statistical significance in relation to morphine (7.5) group (*t*-test)

Table 6

Drugs (mg/kg, i.p.)	Anticonvulsant effect (%)	P
Diphenylhydantoin (2.5)	0	—
Nuciferine (25)	0	—
Atherosperminine (50)	0	—
Nuciferine (25)		
+ diphenylhydantoin (2.5)	50	< 0.05
Atherosperminine (50)		
+ diphenylhydantoin (2.5)	70	< 0.01

P = Statistical significance in relation to diphenylhydantoin group (χ^2 test)

respectively. This possibility is further strengthened by the ability of nuciferine to antagonise amphetamine-induced stereotypy, which is known to result from stimulation of DA receptors (Fog, 1972; Randrup et al., 1975). Similarly, atherosperminine's antagonism of the cataleptic effect of haloperidol can also be attributed to DA-receptor stimulation, since haloperidol is known to be a selective antagonist of DA receptors (Van Rossum, 1966; Fog et al., 1968, 1971). DA-receptor stimulants are known to have an anticataleptic effect (Zettler, 1968).

Although there is some controversy regarding the relative importance of brain noradrenaline and DA in motor activity, recent evidence favours a primary role for DA (Thornburg, 1972). Hence, the stimulation and inhibition of SMA by atherosperminine and nuciferine, respectively, is attributable to possible DA-receptor stimulation and blockade, respectively. Similarly, it is generally conceded that the central pharmacologic actions of amphetamine are due to either direct stimulation of DA receptors or to an indirect effect mediated by enhanced release and inhibition of reuptake of DA at specific neurones (Glowinski, 1970; Scheel-Krüger, 1972; Horn et al., 1974). As such, the potentiation of amphetamine toxicity in grouped mice by atherosperminine and its inhibition by nuciferine can be related to possible DA-receptor stimulation or blockade, respectively, by the two drugs.

CAR has also been shown to be a DA-mediated response (Davies et al., 1973), and the inhibition of CAR by neuroleptics has been attributed to blockade of DA receptors in the nigrostriatal dopaminergic system (Janssen, 1965). As such, inhibition of CAR by nuciferine provides added evidence for DA-receptor blockade induced by the drug. Conversely, reversal of haloperidol-induced inhibition of CAR by atherosperminine is indicative of its DA-receptor stimulant effect.

Morphine analgesia in the rat has been shown to be a serotonin-mediated response (Tenen, 1968; Samanin et al., 1971; Genovese et al., 1973; Bhattacharya et al., 1975, 1976a), while it has been postulated that DA exerts an inhibitory modulator influence (Major and Pleuvry, 1971; Bhattacharya et al., 1975, 1976a). The marked potentiation of morphine analgesia by nuciferine is in keeping with the well-known analgesia-potentiating action of neuroleptics in rats (Wirth, 1954) and in man (Zettler, 1953). On the other hand, the inhibition of morphine analgesia by atherosperminine is probably due to DA-receptor stimulation.

Both drugs showed one common pharmacologic action in potentiating the anticonvulsant action of diphenylhydantoin. The effect of nuciferine can be explained on the well-known anticonvulsant-potentiating action of chlorpromazine-like neuroleptics (Brucke et al., 1966). The effect of atherosperminine

is similarly in harmony with its possible DA-receptor stimulant action. Apomorphine, a selective DA-receptor agonist (Ernst and Smelik, 1968; Ernst, 1967), has been recently shown to potentiate the anticonvulsant action of diphenylhydantoin in rats (Bhattacharya et al., 1976b).

The results thus suggest that while nuciferine behaves as a DA-receptor antagonist, like other neuroleptics which exhibit a chlorpromazine-like profile of activity, its derivative, atherosperminine, acts as a DA-receptor agonist.

The reversal of the pharmacologic profile of activity of nuciferine (see Fig. 1) by mere fission of a bond is interesting but not unexpected. A compound in which the aminoethyl side chain of DA or DA-like unit is folded in such a manner that the amino nitrogen and the oxygen containing phenyl nucleus are in *gauche* disposition is generally found to be a neuroleptic. Such folding is found in isoquinoline derivatives and, as such, tetrabenazine and an alkaloid like tetrahydrocoptisine (Bhattacharya et al., 1976c) exhibit neuroleptic properties. On the other hand, a compound is expected to exhibit DA-receptor agonist activity if the aminoethyl side chain of the DA-like unit is folded like apomorphine, in which the amino nitrogen and the oxygenated phenyl nucleus are in *anti* conformation (Pinder et al., 1971; Cannon et al., 1975). In nuciferine the aminoethyl side chain is held in an isoquinoline ring system, and hence it exhibits neuroleptic properties. The flexible side chain in atherosperminine (see Fig. 1) can assume the required *anti* conformation for proper interaction with DA receptors to make this alkaloid a DA-receptor agonist. An enhancement of activity by demethylation of atherosperminine is a logical speculation, and work in this direction is in progress.

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Exhibit I-G



The Massachusetts Department of Public Health
Bureau of Substance Abuse Services

BULLETIN

Nitrous Oxide Alert

Introduction: Nitrous oxide (N_2O), also known as “laughing gas,” is a colorless, odorless, weak anesthetic gas that is being abused for its drug-like effects by teenagers and adults. Many people are unaware of the dangers of active inhalation (as a form of *inhalant abuse*) or chronic low level exposure (in medical, dental, and veterinary settings). The Massachusetts Department of Public Health is issuing this bulletin to alert youth-serving professionals and the public about the dangers of chronic exposure and especially non-medically supervised use of this gas.

The Massachusetts Department of Public Health is seeking to reduce the accessibility of N_2O by enlisting the cooperation of law enforcement, retailers, and wholesale distributors in curtailing the illegal use of nitrous oxide. Retailers are asked to monitor the sale of whipped cream chargers and canned whipped cream. Wholesale distributors are asked to restrict sales and sell only to clearly identified legitimate users. People responsible for the sale of nitrous filled balloons at concerts and sporting events, a clear violation of Massachusetts Law, should be prosecuted.

Why is nitrous oxide dangerous? N_2O is a central nervous system depressant that is absorbed through the lungs and is rapidly distributed throughout the body. It can cause health problems, accidents, and death. Frostbite damage to the throat and vocal cords results when the gas is inhaled directly from high pressure tanks; it becomes very cold when it changes from a liquid in the tank to a gas as it leaves the tank. Accidents result when impaired users have toppled heavy tanks onto themselves. Long term exposure, even at very low levels, may result in infertility or a vitamin B_{12} deficiency (which causes anemia and nerve degeneration, producing painful sensations in the arms and legs, an unsteady gait, loss of balance, irritability, and intellectual deterioration).¹

How does nitrous oxide cause death? Most deaths are caused by suffocation. Breathing the pure gas without sufficient oxygen will produce asphyxiation. This occurs when the gas is used without auxiliary oxygen or in a small enclosure such as when a plastic bag is used as a hood, or in a bathroom, closet, or car. Also, a user may be breathing the gas from a plastic bag, lose consciousness, and choke on the bag as it is sucked into the mouth. Another danger is choking on vomit while unconscious. Exposure to concentrations of N_2O in excess of 10% combined with oxygen deficiency will compromise a person’s ability to think and act safely and has been a factor in deaths related to accidents and car crashes.

What are the patterns of N_2O abuse? Most abusers are using the gas occasionally. Nitrous is being used at parties, in dormitories, fraternities, and at concerts and sporting events. There are a number of reports of abuse by dentists,

though this has decreased as more dental personnel have become aware of the dangers.³ Restaurant workers may obtain N_2O from whipped cream dispensers. At least one study has shown that nitrous oxide may be addictive.⁴

What are the workplace dangers? While medically approved for patients when used as an anesthetic, health concerns have been raised for medical, dental, and veterinary personnel exposed to long term, low levels of nitrous oxide in the workplace. The National Institute for Occupational Safety and Health (NIOSH) has concluded that, “exposure to N_2O causes decreased mental performance, audiovisual ability, and manual dexterity. Data from animal studies demonstrate that exposure to N_2O may cause adverse reproductive effects such as reduced fertility, spontaneous abortion, and neurological, renal, and liver disease.” In medical settings where N_2O is utilized, NIOSH recommends scavenger systems to remove exhaled N_2O from the air and maintain an ambient level of less than 25 parts per million.⁵

What are the legal issues? In Massachusetts, inhalant abuse is illegal [Massachusetts General Law, Chapter 270-18. See www.state.ma.us/dph/inhalant]. However, the law has been difficult to enforce because it requires a sworn officer to witness the sale, purchase or use of an inhalant. Recently, there has been a successful prosecution in the death of a Virginia student based on the Federal Food, Drug, and Cosmetic Act. The owner of a web site was convicted for selling the nitrous oxide in “whippets” as a drug.⁶ “Whippets” are whipped cream chargers—small metal cartridges about 2½ inches long.

What are the effects of nitrous oxide on the human body? The painkilling and numbing qualities of nitrous oxide begin to take effect when the gas is at concentrations of 10 percent. At higher concentrations, approaching 50%, a sense of wellbeing or euphoria is experienced. A person experiencing the effects of nitrous oxide may:

- Have slurred speech
- Have difficulty in maintaining his or her balance or walking
- Be slow to respond to questions
- Be immune to any stimulus such as pain, loud noise, and speech
- Lapse into unconsciousness (at higher concentrations)

If a person remains conscious and stops breathing the nitrous oxide, recovery can occur within minutes. A person who is rendered unconscious by nitrous oxide is likely to stop breathing within a few seconds as a result of a depressed central nervous system—brain, brain stem, and spinal cord. This depression is caused by a combination of the effects of nitrous oxide and the lowered oxygen content that occurs as pure N_2O displaces oxygen from the lungs with each succeeding inhalation of the gas. The end result is that the person can be asphyxiated.

Death usually occurs when abusers, in their attempt to achieve a higher state of euphoria, breathe pure N₂O in a confined space -- in a small room or an automobile, or by placing their head inside a plastic bag. Tragedy can occur very quickly. Prolonged exposure to high concentrations of N₂O without supplemental oxygen, or a series of inhalations (without breathing clean air between inhalations) can result in death. This can happen in seconds. Since the narcotic effect of a single breath of nitrous oxide is very brief (lasting for only seconds), abusers tend to repeatedly inhale in order to stay "high," increasing the danger. With N₂O, there is no sensation of choking or gasping for air to warn the abuser that asphyxiation is imminent. A person who loses consciousness, and continues to inhale the pure gas, will die.⁷

How does nitrous oxide get into the hands of abusers?

Nitrous Oxide is readily available and can be obtained from many different commercial, medical, and retail sources. It is found in homes, schools, restaurants, and medical and industrial settings where it is often easily accessible and not closely regulated. Used to foam dairy cream, it is found in canned whipped cream and whipped cream chargers ("whippets"). A small device called a "cracker" is used to break the seal on the cartridge and release the gas so it may be stored in a heavy duty balloon. The cartridges are easily available at restaurant supply stores, kitchen stores, "head shops," hardware stores, and over the internet. Whipped cream cans may be purchased or stolen from grocery and convenience stores or found in the home, cooking programs or restaurants.

Large tanks of nitrous oxide are stolen from hospitals, delivery trucks, and dental offices or purchased from commercial gas suppliers under the pretext of legitimate use. Balloons filled from the tanks are illegally sold at concerts and sporting events or distributed at parties and in college dormitories. Nitrous oxide cylinders range in size from roughly two feet in height to more than five feet and are color-coded light blue. Contents range from about six pounds to more than sixty pounds of liquid in a large cylinder. Depending on cylinder size and product purity, legitimate users pay between \$40 and \$75 per cylinder. The highest purity level, used in semiconductor processing, costs considerably more. Welding supply companies and auto supply stores are another source of nitrous oxide tanks. These tanks are black and the gas is denatured by adding sulphur dioxide. This product may be transfilled into smaller cylinders and sold without being labeled as denatured.⁷

What do you do if you suspect a young person is using nitrous oxide use? Experts recommend several steps during a crisis:

- See that he or she is quickly removed from the source of N₂O and gets fresh air.
- If not breathing, administer artificial respiration.

- Call an ambulance.
- Stay with the person until he or she receives medical attention.
- For more information, call the Massachusetts Poison Control Center at 1-800-222-1222 [TTY: 1-888-244-5313].

Assessment Issues: 1) Because inhalants are seen by many substance abusers as "low status" or "childish," adults and teenagers may be especially reluctant or embarrassed to admit use. 2) Many youth confuse "inhaling" with "smoking" or "snorting." For example, you might ask, "Have you ever inhaled anything to get high, such as the gases or fumes or vapors from household products or products used in a shop or a garage or in an art project. I am **not** talking about anything you might *smoke*, like tobacco, marijuana, or crack or anything you might *snort* like cocaine." 3) Because people may not be aware of the special dangers of inhalants, anyone who has experimented with them even once should receive inhalant abuse prevention education. Parent education and involvement is also essential.

Treatment Considerations: Nitrous oxide abuse as well as other types of inhalant abuse will often be part of a larger picture of substance abuse which may require treatment. In addition, inhalant abusers have very high relapse rates. Aftercare and follow-up are extremely important.

Treatment Options: Through its network of community providers, the Massachusetts Department of Public Health supports outpatient and residential programs for people who are abusing inhalants and other substances. For information on programs, call the Massachusetts Substance Abuse Information and Education Helpline (617-445-1500 in the Boston metropolitan area or 1-800-327-5050 statewide).

What can be done to prevent inhalant abuse? Telling youth the names and types of products that can be abused increases the likelihood that some youth will experiment with inhalants. A key prevention message is that products should be used for their intended purpose and in a safe manner. Inhalants should be equated with poisons, pollutants, and toxins, and **not** drugs. Children should not be taught what products can be abused or that they can be used "to get high"; rather the damaging effects of inhalants should be stressed. Other strategies include teaching refusal skills; supporting positive youth development and leadership; and educating parents and other community members. To learn more about comprehensive, science-based prevention, contact your local Massachusetts Prevention Center (to find the location, call the Massachusetts Substance Abuse Information and Education Helpline (617-445-1500 in the Boston metropolitan area or 1-800-327-5050 statewide). Additional information and materials can be obtained from the Massachusetts Inhalant Abuse Task Force at CASPAR Youth Services (617-623-2080), or visit our web site www.state.ma.us/dph/inhalant.

1. "Nitrous Oxide Fact Sheet." Compressed Gas Association [www.cganet.com] Arlington, VA [703-412-0900] See also, "Occupational Safety and Health Guideline for Nitrous Oxide." Occupational Safety and Health Administration [www.osha-slc.gov/SLTC/healthguidelines/nitrousoxide]

2. Paulson, G. W. "Recreational Misuse of Nitrous Oxide." Journal of the American Dental Association. 1979 March 98(3): 410-1.

3. NIOSH [1996] "Control of Nitrous Oxide in Dental Operations." US Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Publication No. 96-107. [www.dtc.gov/niosh/nitoxide.html]

4. Gilman, M. "Review: Nitrous Oxide in Perspective." Clinical Neuropharmacology (1992) 15:pp297-306.

5. NIOSH [1994]. "NIOSH Alert: Request for Assistance in Controlling Exposure to Nitrous Oxide During Anesthetic Administration." US Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Publication No. 94-100, April 1994. [www.dtc.gov/niosh/noxidalr.html]

6. Meadows, Michelle. "Investigators' Reports: Arizona Man Sentenced for Selling Nitrous Oxide." FDA Consumer Magazine (May-June 2001) Federal Drug Administration. [http://www.fda.gov/fdac/depart/2001/301_irs.html]

7. Compressed Gas Association [www.cganet.com] Arlington, VA [703-412-0900]

Exhibit II

**Affidavit of Department of Law Senior
Investigator Chad Shelmidine, sworn to on
June 26, 2012 ("Shelmidine Aff.")**

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF ROCKLAND

PEOPLE OF THE STATE OF NEW YORK, by
ERIC T. SCHNEIDERMAN, Attorney General of the
State of New York,

Petitioner,

AFFIDAVIT

Index No.:

-against-

VILLAGE SENSATIONS, LLC,

Respondent.

STATE OF NEW YORK)
COUNTY OF JEFFERSON) SS:

Chad Shelmidine, being duly sworn, deposes and says:

1. I am a Senior Investigator employed by the Office of New York State Attorney General Eric T. Schneiderman.
2. The facts set forth in this affidavit are the results of an investigation I have performed in the course of my job duties.
3. All statements are based upon my personal knowledge and investigation.
4. On May 29, 2012, at approximately 12:00pm, posing as a consumer, I went to Village Sensations, a store located at 111 Main Street, #A, Nanuet, New York.
5. Village Sensations, LLC, is a Domestic Limited Liability Company registered with the New York State Secretary of State (Ex. 1).
6. As I entered the store, I observed numerous individuals who appeared to be working in the store assisting customers.

7. Further, I observed numerous items which, based on my knowledge and experience, I recognized to be intoxicants and synthetic drugs.
8. One employee, a white male approximately 28 years old, approximately 5 feet 11 inches tall and weighing approximately 200 pounds, asked if he could help me find anything.
9. I noticed various packages of Kratom on display for sale behind the cash register counter.
10. I asked the clerk how much the Kratom cost. He told me the price of some of the packages of Kratom, including a brand called "Mr. Nice Guy" (Ex. 2).
11. The clerk said that they sold Mr. Nice Guy (Ex. 2) Kratom for thirty five dollars for a two gram package, and forty dollars for a five gram package.
12. I told the clerk I would take a two gram package of the Mr. Nice Guy (Ex. 2) Kratom.
13. The Mr. Nice Guy (Ex. 2) Kratom was labeled "NOT FOR HUMAN CONSUMPTION" and contained the following product description "BUREAUKRAT IS AMONG THE HIGHEST QUALITY KRATOM PRODUCTS IN THE WORLD. WE USE THE MOST MATURE LEAVES COMBINED WITH THE MOST ADVANCED EXTRACTION METHODS ON EARTH TO PRODUCE THIS NEARLY PERFECT POWDER." There were no instructions or directions anywhere on the package. With the exception of a website address, the package was also void of any address, telephone number, or contact information for the manufacturer or packager of this product.

14. I also told the clerk I wanted a package of the Molly Mosquito Caps (Ex. 3).
15. The Molly Mosquito Caps (Ex. 3) package said the following: "CONTAINS ONE CAP" and "NOT FOR HUMAN CONSUMPTION". The back of the package was void of any stickers, writing, or other information. There were no instructions or directions for using this product. The package did not contain an ingredients list. The package also did not contain contact information for the product manufacturer or packager.
16. I then asked how you use the powder form of the Kratom. The clerk told me that you can mix it with tea.
17. I then asked about the "experience" brand Kratom (Ex. 4). The clerk explained that they sold it in varying strengths, such as "15x, 30x, 60x".
18. The clerk said that the 60x strength of 'experience Kratom' was thirty dollars, and the 15x strength of 'experience Kratom' (Ex. 4) was twenty dollars.
19. I told the clerk I would take a package of the 15x of experience Kratom (Ex. 4).
20. The experience Kratom (Ex. 4) contained the following information on the back label: "100% EFFECTIVE - 100% ORGANIC", "Ingredients: 100% Pure Extracted Mitragyna Speciosa Leaf", "Use with caution. Do not use while operating a motor vehicle or machinery, if you are pregnant or nursing, or if you are taking any prescription or non-prescription medication or drugs. This product has not been evaluated by the FDA & is not intended to treat, prevent, cure or diagnose any illness. Must be 18 years of age to use this product.", "Manufactured exclusively by Experience Alternatives Inc.", and "www.ExperienceAlternatives.com". With the exception of a website address, the

package was also void of any address, telephone number, or contact information for the manufacturer or packager of this product.

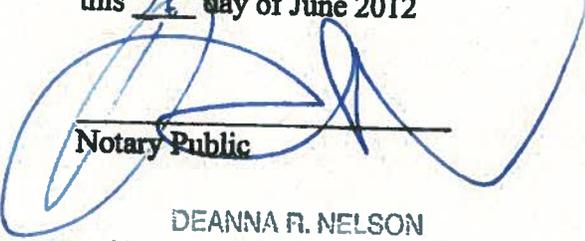
21. I then asked the clerk what type of pipe I should use with the experience Kratom (Ex. 4) and the Mr. Nice Guy (Ex. 2) Kratom. The clerk said "You're not smoking it. It's a tea base."
22. The clerk then went on to say that "There's no more spice or herbal incense" because of recent laws. He said his store does not carry any smokable products.
23. At this time I noticed boxes of nitrous oxide chargers (Ex. 5) on display for sale behind the cash register counter, in an area inaccessible to customers.
24. Based on my knowledge and experience, nitrous oxide gas is a drug that is inhaled by individuals to obtain a 'high'.
25. I told the clerk I wanted a box of these nitrous oxide chargers (Ex. 5).
26. I then asked the clerk if he sold crackers.
27. The clerk told me they did not have any crackers.
28. I understand a cracker to be to be a device used to 'crack' the seal on nitrous oxide chargers (Ex. 5) for inhaling the N20 for a high. The cracker is commonly aluminum, brass or plastic and simply accepts a N20 charger (Ex. 5) and pierces the seal, allowing the gas to escape in a controlled fashion. A balloon is attached to the cracker to capture the gas and allow it to absorb enough heat to be inhaled safely.
29. The clerk then rang me up for the Mr. Nice Guy (Ex. 2) Kratom, the Molly Mosquito Caps (Ex. 3), the experience 15x (Ex. 4) Kratom, and the box of nitrous oxide chargers (Ex. 5).

30. My total came to \$97.54.
31. I paid with a credit card and was given a receipt (Ex. 6).
32. The items I purchased as mentioned above were merely a sampling of several similar products that Village Sensations offered for sale to the public, all of which are offered for human consumption.
33. The above purchase was recorded using a covert audio and video recording device.

Date: June 26, 2012

Chad Shelmidine
CHAD SHELMIDINE, SR. INVESTIGATOR

Duly sworn to before me on
this 26th day of June 2012



Notary Public

DEANNA R. NELSON
Notary Public, State of New York
Registration No. 02NE5028585

Exp. 5/31/17

Exhibit II-1

20100108015

NYS Department of State
Division of Corporations, State Records and UCC
One Commerce Plaza, 99 Washington Ave,
Albany, NY 12231-0001
www.dos.state.ny.us

Certificate of Assumed Name
Pursuant to General Business Law, §130

1. NAME OF ENTITY

SMOKEN, LLC

1a. FOREIGN ENTITIES ONLY. If applicable, the fictitious name the entity agreed to use in New York State is:

2. NEW YORK LAW FORMED OR AUTHORIZED UNDER (CHECK ONE):

- Business Corporation Law
- Education Law
- Insurance Law
- Limited Liability Company Law
- Not-for-Profit Corporation Law
- Revised Limited Partnership Act

Other (specify law):

3. ASSUMED NAME

VILLAGE SENSATIONS

4. PRINCIPAL PLACE OF BUSINESS IN NEW YORK STATE (MUST BE NUMBER AND STREET. IF NONE, INSERT OUT-OF-STATE ADDRESS)

111 Main Street, Nanuet, New York 10954

5. COUNTIES IN WHICH BUSINESS WILL BE CONDUCTED UNDER ASSUMED NAME

ALL COUNTIES (if not, circle county[ies] below)

Albany	Clinton	Genesee	Monroe	Orleans	Saratoga	Tompkins
Allegany	Columbia	Greene	Montgomery	Oswego	Schenectady	Ulster
Bronx	Cortland	Hamilton	Nassau	Otsego	Schoharie	Warren
Broome	Delaware	Herkimer	New York	Putnam	Schuyler	Washington
Cattaraugus	Dutchess	Jefferson	Niagara	Queens	Seneca	Wayne
Cayuga	Erie	Kings	Onondaga	Rensselaer	Steuben	Westchester
Chautauqua	Essex	Lewis	Ontario	Richmond	Suffolk	Wyoming
Chemung	Franklin	Livingston	Orange	<u>Rockland</u>	Sullivan	Yates
Chenango	Fulton	Madison		St. Lawrence	Tioga	

6. INSERT THE ADDRESS OF EACH LOCATION WHERE BUSINESS WILL BE CARRIED ON OR TRANSACTED UNDER THE ASSUMED NAME. Use a continuous sheet, if needed. (The address must be set forth in terms of a number and street, city, state and zip code. Please note that the address(es) reflected in paragraph 6 must be within the county(ies) circled in paragraph 5. If the entity does not have a specific location where it will conduct business under the assumed name please check the statement below.)

111 Main Street, Nanuet, New York 10954

No New York State Business Location

20100108015

INSTRUCTIONS FOR SIGNATURE: If corporation, by an officer; if limited partnership, by a general partner; if limited liability company, by a member or manager or by an authorized person or attorney-in-fact for such corporation, limited partnership, or limited liability company. If the certificate is signed by an attorney-in-fact, include the name and title of the person for whom the attorney-in-fact is acting. (Example, John Smith, attorney-in-fact for Robert Johnson, president.)

Kenneth Newman
Name of Signer

Kenneth Newman
Signature

member
Title of Signer

091006000969 LAP

CERTIFICATE OF ASSUMED NAME
OF

SMOKEN, LLC

(Insert Entity Name)

Pursuant to §130, General Business Law

FILER'S NAME AND MAILING ADDRESS

Barry D. Haberman, Esq.
254 South Main Street, #404
New City, New York 10956

STATE OF NEW YORK
DEPARTMENT OF STATE
FILED JAN 08 2010
229624
LAP

NOTE: This form was prepared by the New York State Department of State. You are not required to use this form. You may draft your own form or use forms available at legal stationery stores. The Department of State recommends that all documents be prepared under the guidance of an attorney. The certificate must be submitted with a \$25 fee. The Department of State also collects the following, additional, county clerk fees for each county in which a corporation does or transacts business: \$100 for each county within New York City (Bronx, Kings, New York, Queens and Richmond) and \$25 for each county outside New York City. All checks over \$500 must be certified.

(For office use only)

A/LAP

Limited Liability Company Biennial Statement

For Internal Use Only

3864441

Business Name:

SMOKEN, LLC

SMOKEN, LLC
254 SOUTH MAIN ST. #404
NEW CITY, NY 10956

3864441

AR11103100 2352	
Filed By:	KH
Cash # (if different than firm #):	
Required Fee:	\$9.00
Filing Period:	10/2011
<small>(Make checks payable to the Department of State)</small>	

The Limited Liability Company Law requires limited liability companies to provide a current address for service of process to the Department of State every two years in the calendar month in which the limited liability company was formed or authorized. Please review the address for service of process in Part 1. Update the information in the space provided, if necessary. If no changes are necessary, proceed to Part 2. A limited liability company which fails to timely file its Biennial Statement shall be shown to be past due on the Department of State's records.

Part 1: Address for Service of Process (Address must be within the United States)

SMOKEN, LLC 254 SOUTH MAIN ST. #404 NEW CITY, NY 10956	Name		
	Address		
	City	State	Zip

Part 2: Signature of Member, Manager, Attorney-in-Fact or Authorized Person

 Signature	 Name of Signer (Please Print)
<u>managing member</u> Title of Signer (Please Print)	

Send the completed form, together with the \$9.00 filing fee made payable to the Department of State, in the self-mailer envelope, to the Department of State, Division of Corporations, 99 Washington Ave. Albany, NY 12231-0001.

To pay with a credit card, send a Credit Card Authorization Form to the Department of State with your Biennial Statement. The Credit Card Authorization Form is available from the Department of State's website at www.dos.state.ny.us or by calling (518) 473-2492. The Biennial Statement with the Credit Card Authorization Form may be faxed to (518) 486-4680.

Call (518) 473-6385 if you have questions regarding this form.

A domestic limited liability company must file this form until it files Articles of Dissolution. A foreign limited liability company must file this form until it files a Certificate of Surrender of Authority or a Certificate of Termination of Existence.

New York State
Department of State
Division of Corporations, State Records
and Uniform Commercial Code
One Commerce Plaza, 99 Washington Avenue
Albany, NY 12231
www.dos.state.ny.us

091006000969

(This form must be printed or typed in black ink)

ARTICLES OF ORGANIZATION
OF

SMOKEN, LLC

(Insert name of Limited Liability Company)

Under Section 203 of the Limited Liability Company Law

FIRST: The name of the limited liability company is: **SMOKEN, LLC**

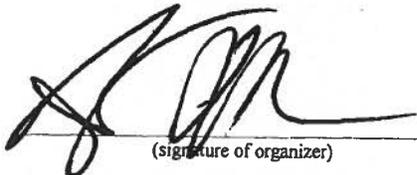
SECOND: The county within this state in which the office of the limited liability company is to be located is: **ROCKLAND**

THIRD: The Secretary of State is designated as agent of the limited liability company upon whom process against it may be served. The address within or without this state to which the Secretary of State shall mail a copy of any process against the limited liability company served upon him or her is:

THE LLC

254 SOUTH MAIN STREET, #404

NEW CITY, NEW YORK 10956



(signature of organizer)

BARRY D. HABERMAN, ESQ.

(print or type name of organizer)

091006000969

ARTICLES OF ORGANIZATION
OF

SMOKEN, LLC

(Insert name of Limited Liability Company)

Under Section 203 of the Limited Liability Company Law

Filed by: Barry D. Haberman, Esq.
(Name)
254 South Main Street, #404
(Mailing address)
New City, New York 10956
(City, State and ZIP code)

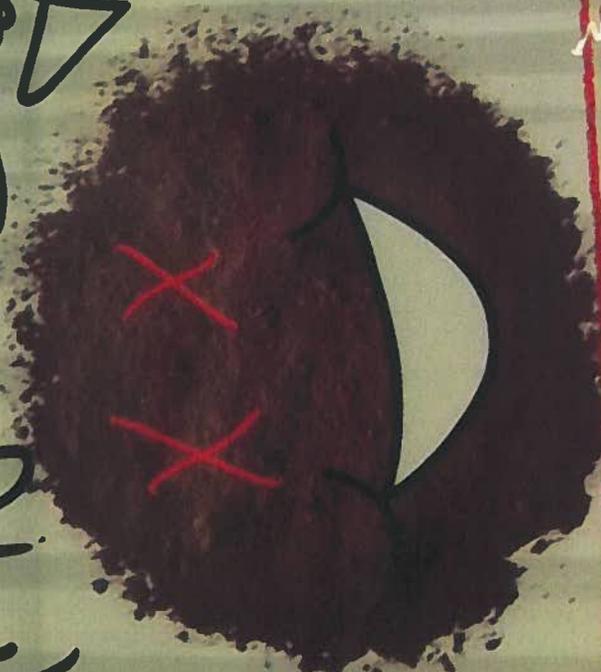
NOTE: This form was prepared by the New York State Department of State for filing articles of organization for a domestic limited liability company. It does not contain all optional provisions under the law. You are not required to use this form. You may draft your own form or use forms available at legal stationery stores. The Department of State recommends that legal documents be prepared under the guidance of an attorney. The certificate must be submitted with a \$200 filing fee made payable to the Department of State.

STATE OF NEW YORK
DEPARTMENT OF STATE
FILED OCT 06 2009
TAXS
BY: KT

1059

Exhibit II-2

Mr. Nice Guy



BURBANK AUKIE A'I

KRATOM EXTRACT

NET WEIGHT-2G



NOT FOR HUMAN CONSUMPTION

BUREAUKRAT IS AMONG THE HIGHEST QUALITY KRATOM PRODUCTS IN THE WORLD. WE USE THE MOST MATURE LEAVES COMBINED WITH THE MOST ADVANCED EXTRACTION METHODS ON EARTH TO PRODUCE THIS NEARLY PERFECT POWDER.



CAS
5129/12
1200 mg

WWW.MR-NICE-GUY.COM

Exhibit II-3

MOLLYS



MOSQUITO CAPS

1200 hrs

50000

CONTAINS ONE CAP

NOT FOR HUMAN CONSUMPTION



Exhibit II-4

CAS 5129/12
1200 hrs

experience™

da pimp BOMB

KRATOM 15x

07\$X+

da★pimp BOMB



100% EFFECTIVE – 100% ORGANIC

Ingredients: 100% Pure Extracted Mitragyna Speciosa Leaf

Use with caution. Do not use while operating a motor vehicle or machinery.
If you are pregnant or nursing, or if you are taking any prescription or
non-prescription medication or drugs. This product has not been evaluated by
the FDA & is not intended to treat, prevent, cure or diagnose any illness.
Must be 18 years of age to use this product

Manufactured exclusively by Experience™ Alternatives Inc.

www.ExperienceAlternatives.com

BAG IS ROHS COMPLIANT



Exhibit II-5

5/29/12 1200 hrs CAS



Crème

Fine Gourmet Creme Chargers

24



Crème

Dessert Cream Charger

For the preparation of food only.

1 cylinder makes up to 1 pint of cream.

Misuse can be dangerous to your health.

Do not inhale contents. Contents under pressure.

Do not incinerate or expose to sun or heat.

Temperature not to exceed 50 c 122 f.

Never dispose of full chargers.

Keep out of reach of children.

Bon appetite!



24 Nettoyage exclusivement pour préparations
alimentaires. Une seule cartouche fait près d'un demi litre
de Crème Fraîche. Utilisation contre-indiquée pour mettre
en danger votre santé. Ne pas inhaler le contenu. Contenu
sous pression. Ne pas incinérer ni exposer à températures en
excès de 50 degrés centigrades / 122 degrés Fahrenheit.
Ne jamais mettre des cartouches pleines à la poubelle.
Ne pas laisser à la portée des enfants. Bon appétit!

1 Pint = 473 milliliters

1 demi litre = 500 milliliters



Crème



- Gourmet Quality
- Create delicious dessert toppings
- Fits all cream machines
- Lasts up to one week when chilled

AM
x 18/5

Crème

24

Fine Gourmet Creme Chargers

Contents imported from France, Switzerland or Hungary
Contains 10 cm³ (0.61 cu. in.) pure N20 under pressure

Product ID - 735r6

1592

Exhibit II-6

CAS
VILLAGE SENSATION
111 MAIN STREET
MANUET, NY. 10954
845-623-2222

TERMINAL ID.: 0010540008018194301000
MERCHANT #: 8018194301

MASTERCARD
*****0102 EXP:XX/XX SWIPED
SALE
RECORD: 2 INU: 000002
DATE: May 29, 12 TIME: 10:54
BATCH: 000672 AUTH: 47684B

TOTAL \$97.54

MICHAEL ROBERTS

CUSTOMER COPY

Exhibit III

Exhibit III-1

FDA Guidance for Industry Street Drug Alternatives

Guidance for Industry

Street Drug Alternatives

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2000
Compliance**

Guidance for Industry

Street Drug Alternatives

Additional copies of this Guidance are available from:

*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)*

Internet: <http://www.fda.gov/cder/guidance/index.htm>.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2000
Compliance**

Guidance for Industry¹

Street Drug Alternatives

I. INTRODUCTION

This guidance is intended for those persons who are manufacturing, marketing, or distributing alternatives to illicit street drugs. FDA considers any product that is promoted as a street drug alternative to be an unapproved new drug and a misbranded drug in violation of sections 505 and 502 of the Federal Food, Drug, and Cosmetic Act (the Act). Such violations may result in regulatory action, including seizure and injunction.

II. BACKGROUND

The Agency has become aware of the proliferation of various products that are being manufactured, marketed, or distributed as alternatives to illicit street drugs (*street drug alternatives*). FDA is concerned that these products are being abused by individuals, including minors, and pose a potential threat to the public health.

Street drug alternatives are generally labeled as containing botanicals, and some are also labeled as containing other ingredients, such as vitamins, minerals, or amino acids. They are marketed under a variety of brand names with claims implying that these products mimic the effects of controlled substances. Many of these products are promoted on the Internet and in counterculture magazines as alternatives to illicit street drugs such as MDMA (4-methyl-2, dimethoxyamphetamine), a methamphetamine analogue, also known as *ecstasy*, *XTC*, and *X*. Other examples of products whose names imply street drug alternative use are *e-Ludes*, *Hextacy*, and *Herbal Koke*.

These products are intended to be used for recreational purposes to effect psychological states (e.g., to get high, to promote euphoria, or to induce hallucinations) and have potential for abuse. FDA considers these street drug alternatives to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act.

¹This guidance has been prepared by the Office of Compliance, Division of Labeling and Nonprescription Drug Compliance, in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration. This guidance represents the Agency's current thinking on street drug alternatives. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

FDA is also aware that some of these street drug alternatives are being marketed as dietary supplements. FDA does not consider street drug alternatives to be dietary supplements. The term *dietary supplement* as defined in section 201(ff) of the Act means, inter alia, a product "intended to supplement the diet." While the Act does not elaborate on the meaning of this phrase, many congressional findings, set forth in the Dietary Supplement Health and Education Act of 1994, suggest that dietary supplements are intended to be used to augment the diet to promote health and reduce the risk of disease. FDA does not believe that street drug alternatives are intended to be used to augment the diet to promote health or reduce the risk of disease. Moreover, FDA considers the diet to be composed of usual food and drink that may be designed to meet specific nutritional requirements. Illicit street drugs are not food or drink, and neither they, nor alternative street drugs, can be said to supplement the diet. Rather, these products are intended to be used for recreational purposes to effect psychological states (e.g., to get high, to promote euphoria, or to induce hallucinations). Accordingly, street drug alternatives are not intended to supplement the diet and are not dietary supplements. This position is consistent with that set forth at 62 Fed. Reg. 30678, 30699-700 (June 4, 1997).

III. POLICY

FDA considers any product that is promoted as a street drug alternative to be an unapproved new drug and a misbranded drug in violation of sections 505 and 502 of the Federal Food, Drug, and Cosmetic Act. Such violations may result in regulatory action, including seizure and injunction

Exhibit III-2

DEA Press Release, September 7, 2011



UNITED STATES
DRUG ENFORCEMENT ADMINISTRATION

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News Release [print-friendly page]
FOR IMMEDIATE RELEASE
September 07, 2011
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202-307-7977

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DEA Moves to Emergency Control Synthetic Stimulants
Agency Will Study Whether To Permanently Control Three Substances

SEP 07 – WASHINGTON, D.C. – The United States Drug Enforcement Administration (DEA) is using its emergency scheduling authority to temporarily control three synthetic stimulants (Mephedrone, 3,4 methylenedioxypropylvalerone (MDPV) and Methylone). This action was necessary to protect the public from the imminent hazard posed by these dangerous chemicals. Except as authorized by law, this action will make possessing and selling these chemicals or the products that contain them illegal in the U.S. for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled.

A Notice of Intent to temporarily control was published in the Federal Register today to alert the public to this action. This alert is required by law as part of the Controlled Substances Act. In 30 days or more, DEA intends to publish in the Federal Register a Final Order to temporarily control these chemicals for at least 12 months, with the possibility of a six-month extension. The final order will be published in the *Federal Register* and will designate these chemicals as Schedule I substances, the most restrictive category, which is reserved for unsafe, highly abused substances with no currently accepted medical use in the United States.

"This imminent action by the DEA demonstrates that there is no tolerance for those who manufacture, distribute, or sell these drugs anywhere in the country, and that those who do will be shut down, arrested, and prosecuted to the fullest extent of the law," said DEA Administrator Michele M. Leonhart. "DEA has made it clear we will not hesitate to use our emergency scheduling authority to control these dangerous chemicals that pose a significant and growing threat to our nation."

Over the past few months, there has been a growing use of, and interest in, synthetic stimulants sold under the guise of "bath salts" or "plant food". Marketed under names such as "Ivory Wave", "Purple Wave", "Vanilla Sky" or "Bliss", these products are comprised of a class of chemicals perceived as mimics of cocaine, LSD, MDMA, and/or methamphetamine. Users have reported impaired perception, reduced motor control, disorientation, extreme paranoia, and violent episodes. The long-term physical and psychological effects of use are unknown but potentially severe. These products have become increasingly popular, particularly among teens and young adults, and are sold at a variety of retail outlets, in head shops and over the Internet. However, they have not been approved by the FDA for human consumption or for medical use, and there is no oversight of the manufacturing process.

In the last six months, DEA has received an increasing number of reports from poison centers, hospitals and law enforcement regarding products containing one or more of these chemicals. Thirty-three states have already taken action to control or ban these or other synthetic stimulants. The Comprehensive Crime Control Act of 1984 amends the Controlled Substances Act (CSA) to allow the DEA Administrator to temporarily schedule an abused, harmful, non-medical substance in order to avoid an imminent hazard to public safety while the formal rule-making procedures described in the CSA are being conducted.

Editor's Note: DEA will issue an additional press release when the Final Order to Temporarily Control these chemicals is published in the Federal Register.

###



Exhibit III-3

DEA Press Release, March 1, 2011



UNITED STATES
DRUG ENFORCEMENT ADMINISTRATION

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FOR IMMEDIATE RELEASE

March 01, 2011

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Chemicals Used in "Spice" and "K2" Type Products Now Under Federal Control and Regulation

DEA Will Study Whether To Permanently Control Five Substances

MAR 01 - WASHINGTON, D.C. – The United States Drug Enforcement Administration (DEA) today exercised its emergency scheduling authority to control five chemicals (JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol) used to make so-called "fake pot" products. Except as authorized by law, this action makes possessing and selling these chemicals or the products that contain them illegal in the United States. This emergency action was necessary to prevent an imminent threat to public health and safety. The temporary scheduling action will remain in effect for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled.



Chemicals like K-2 and Spice are designated as Schedule I substances, the most restrictive category under the Controlled Substances Act.

The Final Order was published today in the *Federal Register* to alert the public to this action. These chemicals will be controlled for at least 12 months, with the possibility of a six month extension. They are designated as Schedule I substances, the most restrictive category under the Controlled Substances Act. Schedule I substances are reserved for those substances with a high potential for abuse, no accepted medical use for treatment in the United States and a lack of accepted safety for use of the drug under medical supervision.

Over the past couple of years, smokeable herbal products marketed as being "legal" and as providing a marijuana-like high, have become increasingly popular, particularly among teens and young adults. These products consist of plant material that has been coated with research chemicals that claim to mimic THC, the active ingredient in marijuana, and are sold at a variety of retail outlets, in head shops, and over the Internet. These chemicals, however, have not been approved by the FDA for human consumption, and there is no oversight of the manufacturing process. Brands such as "Spice," "K2," "Blaze," and "Red X Dawn" are labeled as herbal incense to mask their intended purpose.

Since 2009, DEA has received an increasing number of reports from poison control centers, hospitals and law enforcement regarding these products. At least 18 states have already taken action to control one or more of these chemicals. The Comprehensive Crime Control Act of 1984 amends the Controlled Substances Act (CSA) to allow the DEA Administrator to place a substance temporarily in schedule I when it is necessary to avoid an imminent threat to the public safety. Emergency room physicians report that individuals that use these types of products experience serious side effects which include: convulsions, anxiety attacks, dangerously elevated heart rates, increased blood pressure, vomiting, and disorientation.

"Young people are being harmed when they smoke these dangerous 'fake pot' products and wrongly equate the products' 'legal' retail availability with being 'safe'," said DEA Administrator Michele M. Leonhart. "Parents and community leaders look to us to help them protect their kids, and we have not let them down. Today's action, while temporary, will reduce the number of young people being seen in hospital emergency rooms after ingesting these synthetic chemicals to get high."

>> Notice of Intent to Temporarily Control Five Synthetic Cannabinoids

NEW FACT

JUST THINK TWICE

THE HEADS OF FEDERAL BUREAU OF INVESTIGATION

Exhibit III-4

DEA Press Release, June 19, 2012



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DRUG ENFORCEMENT ADMINISTRATION

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Congress Agrees to Add 26 Synthetic Drugs to Controlled Substances Act

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The Drug Enforcement Administration today commended House and Senate negotiators for agreeing on legislation to control 26 synthetic drugs under the Controlled Substances Act. These drugs include those commonly found in products marketed as "K2" and "Spice."

The addition of these chemicals to Schedule I of the Controlled Substances Act will be included as part of S. 3187, the Food and Drug Administration Safety and Innovation Act. Schedule I substances are those with a high potential for abuse; have no medical use in treatment in the United States; and lack an accepted safety for use of the drug.

In addition to scheduling the 26 drugs, the new law would double the length of time a substance may be temporarily placed in Schedule I (from 18 to 36 months). In addition to explicitly naming 26 substances, the legislation creates a new definition for "cannabimimetic agents," creating criteria by which similar chemical compounds are controlled.

In recent years, a growing number of dangerous products have been introduced into the U.S. marketplace. Products labeled as "herbal incense" have become especially popular, especially among teens and young adults. These products consist of plant material laced with synthetic cannabinoids which, when smoked, mimic the delirious effects of THC, the psychoactive ingredient of marijuana. According to the United Nations Office on Drugs and Crime, more than 100 such substances have been synthesized and identified to date. DEA has used its emergency scheduling authority to place in schedule I several of these harmful chemicals.

Newly developed drugs, particularly from the "2C family" (dimethoxyphenethylamines), are generally referred to as synthetic psychedelic/hallucinogens. 2C-E caused the recent death of a 19 year-old in Minnesota.

The substances added to Schedule I of the Controlled Substances Act also include 9 different 2C chemicals, and 15 different synthetic cannabinoids.

The American Association of Poison Control Centers reported that they received 6,959 calls related to synthetic marijuana in 2011, up from 2,906 in 2010.

###



Exhibit III-5

H.R. 1254: “Synthetic Drug Control Act of 2011,
112th Congress, 2011–2012

There have been a lot of site improvements this month, such as adding bills from all 50 states. Read our Site Updates blog post.

HOME BROWSE TRACK ABOUT CONTACT DATA

CONGRESS BILLS H.R. 1254 BILL TEXT

H.R. 1254: Synthetic Drug Control Act of 2011

112th Congress, 2011-2012. Text as of Dec 08, 2011 (Referred to Senate Committee).

Status & Summary | PDF | Source: GPO

H.R. 1254 RFS

112th CONGRESS

1st Session

H. R. 1254

IN THE SENATE OF THE UNITED STATES

December 8, 2011

Received; read twice and referred to the Committee on the Judiciary

AN ACT

To amend the Controlled Substances Act to place synthetic drugs in Schedule I.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the 'Synthetic Drug Control Act of 2011'.

SEC. 2. ADDITION OF SYNTHETIC DRUGS TO SCHEDULE I OF THE CONTROLLED SUBSTANCES ACT.

(a) Cannabimimetic Agents- Schedule I, as set forth in section 202(c) of the Controlled Substances Act (21 U.S.C. 812(c)) is amended by adding at the end the following:

(d)(1) Unless specifically exempted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of cannabimimetic agents, or which contains their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation.

(2) In paragraph (1):

(A) The term 'cannabimimetic agents' means any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays within any of the following structural classes:

You are reading the latest text of the bill. The text of a bill may change in committee or through the amendment process.

Select a version of this bill to view:

- Mar 29, 2011: Introduced
- Nov 29, 2011: Reported by House Committee
- Dec 08, 2011: Passed the House (Engrossed)
- Dec 08, 2011: Referred to Senate Committee

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- Mar 29, 2011: Introduced
- Nov 29, 2011: Reported by House Committee
- Dec 08, 2011: Passed the House (Engrossed)
- Dec 08, 2011: Referred to Senate Committee

Compare this bill to another bill:

- S. 2011-2: Omnibus Synthetic Drug Control Act of 2011
- H.R. 1254: Synthetic Drug Control Act of 2011
- H.R. 1254: Synthetic Drug Abuse Prevention Act of 2011

(i) 2-(3-hydroxycyclohexyl)phenol with substitution at the 5-position of the phenolic ring by alkyl or alkenyl, whether or not substituted on the cyclohexyl ring to any extent.

(ii) 3-(1-naphthoyl)indole or 3-(1-naphthylmethane)indole by substitution at the nitrogen atom of the indole ring, whether or not further substituted on the indole ring to any extent, whether or not substituted on the naphthoyl or naphthyl ring to any extent.

(iii) 3-(1-naphthoyl)pyrrole by substitution at the nitrogen atom of the pyrrole ring, whether or not further substituted in the pyrrole ring to any extent, whether or not substituted on the naphthoyl ring to any extent.

(iv) 1-(1-naphthylmethylene)indene by substitution of the 3-position of the indene ring, whether or not further substituted in the indene ring to any extent, whether or not substituted on the naphthyl ring to any extent.

(v) 3-phenylacetylindole or 3-benzoylindole by substitution at the nitrogen atom of the indole ring, whether or not further substituted in the indole ring to any extent, whether or not substituted on the phenyl ring to any extent.

(B) Such term includes--

(i) 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (CP-47,497);

(ii) 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol or CP-47,497 C8-homolog);

(iii) 1-pentyl-3-(1-naphthoyl)indole (JWH-018 and AM678);

(iv) 1-butyl-3-(1-naphthoyl)indole (JWH-073);

(v) 1-hexyl-3-(1-naphthoyl)indole (JWH-019);

(vi) 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200);

(vii) 1-pentyl-3-(2-methoxyphenylacetyl)indole (JWH-250);

(viii) 1-pentyl-3-[1-(4-methoxynaphthoyl)]indole (JWH-081);

(ix) 1-pentyl-3-(4-methyl-1-naphthoyl)indole (JWH-122);

(x) 1-pentyl-3-(4-chloro-1-naphthoyl)indole (JWH-398);

(xi) 1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM2201);

(xii) 1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole (AM694);

(xiii) 1-pentyl-3-[(4-methoxy)-benzoyl]indole (SR-19 and RCS-4);

(xiv) 1-cyclohexylethyl-3-(2-methoxyphenylacetyl)indole (SR-18 and RCS-8); and

(xv) 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203).

(b) Other Drugs- Schedule I of section 202(c) of the Controlled Substances Act (21 U.S.C. 812(c)) is amended in subsection (c) by adding at the end the following:

(18) 4-methylmethcathinone (Mephedrone).

(19) 3,4-methylenedioxypropylvalerone (MDPV).

(20) 3,4-methylenedioxy methcathinone (methyone)

(21) Naphthylpyrovalerone (naphyrone).

(22) 4-fluoromethcathinone (flephedrone)

(23) 4-methoxymethcathinone (methedrone; Bk-PMMA).

- *(24) Ethcathinone (N-Ethylcathinone).
- *(25) 3,4-methylenedioxyethcathinone (ethylone).
- *(26) Beta-keto-N-methyl-3,1-benzodioxolybutanamine (butylone).
- *(27) N,N-dimethylcathinone (metamfepramone).
- *(28) Alpha-pyrrolidinopropiophenone (alpha-PPP).
- *(29) 4-methoxy-alpha-pyrrolidinopropiophenone (MOPPP).
- *(30) 3,4-methylenedioxy-alpha-pyrrolidinopropiophenone (MDPPP).
- *(31) Alpha-pyrrolidinovalerophenone (alpha-PVP).
- *(32) 6,7-dihydro-5H-indeno-(5,6-d)-1,3-dioxol-6-amine (MDAI).
- *(33) 3-fluoromethcathinone.
- *(34) 4'-Methyl-alpha-pyrrolidinobutiophenone (MPBP).
- *(35) 2-(2,5-Dimethoxy-4-ethylphenyl)ethanamine (2C-E).
- *(36) 2-(2,5-Dimethoxy-4-methylphenyl)ethanamine (2C-D).
- *(37) 2-(4-Chloro-2,5-dimethoxyphenyl)ethanamine (2C-C).
- *(38) 2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine (2C-I).
- *(39) 2-[4-(Ethylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-2).
- *(40) 2-[4-(Isopropylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-4).
- *(41) 2-(2,5-Dimethoxyphenyl)ethanamine (2C-H).
- *(42) 2-(2,5-Dimethoxy-4-nitro-phenyl)ethanamine (2C-N).
- *(43) 2-(2,5-Dimethoxy-4-(n)-propylphenyl)ethanamine (2C-P).

SEC. 3. TEMPORARY SCHEDULING TO AVOID IMMINENT HAZARDS TO PUBLIC SAFETY EXPANSION.

Section 201(h)(2) of the Controlled Substances Act (21 U.S.C 811(h)(2)) is amended--

(1) by striking 'one year' and inserting '2 years'; and

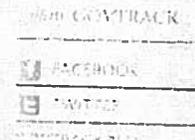
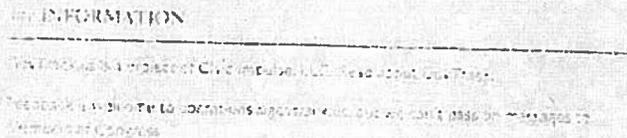
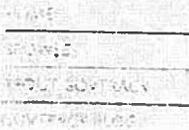
(2) by striking 'six months' and inserting '1 year'.

Passed the House of Representatives December 8, 2011.

Attest

KAREN L. HAAS,

Clerk.



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Exhibit III-6

Order, In The Matter The Sale And Distribution Of
Synthetic Cannabinoids, NYS Commissioner of
Health, March 28, 2012

STATE OF NEW YORK : DEPARTMENT OF HEALTH
-----X

IN THE MATTER

OF

THE SALE AND DISTRIBUTION
OF SYNTHETIC CANNABINOIDS

ORDER FOR
SUMMARY
ACTION

-----X

WHEREAS, a "cannabinoid" is a class of chemical compounds in the marijuana plant and the cannabinoid Δ^9 -tetrahydrocannabinol (THC) is the primary psychoactive constituent of marijuana. "Synthetic cannabinoids" encompass a wide variety of chemicals that are synthesized and marketed to mimic the action of THC. A "synthetic cannabinoid" is defined herein as any chemical compound that is a cannabinoid receptor agonist and includes, but is not limited to any material, compound, mixture, or preparation that is not listed as a controlled substance in the Schedule I through V of § 3306 of the Public Health Law, is not a federal Food and Drug Administration (FDA) approved drug, and contains any quantity of the following substances, their salts, isomers (whether optical, positional, or geometric), homologues (analogs), and salts of isomers and homologues (analogs), unless specifically exempted, whenever the existence of these salts, isomers, homologues (analogs), and salts of isomers and homologues (analogs) is possible within the specific chemical designation:

- i. Naphthoylindoles. Any compound containing a 3-(1-Naphthyl)indole structure with substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the indole ring to any

extent and whether or not substituted in the naphthyl ring to any extent. (Other names in this structural class include but are not limited to: JWH 015, JWH 018, JWH 019, JWH 073, JWH 081, JWH 122, JWH 200, JWH 210, JWH 398, AM 2201, and WIN 55 212).

ii. Naphthylmethyloindoles. Any compound containing a 1 H-indol-3-yl-(1-naphthyl)methane structure with substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the naphthyl ring to any extent. (Other names in this structural class include but are not limited to: JWH-175, and JWH-184).

iii. Naphthoylpyrroles. Any compound containing a 3-(1-naphthoyl) pyrrole structure with substitution at the nitrogen atom of the pyrrole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the pyrrole ring to any extent and whether or not substituted in the naphthyl ring to any extent. (Other names in this structural class include but are not limited: JWH 307).

iv. Naphthylmethyloindenes. Any compound containing a naphthylidene indene structure with substitution at the 3-position of the indene ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the indene ring to any extent and whether or not substituted in the naphthyl ring to any extent. (Other names in this structural class include but are not limited: JWH-176).

- v. **Phenylacetylindoles.** Any compound containing a 3-phenylacetylindole structure with substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent. (Other names in this structural class include but are not limited to: RCS-8 (SR-18), JWH 250, JWH 203, JWH-251, and JWH-302).
- vi. **Cyclohexylphenols.** Any compound containing a 2-(3-hydroxycyclohexyl)phenol structure with substitution at the 5-position of the phenolic ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not substituted in the cyclohexyl ring to any extent. (Other names in this structural class include but are not limited to: CP 47,497 (and homologues (analogs)), cannabicyclohexanol, and CP 55,940).
- vii. **Benzoylindoles.** Any compound containing a 3-(benzoyl)indole structure with substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidiny)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent. (Other names in this structural class include but are not limited to: AM 694, Pravadoline (WIN 48,098), RCS 4, and AM-679).

viii. [2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo [1,2,3-de]-1, 4-benzoxazin-6-yl]-1-naphthalenylmethanone. (Other names in this structural class include but are not limited to: WIN 55,212-2).

ix. (6aR,10aR)-9-(hydroxymethyl)-6, 6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10, 10a-tetrahydrobenzo[c]chromen-1-ol 7370. (Other names in this structural class include but are not limited to: HU-210).

x. Adamantoylindoles. Any compound containing a 3-(1-adamantoyl)indole structure with substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted in the adamantyl ring system to any extent. (Other names in this structural class include but are not limited to: AM-1248).

xi. Any other synthetic chemical compound that is a cannabinoid receptor agonist that is not listed in Schedules I through V of § 3306 of the Public Health Law, or is not an FDA approved drug; and

WHEREAS, synthetic cannabinoids are frequently applied to plant materials and then packaged and marketed online, and in convenience stores, gas stations and smoke shops as incense, herbal mixtures or potpourri, and often carry a "not for human consumption" label, and are not approved for medical use in the United States; and

WHEREAS, products containing synthetic cannabinoids are, in actuality, produced, distributed, marketed and sold, as a supposed "legal alternative" to marijuana and for the purpose of being consumed by an individual, most often by smoking, either through a pipe, a water pipe,

or rolled in cigarette papers; and

WHEREAS, synthetic cannabinoids have been linked to severe adverse reactions, including death and acute renal failure, and reported side effects include: tachycardia (increased heart rate); paranoid behavior, agitation and irritability; nausea and vomiting; confusion; drowsiness; headache; hypertension; electrolyte abnormalities; seizures; and syncope (loss of consciousness); and

WHEREAS, products containing synthetic cannabinoids have become prevalent drugs of abuse, especially among teens and young adults. Calls to New York State Poison Control centers relating to the consumption of synthetic cannabinoids have increased dramatically, with a total of 105 reported incidents of exposure to these substances having been reported since 2011, compared to four reported instances in 2009 and 2010. Over half of the calls to the Upstate Poison Control Center this year involved children under the age of 19 years of age. Nationally, poison control centers have received approximately 8,000 calls relating to exposure to these substances since 2011. Calls received by poison control centers generally reflect only a small percentage of actual instances of poisoning. Therefore, it is clear that many additional New York residents have been harmed as a result of using products containing synthetic cannabinoids; and

WHEREAS, on March 1, 2011, the United States Drug Enforcement Administration (DEA) temporarily scheduled five synthetic cannabinoids, JWH-018, JWH-073, JWH-200, CP 47, 497 and cannabicyclohexanol (CP 47, 497, C8, which is a homologue of CP 47, 497), as Schedule I substances under the federal Controlled Substances Act (21 U.S.C. § 812[c]), in order to avoid an imminent hazard to public safety, because the substances have a high potential for

abuse and have no currently accepted medical use in treatment in the United States. On March 1, 2012, the federal DEA ban was extended for six months; and

WHEREAS, individuals and entities can avoid -- and have avoided -- the federal ban of specifically identified synthetic cannabinoids by developing or synthesizing cannabinoids that are not expressly covered under any such ban; and

WHEREAS, based upon the foregoing, the Commissioner of Health of the State of New York, after investigation, is of the opinion that the sale or distribution of products containing synthetic cannabinoids, including, but not limited to, the products identified in the Appendix, is an activity which constitutes danger to the health, safety and welfare of the people of the State of New York; and

WHEREAS, it therefore appears to be prejudicial to the interest of the people to delay action for fifteen (15) days until an opportunity for a hearing can be provided in accordance with the provisions of Public Health Law § 12-a.

NOW, THEREFORE, THE COMMISSIONER OF HEALTH DOES HEREBY ORDER THAT:

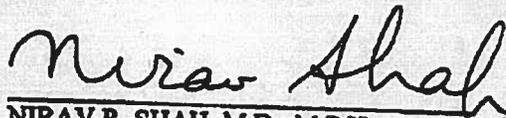
- 1) Pursuant to Public Health Law § 16, any individual or entity in the State of New York engaged in the sale or distribution of products containing synthetic cannabinoids, including, but not limited to, those products identified in the Appendix, and that receives notice of this Order, shall immediately cease the sale and/or distribution of said products in New York State.
- 2) The presiding officer of each local health unit or local board of health in the State of New York, is hereby directed, pursuant to Public Health Law § 1303(4) and Title 10 NYCRR

8.5, to convene each such local health unit or local board of health as is necessary to disseminate this Order and to ensure compliance with this Order.

FURTHER, I DO HEREBY give notice that any individual or entity that receives notice of and is subject to this Order shall be provided an opportunity to be heard within fifteen (15) days of service of this Order, at the offices of the New York State Department of Health, to present proof that the sale or distribution of products containing synthetic cannabinoids does not constitute a danger to the health of the people of the State of New York. Any such individual or entity that wishes to avail themselves of this opportunity, should notify the Department of Health in writing, within five (5) days of receipt of service of this Order, to the following address: New York State Department of Health, Bureau of Administrative Hearings, Corning Tower, Room 2438, Governor Nelson A. Rockefeller Empire State Plaza, Albany, New York 12237. This notice may also be submitted by FAX at (518) 486-1858, or by email at mdf01@health.state.ny.us. The Department will, within five business days of its receipt of a request for hearing, provide written notice of the date, place and time of the scheduled hearing.

DATED: Albany, New York
March 28, 2012

NEW YORK STATE DEPARTMENT OF
HEALTH



NIRAV R. SHAH, M.D., M.P.H.
Commissioner of Health

APPENDIX

**K2
Spice
Chronic Spice
Spice Gold
Spice Silver
Skunk
Black Mamba
Zohai
Mr. Nice Guy
K3
K3 Legal
Genie
Sence
Smoke
Chill X
Earth Impact
Galaxy Gold
Space Truckin
Solar Flare
Moon Rocks
Aroma
Scope
Sky High**

Exhibit III-7

**Gregory Kau, Flashback To The Federal Analog Act
Of 1986: Mixing Rules And Standards In The
Cauldron; 156 U. Pa. L. Rev. at 1084 (2008)**

156 U. Pa. L. Rev. 1077

University of Pennsylvania Law Review

April, 2008

Comments

FLASHBACK TO THE FEDERAL ANALOG ACT OF 1986:
MIXING RULES AND STANDARDS IN THE CAULDRONGregory Kau^{d1}

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***1078 Introduction**

In 1982, a forty-two-year-old heroin addict staggered into a San Jose medical clinic.¹ His muscles were virtually frozen in place, so much so that "he seemed more of a mannequin than a man."² Upon closer examination, the attending neurologist found that the patient exhibited symptoms of advanced Parkinson's disease.³ The neurologist was astonished: Parkinson's rarely struck before the age of fifty.⁴ The parties responsible for this early onset of Parkinson's were two legal professionals who moonlighted as clandestine drug chemists.⁵ In the basement of their law office, they produced 1-methyl-4-propionoxy-4-phenylpyridine (MPPP), a synthetic version of heroin that was perfectly legal to manufacture.⁶ Unfortunately, the entrepreneurs were better lawyers

than chemists. Even though they found the correct recipe for their concoction, they failed to keep the reaction at the proper temperature and acidity.⁷ As a result, they unknowingly introduced a highly poisonous by-product into the brew that caused severe brain damage.⁸ The chaos that ensued was the first “designer drug disaster” recorded in American history.⁹

The federal government was powerless to prosecute this behavior under existing federal drug statutes. The perpetrators had--quite literally--played by the rules, and had properly exploited loopholes to *1079 avoid punishment. Other clandestine chemists were inspired and followed their lead. Public pressure on Congress escalated as designer drugs spread around the world.¹⁰ In this atmosphere of panic, Congress responded¹¹ by enacting the Federal Analog Act¹² with the express purpose of preventing minor structural modifications to drugs prohibited under Schedule I of the Controlled Substances Act in order to evade legal penalty.¹³ The Federal Analog Act replaced rules with standards. Under the Federal Analog Act, if a chemical is “substantially similar” in structure and pharmacological effect to a drug prohibited by the Controlled Substances Act, this chemical is also prohibited. In the words of one Senator, “if it looks and quacks like a duck--then it's a duck.”¹⁴ The Federal Analog Act is arguably one of the furthest-reaching federal drug laws enacted in the United States, prohibiting numerous chemical permutations and treating these substances on par with other Schedule I drugs like lysergic acid diethylamide (LSD) and heroin.¹⁵

*1080 Twenty years later, the backlash against “designer drugs” has begun to subside.¹⁶ Doctors and pharmacologists are beginning to take cautious steps toward reevaluating the medical value of these compounds.¹⁷ It is now possible to revisit the Federal Analog Act and examine whether replacing rules with standards was the correct move. This Comment focuses on the structural prong of the Federal Analog Act¹⁸ and argues that a rules-standards hybrid definition of a controlled substance analog under the Federal Analog Act offers both *1081 practical and theoretical advantages to the current standards-based incarnation. After providing a brief overview of the “designer drug” phenomenon, Part I introduces the Federal Analog Act. Part II considers the rules versus standards debate in the context of “designer drugs” and discusses advantages and disadvantages associated with each model. Part III explores peculiar problems that arise from the Federal Analog Act's current standards-based implementation, explores justifications for deploying a hybrid rules-standards approach to the Federal Analog Act, and considers possible methods of implementing a hybrid rules-standards approach in the Federal Analog Act.

I. What Are Designer Drugs and Where Did They Come From?

A. The Federal Analog Act: History of Designer Drugs

The Federal Analog Act was originally called the “Designer Drug Enforcement Act.”¹⁹ Instead of requiring the Drug Enforcement Administration (DEA) to promulgate a rule banning each chemical as it emerges on the black market, the Federal Analog Act automatically prohibits a chemical if it is “substantially similar in structure” to an already-prohibited drug, and has a “substantially similar chemical effect” or is “represented to have such an effect.”²⁰ The Federal Analog Act classifies these controlled substance analogs as Schedule I drugs²¹ --the most stringently controlled drugs in the United States, including heroin and LSD.²² To understand how the Federal Analog Act operates in the context of drug trends, it is useful to explore a brief history of federal controlled substance legislation and designer drugs in the United States.

The cultural upheaval of the 1960s brought a vast proliferation of recreational drugs to America. In 1973, President Richard Nixon declared an “all-out global war on the drug menace.”²³ “Right now,” he said, “the federal government is fighting the war on drug abuse under *1082 a distinct handicap, for its efforts are those of a loosely confederated alliance facing a resourceful, elusive, worldwide enemy.”²⁴ In an effort to contain the burgeoning drug epidemic, Congress enacted the Controlled Substances Act of 1970, the first comprehensive federal drug prohibition legislation.²⁵ President Nixon also sent Reorganization Plan No. 2 to Congress, creating the DEA and tasking it with enforcing the Controlled Substances Act of 1970.²⁶

From 1973 through 1980, the DEA fought the influx of stock controlled substances--such as cocaine, marijuana, and heroin--on an international scale. The DEA infiltrated Colombian cocaine and marijuana cartels, broke up Mexican heroin syndicates, and shut down central Asian drug pipelines.²⁷ However, the 1980s opened up a new domestic front in the War on Drugs. Synthetic drugs came into vogue again--drugs like methamphetamine, 3,4-methylenedioxy-N-methyl-amphetamine (MDMA), and 3,4-methylenedioxyamphetamine (MDA). Unlike stock drugs such as cocaine and heroin, synthetic drugs did not require a large initial investment and the support infrastructure of an international cartel. Instead, a small laboratory, supplied with a cheap investment of precursor chemicals and reagents, could produce a staggeringly large number of doses.²⁸ Furthermore, a laboratory was easily concealed and moved from state to state to avoid detection. The United States faced a new menace that seemed to be everywhere and nowhere at once. Synthetic drugs brought the War on Drugs to home turf. The old enemy--stodgy drug syndicates abroad--was dwarfed by a new fluid adversary at home.

***1083 B. The Source of Designer Drugs: A Close Relationship Between the Pharmaceutical Industry and Clandestine Chemists**

The term “designer drug” was originally coined to describe these seemingly novel concoctions. But twenty years later, this branding has proved to be misleading. As the DEA noted, the label “designer drug” “tends to cast a somewhat glamorous aura onto the concept”²⁹ --a perception that

is especially misguided considering that designer drugs are not new at all. Virtually all “designer drugs” are either legitimate pharmaceutical products on the market or potential products that were synthesized in medical research and development³⁰ but discarded because they didn't produce an intended effect. As Albert Hofmann--the first chemist to synthesize LSD³¹ -- explains:

When a new type of active compound is discovered in pharmaceutical-chemical research, whether by isolation from a plant drug or from animal organs, or through synthetic production as in the case of LSD, then the chemist attempts, through alterations in its molecular structure, to produce new compounds with similar, perhaps improved activity, or with other valuable active properties. We call this process a chemical modification of this type of active substance. Of the approximately 20,000 new substances that are produced annually in the pharmaceutical-chemical research laboratories of the world, the overwhelming majority are modification products of proportionally few types of active compounds. The discovery of a really new type of active substance--new with regard to chemical structure and pharmacological effect--is a rare stroke of luck.³²

As new pharmaceuticals emerged in academic and industrial research, clandestine chemists and drug distributors found a winning business strategy. They would wait until a psychoactive compound was *1084 discovered, and then they would copy and sell it. When researcher Albert Hofmann of Sandoz, Inc. discovered LSD-25 and began exploring its different variations,³³ clandestine chemists hijacked the molecule and sold it on the black market. Similarly, in the 1980s, Alexander Shulgin of Dow Chemical--an eminent Berkeley pharmacologist who The New York Times called a “one-man psychopharmaceutical research sector”³⁴ --discovered and rediscovered hundreds of variations on phenylethylamines and tryptamines. One of these was MDMA (known commonly as Ecstasy), a forgotten compound discovered by German pharmaceutical company Merck in 1912 that had been relegated to obscurity in dusty old academic journals.³⁵ Shulgin's discoveries were hijacked by clandestine chemists and released into the black market. This misappropriation fueled the MDMA crisis of the 1980s, much to the chagrin of medical professionals who believed that the illicit distribution of drugs would provoke a political backlash and prevent research into the drug's legitimate use.

This copy-and-sell approach offered twin advantages to black market entrepreneurs. First, black market entrepreneurs could free-ride on the research and development costs of legitimate pharmaceutical companies. Since the average cost of developing a new innovative drug is staggering,³⁶ this gave black market entrepreneurs a cheap and guaranteed method of determining which compounds had potential black market value. As a DEA official remarked, “The most important of the[] factors [that control the appearance of future synthetic drugs of abuse] is user acceptance of the marketed drug. . . . A reputation for selling ‘bad stuff’ would not be conducive to

good business.”³⁷ Second, once black market entrepreneurs identified a target drug for production, prior academic and industrial research provided a virtual *1085 blueprint for production. The same academic journals that published cutting-edge pharmaceutical and chemical research also published the synthetic methods required to produce new compounds.³⁸ Clandestine chemists simply copied chemical blueprints out of university libraries.³⁹

Thus, a “designer drug” is nothing more than a legitimate pharmaceutical product, or a rejected pharmaceutical research and development project, that has been released into the black market.⁴⁰

***1086 C. Designer Drugs: Legal Loopholes and Problems**

The close relationship between legitimate pharmaceutical research and black market products is the key to understanding the evolution of the Federal Analog Act. The importance of legitimate pharmaceutical research is too compelling to be overstated. However, the designer drug crisis, unintentionally fueled by pharmaceutical research, highlights the pitfalls of the Controlled Substances Act's purely rules-based system.

Before the passage of the Federal Analog Act, the DEA administrator issued individual prohibitions for each illicit chemical. Under the directives of the Controlled Substances Act, this was a very slow and costly process. First, the DEA had to gather data and investigate the drug.⁴¹ The DEA would then request an assessment from the Department of Health and Human Services (HHS). The HHS would confer with two agencies--the Food and Drug Agency (FDA) and the National Institute of Drug Abuse (NIDA)--and return a recommendation to the DEA. The DEA administrator would then decide whether the drug should be prohibited.⁴² Since other interested parties could challenge the decision in an adversarial proceeding, it sometimes took years for the DEA to ban a single drug.⁴³

Clandestine chemists became adept at taking advantage of the DEA's slow, rules-based system. The Controlled Substances Act prohibited a number of particular drugs, but clandestine chemists easily circumvented the rules by producing a slight variation on the chemical, resulting in a completely legal drug--often with similar pharmacological properties and potency.

Congress enacted the Federal Analog Act to stop the exploitation of these loopholes with a model based on standards, not rules. At first glance, the Federal Analog Act appears to completely solve the problem *1087 of controlled substance analogs by implementing a universal standard. However, the passage of twenty years has revealed both theoretical and practical problems with the Federal Analog Act's implementation of a standards-based model. Some of these problems appear to be a direct result of the use of a standard, and thus incurable. Other problems appear to be correctable. This Comment begins by considering the theoretical foundations of the rules versus standards debate in the context of the designer drug problem.

II. Rules Versus Standards and the Current State of Designer Drug Legislation

A. Rules Versus Standards: A Witch's Brew of Approaches in Controlled Substance Analog Legislation

The rules versus standards debate existed before the designer drug problem, but there has been a lack of attention in scholarly literature on the Federal Analog Act's use of a standard instead of a rule. This lack of attention is made even more curious by the diverse policies of different countries and states toward the global designer drug epidemic. While the Federal Analog Act implements a pure standards-based approach, this is by no means the only solution to the problem.

For example, many European countries use a rules-based approach. As of the writing of this Comment, France, Germany, the Netherlands, and Thailand have not enacted analog acts, but simply ban each individual chemical as it emerges on the black market.⁴⁴

Other jurisdictions, like the United States, use standards. However, there are wide-ranging differences even among jurisdictions that use standards. Some jurisdictions use a very open-ended standards approach toward controlled substance analogs. Arkansas, California, South Australia, Canada, and the United Kingdom deploy particularly broad standards. These jurisdictions treat chemicals as controlled substance analogs if they (1) have a "substantially similar" structure to *1088 a controlled substance; or (2) have a hallucinogenic or stimulant effect, or are represented or intended to have a hallucinogenic or stimulant effect.⁴⁵ Under these "disjunctive" jurisdictions, analog laws are very broad and potentially reach chemicals that are not outlawed under U.S. federal law. For example, in a disjunctive jurisdiction, a hallucinogen like salvinorin A--which has a unique and complex chemical structure unlike that of any currently controlled substance--would probably be prohibited because its hallucinogenic effect may be "substantially similar" to other controlled substances like DMT or LSD. Indeed, some courts have pointed out the problems with this approach in less obvious situations: an actor could be convicted of distributing a Schedule I drug like cocaine, even if she actually distributed caffeine and only represented that the caffeine was "a lot like cocaine."⁴⁶

On the other hand, other standards-based jurisdictions mirror the Federal Analog Act's language⁴⁷ and treat chemicals as controlled substance analogs only if they (1) have a "substantially similar" structure to a controlled substance; and (2) have a hallucinogenic or stimulant effect, or are represented or intended to have a hallucinogenic or stimulant effect.⁴⁸ Although the Federal Analog Act's language is ambiguous, federal courts have generally found that a conjunctive interpretation is necessary to prevent absurd results.⁴⁹ Under a conjunctive *1089 jurisdiction, a chemical with a truly novel structure like salvinorin A would be legal, even though it is the most powerful naturally occurring hallucinogen ever discovered.⁵⁰

Still other jurisdictions take a more creative approach by mixing rules with standards. For example, Illinois' controlled substance analog statute uses a blend of permissive inferences to signal what types of analogs are prohibited.⁵¹ In these hybrid jurisdictions, the legal status of a chemical like salvinorin A would depend on the particular wording of the statute. Under Illinois state law, for instance, salvinorin A would be legal.

B. Rules and Standards: Different Ingredients for Different Flavors

The main distinction between rules and standards is that rules give ex ante “content” to the law, while standards give ex post “content” to the law.⁵² In the context of controlled substance analog legislation, rules explicitly define which chemicals are prohibited ex ante. *1090 For example, if the legislature in a rules district wanted to prohibit methamphetamine, MDMA, and MDBU, it might issue this law: “Methamphetamine, 3,4-methylenedioxyamphetamine (MDMA), and 3,4-methylenedioxy-N-butylamphetamine (MDBU) are prohibited.” Conversely, a standards-based jurisdiction might issue a law like the Federal Analog Act: “All drugs that are substantially similar to amphetamine in structure are prohibited.”

The difference between the results of rules and standards is striking. Rules would signal that MDMA, MDBU, and methamphetamine were explicitly prohibited. Standards, on the other hand, would require an individual to determine whether MDMA, MDBU, or methamphetamine was “substantially similar” to amphetamine. An individual might think that methamphetamine is “substantially similar” to amphetamine, since it only differs by one functional group. On the other hand, the same individual might pause when asked whether MDMA is “substantially similar” to amphetamine, since MDMA adds two additional functional groups—one of them quite exotic—to amphetamine.⁵³ When asked about whether MDBU and methamphetamine are “substantially similar,” an individual might draw the line; the fact that MDBU adds two additional functional groups to methamphetamine—one of them a longer alkane—might be the straw that breaks the camel's back. However, an individual would never know whether he or she was right until the particular matter was litigated in criminal court.

This distinction between ex ante and ex post adjudication gives rise to a set of situations in which either rules may be favored over standards, or vice versa. This Comment examines these situations below as applied the Federal Analog Act's history over the last twenty years.

1. Costs

The starting point in the rules versus standards debate is the costs to the different actors. There are three different types of costs associated with rules and standards: adjudication costs, information costs, and invisible costs.

Adjudication costs are costs to the rulemaker. Rules cost more to promulgate than standards. Because the rulemaker must decide the content of the law *ex ante*, the rulemaker must also make an informed decision as to the rule that she will promulgate. Thus, rules are more *1091 efficient where many similar situations arise, because the initial cost of promulgating the rule will be amortized over many efficient transactions. Standards, on the other hand, are more efficient where there are a relatively small number of heterogeneous situations.⁵⁴

Before the Federal Analog Act was enacted, the DEA was swamped with the costs of promulgating rules--both in terms of time and money. Under the Controlled Substances Act, each rule had to be recommended by multiple agencies before the DEA Administrator could sign it into law. Because designer drugs are highly heterogeneous--arising in many different structural configurations--it would be nearly impossible for the DEA to study each of the potential designer drug's medical effects before deciding whether it should be prohibited. Furthermore, once the decision maker made an *ex post* adjudication, this precedent would effectively transform the standard into an *ex ante* rule for this particular drug. Thus, given the high degree of heterogeneity, the low number of identical transactions that require *ex post* determination, and the fact that only a relatively small number of potential designer drugs have been released on the black market, costs of adjudication appear to favor the use of a standard for the Federal Analog Act.

Information costs, however, cut in a different direction. Information costs determine not only who bears the costs of adjudication, but also who should bear the costs of adjudication. Under the standards-based Federal Analog Act, the information costs fall on the parties to the litigation--the federal prosecutor's office, the defendant, and the court--instead of falling on Congress, as they would in a rules-based system. In the context of controlled substances legislation, these parties are not well equipped to make a decision on a legislative matter. Federal prosecutors have limited resources and are not in an optimal position to litigate whether one chemical is "substantially similar" to a controlled substance. Likewise, defendants may not have sufficient resources to hire expert witnesses to bolster their side. Courts may be able to absorb the costs of litigation, but they should not bear those costs for another reason: they have expertise in determining facts, but they do not have any particular expertise in making policy judgments to determine which drugs should or should not be prohibited. Furthermore, *1092 in a criminal case, the legal determination of a court is vulnerable to information contamination from the irrelevant facts of a case.⁵⁵ Thus, information costs favor rules promulgated by Congress or the DEA⁵⁶--parties that are well equipped with both adequate monetary resources and technical expertise.⁵⁷

Finally, invisible costs are a special type of information cost embedded in rule- or standard-making apparatuses. Invisible costs arise from the collateral effects of interactions between *ex post* and *ex ante* proceedings. Since rules favor a dialogue between the rulemaking body and the citizen, rules create a framework where it is easier for citizens to react, whereas this reaction might be impossible

in a standards-based system. Invisible costs are the most striking costs associated with the Federal Analog Act's standards-based scheme. For example, if an interested party wishes to challenge an ex ante prohibition on a controlled substance such as MDMA, she can file a petition with the DEA and advance her arguments at a special hearing.⁵⁸ This is not uncommon; pharmaceutical companies occasionally file petitions in order to argue for the deregulation of a potential product.⁵⁹ However, this dialogue is simply impossible with ex post standards implementation. For example, under the Federal Analog Act, no content has been given to the law. Thus, no one may file a petition with the DEA to argue for the deregulation of an alleged controlled substance analog, *1093 since the alleged controlled substance analog--no matter how "substantially similar" it is in structure and effect to a controlled substance--is not explicitly regulated. Although declaratory judgments may provide relief in certain cases, standing issues may present problems in adjudication.⁶⁰ Thus, it is possible that no one will discover if the alleged controlled substance analog is in fact a prohibited drug, without risking criminal sanction. Paradoxically, the suspected controlled substance is simultaneously both a Schedule I drug and yet not a Schedule I drug. This gridlock creates an invisible cost--a situation where both the government and the interested party are deadlocked until the government either removes the prohibition on the parent compound or explicitly prohibits the problem compound.⁶¹ Thus, invisible costs favor the use of rules, which allow dialogue to proceed and information to be exchanged.

2. Deterrence

The Federal Analog Act is a criminal statute, and deterrence is one of its primary objectives. The stated congressional intent behind the Federal Analog Act is to stop clandestine chemists from "tinkering" with molecules in order to evade the law.⁶² Thus, the Federal Analog Act was enacted to improve on the underdeterrence of the rules-based Controlled Substances Act.

*1094 It is true that rules fail to capture some who act in socially undesirable ways and create perverse incentives for criminals to violate existing rules. As Cass Sunstein observes,

[c]onduct that is harmful, and that would be banned in an optimal system, will be allowed under most imaginable rules, because it is hard to design rules that ban all conduct that ought to be prohibited. Because rules have clear edges, they allow people to "evade" them by engaging in conduct that is technically exempted but that creates the same or analogous harms.⁶³

In the context of controlled substance analog legislation, rules seem to create perverse incentives for clandestine chemists to modify prohibited drugs into entirely legal structural configurations. Conversely, standards appear to be better suited for designer drug legislation, since standards will deter risk-averse actors when there is no information available.⁶⁴ Indeed, the DEA has praised the extraordinary breadth of the Federal Analog Act for suppressing the development of designer drugs--whether the chemicals involved were or were not actually controlled substance analogs.⁶⁵

However, there are several problems lurking beneath this analysis. First, it assumes that it is difficult to predict what kind of drugs will be made. The argument runs like this: if designer drugs cannot be predicted, then rulemakers don't know which chemicals to prohibit *ex ante*. If rulemakers don't know which drugs should be prohibited *ex ante*, then they will not prohibit enough chemicals--and clandestine chemists will always find a way around the rules. But this argument ignores what we've learned from observing drug trends over the last five years.⁶⁶ Historically, clandestine chemists have copied templates from legitimate pharmaceutical and academic research instead of creating entirely new designer drugs on their own.⁶⁷ Why spend time and *1095 money crafting a novel synthetic pathway to a novel modification of a chemical when there is an established synthetic pathway to a known hallucinogen or stimulant?⁶⁸ The vast majority of chemicals behind the designer drug epidemic have already been discussed at length in peer-reviewed journals, and the economic drive to discover new pharmaceuticals has already mapped out the vast majority of variations on the classical structural backbones.⁶⁹ The implication is that *1096 no "designer drug" in the past five years has come as a surprise.⁷⁰ Even assuming, for the sake of argument, that clandestine chemists somehow discover a novel psychoactive chemical with a completely unique chemical structure--like salvinorin A--even a standards-based approach like the current Federal Analog Act would not prohibit this compound. Indeed, this may be the correct outcome; there may be vastly diminishing psychoactive returns as the original molecule is modified beyond recognition.⁷¹ This type of discovery would be so rare and valuable that it ought to be encouraged, not deterred, because of the opportunities for future research.⁷² The new chemical should be given the full range of review given to all chemicals before it is officially prohibited. Thus, rules are unlikely to be underinclusive, because likely targets for synthesis can be easily identified.

Furthermore, there are information exchange problems with standards-- especially the standards implemented in the Federal Analog Act. For example, reasonable minds could differ on whether a *1097 particular chemical is "substantially similar" to the structure of a listed chemical under the Federal Analog Act.⁷³ Unless more criminals than not are risk-averse rational actors, this uncertainty makes it unlikely that a vague definition will truly deter more people than a more concrete definition.⁷⁴ Recent history suggests that gray market entrepreneurs are not deterred by uncertainty. Instead, because of self-serving bias, they may attempt to exploit uncertainty to their advantage.⁷⁵ For example, in 2004 the DEA broke up a ring of gray market drug entrepreneurs who flourished on the Internet by brazenly setting up websites selling "research chemicals."⁷⁶ Some of these entrepreneurs operated on the theory that the chemicals did not fall under the Federal Analog Act because they were not "substantially similar" in structure to controlled substances.⁷⁷ If the "research chemicals" were in fact controlled substance analogs, it would have been far better if these entrepreneurs had prior warning, from a rules-based system, that their actions were illegal,

presumably deterring them from selling millions of dollars of hallucinogens that ended up killing two people.⁷⁸ Likewise, rules may be better than standards at deterring potential drug consumers. Because criminal drug statutes express information about a particular chemical's danger, explicit prohibitions may be more effective *1098 than hazy standards at conveying warnings about a chemical's health hazards to potential drug consumers.

Even if rules underdeter criminals, standards are also imperfect because they overdeter. By employing a vague definition of "controlled substance analog,"⁷⁹ the Federal Analog Act chills legitimate pharmaceutical and academic research. As discussed below, researchers in these fields are always interested in exploring variations on chemicals--including chemicals that are "substantially similar" in structure and effect to controlled substances.⁸⁰ For example, exploration of the phenylethylamine family of chemicals alone has yielded anorectics,⁸¹ bronchodilators,⁸² and antidepressants,⁸³ among other drugs. Many researchers have also proposed the use of phenylethylamine and tryptamine derivatives and analogs for psychotherapy, and these previously controversial proposals are now gaining traction as the backlash from the designer drug epidemic from the 1960s and 1980s begins to subside.⁸⁴

Since industry chemists and pharmacologists are ultimately interested in distributing these chemicals for human consumption,⁸⁵ and *1099 the new drugs may have effects "substantially similar" to controlled substances, there is a compelling policy interest both in protecting innocent actors from capture and in allowing for the liberation of a potential controlled substance analog from its legal shackles if it has a legitimate medical use.

Thus, while rules may appear at first glance to underdeter, a closer analysis reveals that this underdeterrence may be overstated, while the overdeterrence of a standard--especially the standard employed by the Federal Analog Act--may be understated.

3. Fairness Concerns

The Federal Analog Act's greatest vulnerabilities lie in due process concerns that come with its ex post standards approach. Regardless of whether an individual is developing a pharmaceutical product in good faith or planning on releasing a designer drug on the black market, the law ought to give clear notice of whether a particular chemical is prohibited. Since the Federal Analog Act treats controlled substance analogs as equivalent to Schedule I drugs--the most stringently controlled category of drugs--the potential penalties are very high. When the stakes involve possible lifetime imprisonment, it is absolutely imperative to give fair notice to individuals-- even if the due process concerns fall short of violating the Constitution.⁸⁶

Simple rules generally give better notice than do standards.⁸⁷ This is especially true in the context of designer drugs. Under a rules-based regime like the Controlled Substances Act, it is clear

which chemicals are prohibited and which chemicals are not. MDMA is prohibited; MDBU is not (directly).⁸⁸ Under the standards-based Federal Analog Act, however, it is unclear--without further research into *1100 the case law--whether MDMA would have been illegal before it was officially prohibited. It is still unclear even today if a compound like MDBU would be prohibited under the Federal Analog Act.

Part of the confusion stems from the regulatory nature of the Federal Analog Act. Standards rely heavily on social norms for guidance. A typical standard might say, "Do not use your stereo in an unreasonable way in this apartment." Most people would understand this standard to signal an underlying social norm--unreasonableness--which captures many familiar situations⁸⁹ where it would be socially unacceptable to annoy other people.⁹⁰ For example, most individuals would understand that this command meant: no playing the stereo loudly at night, or in the early morning, etc.⁹¹ However, in the context of controlled substance analogs, there are no social norms about what chemical structures are "substantially similar" to others, or whether the pharmacological effect of a particular chemical is similar to the pharmacological effect of another. Without an underlying social norm, it is wishful thinking to believe that individuals will have fair notice of a subject that is as complex as organic chemistry.⁹² The unholy union of legalese and chemistry jargon is probably enough to bewilder even the most studious individuals.⁹³ In fact, many chemistry *1101 experts disagree on whether a chemical is "substantially similar" in structure to another chemical--so much so that Federal Analog Act litigation often degenerates into a "battle of experts," which is founded more on opinion than on actual scientific evidence.⁹⁴ One survey of Federal Analog Act jurisprudence discovered that courts sometimes considered a chemical's two-dimensional structure rather than the three-dimensional structure as a factor; that courts sometimes ignored the difference in the number of atoms as a meaningful factor; and that courts even ignored quantitative "similarity analysis" results that pharmaceutical companies use to determine whether a chemical is structurally similar to another.⁹⁵

Another problem with the Federal Analog Act's implementation of a standard is the standard's stunted growth through the last twenty years. In theory, standards evolve into a set of rules as the courts lay down precedent.⁹⁶ Although judicial precedent does not provide the same clarity of notice as a promulgated rule,⁹⁷ it provides fair notice after the courts accumulate a critical mass of data points. However, the Federal Analog Act's evolution into a mature statute has been sluggish. The vagueness of the definition of a controlled substance analog under the Federal Analog Act is a double-edged sword. Prosecutors are often unsure if they have a colorable claim and are reluctant to bring Federal Analog Act cases unless they are almost certain to succeed.⁹⁸ Consequently, there have been only about seventy cases *1102 brought under the Federal Analog Act over the span of more than two decades and even fewer data points giving clues as to the courts' definition of a "substantially similar" structure.⁹⁹

What chemicals currently fall under the Federal Analog Act as “controlled substances analogs”? The ex post determination of whether a chemical is “substantially similar” to a scheduled drug has been subject to an enormous amount of interpretative leeway by federal courts. The answer seems to be that everything that the courts have examined so far qualifies as a controlled substance analog. This does not mean, however, that every potential analog is in fact an analog. While the courts have found nearly every litigated chemical to be a controlled substance analog, they have not examined every type of potential analog.

Instead, the courts have created legal precedent on several heavily litigated challenges for a narrow spectrum of chemicals. The Federal Courts of Appeals have consistently determined that gamma butyrolactone (GBL) is an analog of gamma hydroxybutyric acid (GHB),¹⁰⁰ MDMA is an analog of MDA,¹⁰¹ N-hydroxy-MDMA is an analog of MDMA,¹⁰² methcathinone and methylcathinone are analogs of cathinone and methamphetamine,¹⁰³ aminorex and phenylethylamine *1103 are analogs of 4-methylaminorex and methamphetamine,¹⁰⁴ 1-(3-oxy-3 phenyl-propyl)-4 phenyl-4-propionoxypiperidine (OPP/PPP) is an analog of MPPP,¹⁰⁵ and MeO-DiPT is an analog of DET,¹⁰⁶ without considering other combinations. Thus, while these particular chemicals surely qualify as controlled substance analogs, we cannot tell with certainty whether a novel and previously unlitigated chemical is also a controlled substance analog.

We can glean some information from the case law. We can infer that the addition of one methyl group (MDMA to MDA, methylcathinone to methcathinone), the cleavage of one methyl group (4-methylaminorex to aminorex), the cleavage of two methyl groups (methamphetamine to phenylethylamine), and the addition of a hydroxyl group (MDMA to N-hydroxy-MDMA) are each sufficient to qualify a substance as a controlled substance analog. Most interestingly, the addition of two alkanes and the addition of a methoxyl group do not prevent a chemical from being “substantially similar” to a parent compound.¹⁰⁷ Thus, roughly speaking, the courts seem to imply that addition or cleavage of up to three first-degree functional groups without alteration of the core molecule results in a controlled substance analog.

However, far fewer courts have answered a much more important question: what is not a controlled substance analog?¹⁰⁸ Is the Federal Analog Act's reach limited to first-order substitutions? Or are second-order substitutions, such as the addition or cleavage of aliphatic chains or rings that themselves contain substitutions, also prohibited? What about third-degree substitutions? What about minor modifications *1104 to the core backbone itself? What about the addition of extremely polar functional groups, or large inhibitory chains or rings that render the compound pharmacologically inactive?¹⁰⁹ There are no good answers to these questions. In order to map this territory, courts must either (1) strike down the application of the Federal Analog Act to certain

chemicals or (2) create a justification for their factual finding that goes beyond relying on the “superiority” of governmental expert testimony in a battle of experts.¹¹⁰

Courts are reluctant to squarely address this question either way. Instead, federal courts have found that every chemical examined has been a controlled substance analog.¹¹¹ Thus, it is impossible to determine the reach of the Federal Analog Act, other than to assume that it casts such a wide net that virtually every variation of every fundamental backbone is controlled. Indeed, at least one court has supported this proposition.¹¹²

***1105** There are only a few courts that are willing to carve out a more limited definition. Just one court has elaborated on what rules should govern the definition of a “substantially similar” structure.¹¹³ State courts are similarly reticent in interpreting their own analog statutes.¹¹⁴ Most courts prefer simply to fall back on a battle between experts, ***1106** which raises the fundamental question again: what does it mean for a chemical to be “substantially similar” to another chemical? Current judicial precedent does not adequately answer this question.

Finally, the Federal Analog Act's use of an ex post standard collides with the Controlled Substances Act's legal framework because the Federal Analog Act is incompatible with scienter requirements.¹¹⁵ Unlike crimes involving explicitly listed chemicals, the Federal Analog Act imposes no scienter requirement on the defendant. If a controlled substance analog is defined through an ex post adjudication, there is surely no way that a defendant could know that a previously unlitigated chemical falls within the purview of the Federal Analog Act. Indeed, since there is no way for a defendant to truly know ex ante whether an unlitigated chemical is an analog, a scienter requirement would be largely meaningless. Thus, the Federal Analog Act creates the possibility for strict liability across the entire spectrum of drug legislation by bootstrapping the definition of a Schedule I drug onto a substance carried by an unknowing actor, and exposing her to full liability under the Controlled Substances Act.¹¹⁶

Some courts have attempted to remedy the intrinsic problems with standards by imposing scienter requirements and patching together a quilt of legal devices such as permissive inferences to remedy the problem.¹¹⁷ While these devices present a virtuosic display of practical judicial ingenuity, these legal sleights-of-hand only recognize, rather than resolve, the fundamental problems created by the Federal Analog Act's use of a standard. At best, they provide a limited practical workaround; at worst, they conflict with the language of the statute and usurp the generally accepted principle that the Federal Analog Act should be read under a conjunctive interpretation.¹¹⁸ Other ***1107** courts inexplicably decline to find any scienter requirement at all.¹¹⁹ Neither approach appears to solve the intrinsic problems posed by an ex post determination.

Thus, fair-notice concerns strongly favor the use of simple rules in controlled substance legislation--or alternatively, the use of standards that have the potential to blossom into a clear set of rules through judicial precedent.

III. Proposed Changes

A. Mixing Rules and Standards in the Federal Analog Act: Putting It All in the Cauldron

The discussion above¹²⁰ reveals that neither standards nor rules alone provide a satisfactory solution to controlled substance legislation. Costs favor standards, deterrence favors standards in some situations and rules in other situations, and due process concerns favor rules. The Federal Analog Act, which uses a standards approach, only partially fulfills these objectives. However, there is a ready solution at hand. By mixing rules and standards, a law can be designed to (1) minimize costs, (2) selectively maximize criminal deterrence and minimize legitimate research deterrence, and (3) maximize fair notice. Since laws exist on a spectrum between standards and rules, there are a variety of ways to achieve this objective.¹²¹

The Federal Analog Act should use translucent standards--standards that are more easily defined than the Federal Analog Act's current opaque standard.¹²² For example, if the Federal Analog Act prohibited chemicals that differed from scheduled drugs only by "functional groups," this standard would reduce the cost of promulgating many heterogeneous rules, selectively deter criminals, and satisfy *1108 due process concerns. First, this translucent standard would be more efficient than the promulgation of rules, because even a translucent standard would have much greater breadth than a simple rule. There are surely some chemicals that are different only by "functional groups" from drugs prohibited by the Controlled Substances Act. For example, a halo-substituted analog is one of the least aggressive variations of a molecule that could be made without the molecule remaining completely identical to a listed chemical.¹²³

Second, a translucent standard would selectively deter criminals because it would only prohibit chemicals within a certain "radius" of a currently controlled substance. This implementation provides an effective filter to target clandestine chemists selectively, since legitimate pharmaceutical and academic researchers are more likely to experiment with more complex deviations from core structural backbones, whereas clandestine chemists are more likely to adhere to simple permutations of a known psychoactive core. As the potential analog becomes less "substantially similar" in structure to a listed chemical, the more likely it is to implicate due process concerns and the less likely it is to serve as a reliable proxy for the pharmacological effect of the listed drug.

Third, a translucent standard would fulfill fair notice requirements, because it would provide a map by employing simple rules as guideposts. Although simple rules are generally better at providing

fair notice, complex rules do not necessarily provide fair notice as well as simple standards do.¹²⁴ A simple but concrete elementary standard can allow an ex post adjudication to cover great breadth without threatening due process.¹²⁵

However, in more complex cases--where the chemical in question is arguably very different in structure than a controlled substance--the Federal Analog Act should rely on transparent, predefined rules, rather than "facts" tied to so-called scientific reality, which are likely to be manipulated by spurious expert opinion.¹²⁶ For example, relating *1109 heavily modified chemicals to controlled chemicals would increase the opacity of a standard to the point where it is virtually impenetrable.¹²⁷ For these cases, it is better to provide rules as guideposts to illuminate the standard. In such complex cases, rules would help to minimize overall costs by offsetting promulgation costs with decreased litigation and information costs. Rules would also selectively deter criminals in complex cases, since pharmacists--not criminals--are interested in studying unexplored pharmacological terrain. Finally, rules would provide fair notice to all. Although standards that could properly cover complex cases would need to incorporate exemptions and factor tests to satisfy policy goals like deterrence, a simple rule banning the problem compound would, at a minimum, provide adequate notice to the interested party.

B. Practical Implementation: Changes to the Federal Analog Act

If Congress decides to amend the Federal Analog Act, there are several ways that rules and standards could be mixed. First, Congress might specify the scope of "substantially similar" in order to encompass preferred policy objectives. As discussed above in Part III.A, the optimal range of policy goals seems to be captured by a translucent standard combined with strategically placed rules.

One approach might be to provide more ex ante guidance on what constitutes a "controlled substance analog." For instance, Congress could statutorily define a "controlled substance analog" as a chemical that is "substantially similar" to (1) a currently scheduled chemical, or (2) a chemical that has previously been considered a controlled substance analog, with the stipulation that a chemical is "substantially similar" to another chemical if it differs only by an "unsubstituted functional group."

*1110 Although the DEA considered a similar proposal when formulating its recommendation to Congress, it ultimately dismissed this proposal because it believed that there were too many different groups available to provide an all-encompassing and coherent model.¹²⁸ While this would certainly be problematic in a pure rules-based model,¹²⁹ it would not raise the same problems in a rules-standards hybrid. In a hybrid model, it would not even be necessary to define "unsubstituted functional group," since this terminology is simple enough for most laypersons to understand and could remain an issue for ex post adjudication. This proposed definition would

both contract and expand the scope of the analog statute. It would expand the scope because the definition itself would be recursive: if a court found that a chemical was an analog, the definition would expand to encompass all immediate permutations of that analog, which would allow the law to provide both clear notice and also to keep pace with black market entrepreneurs.¹³⁰ On the other hand, this hybrid model would also appropriately contract the definition of an analog: it would limit the reach of the statute to permutations of groups and their subsequent spin-offs, instead of potentially barring enormous swathes of unrelated chemicals. Presumably, the definition could also be enhanced by adding a discrete list of exceptions, since only a finite number of permutations would be prohibited, compared to the infinite number potentially prohibited under the current incarnation of the Federal Analog Act.

***1111** Second, Congress could create an exemption for legitimate medical research. When the Federal Analog Act was first proposed, the American Chemical Society lobbied Congress to create an exception to facilitate legitimate industrial and academic research.¹³¹ The original draft of the Federal Analog Act included a small exemption for research scientists who obtained a license from the DEA, but exemption quickly became the focus of controversy from legislators who derided it as the “Timothy Leary” loophole.¹³² However, this provision operated on the important insight that exemptions make rules act more like standards, and can therefore solve some of the overdeterrence problems that might hamper legitimate research efforts without sacrificing criminal deterrence.¹³³ Thus, the exemption provision should be reconsidered, subject to careful scrutiny and better-developed licensing requirements.

C. Institutional Responses

The federal government could also implement a hybrid rules-standards approach at an institutional level, without directly amending the Federal Analog Act. There are different ways to mix rules and standards at this level. For example, Congress could improve the efficiency of the rulemaking process. Jurisdictions that rely on rules often streamline the process of officially prohibiting a particular drug much more efficiently than a jurisdiction that mixes rules and standards.¹³⁴ However, while this approach grants much-needed flexibility to drug enforcement agencies and legislators, it also sacrifices an opportunity ***1112** to carefully consider possible medical uses of the chemical in dispute.¹³⁵

Conversely, in jurisdictions that employ standards--as in the United States-- courts could play an instrumental role in carving out the contours of controlled substance analog jurisprudence.¹³⁶ The Federal Analog Act relies on judicial determination of whether a particular chemical is “substantially similar” to another chemical to give content to its standard. If courts were to define the outer limits of the Act's reach, most of the problems might be solved over time. However, the conversion of standards to rules through judicial precedents has proved to be unworkable in

practice, partly because of the peculiar complexity of chemicals, and partly because few cases are actually brought to trial and/or reviewed on appeal.

Perhaps the simplest solution is for the DEA to strengthen the use of rules by petitioning for the official listing of potential chemical analogs on each appropriate schedule instead of simply waiting for each chemical to become a problem. As discussed above,¹³⁷ the chemicals developed by legitimate academic and industry researchers are the same chemicals that are created by clandestine chemists. Therefore, constructing a database of potential analogs should be as simple as searching the scientific literature for the appropriate structural backbone, along with pharmacological search terms such as "hallucinogen," "stimulant," or "depressant."¹³⁸ Granted, this must be done in combination with a clearer and more limited definition of "substantially similar" structures, or else the tree of potential analogs will simply grow exponentially and cloud the issue once more.

In conjunction with the creation of a more comprehensive list of chemicals, there is also a need to facilitate the listing of a chemical beyond an emergency basis. One solution might be to extend the emergency basis indefinitely, but subject it to effective rebuttal hearings. *1113 Once the DEA has officially listed a chemical, the agency has effectively "captured" the chemical and will rarely remove it from the list. Thus, rebuttal hearings ought to be conducted with procedural safeguards to avoid agency capture, perhaps by federal courts.

Another effective method of satisfying due process concerns is through blunt force. If the DEA provides notification on what it considers to be a potential controlled substance analog, this will soften the blow against law-abiding citizens, who tend to trust governmental agencies' assessments.¹³⁹ A declaration from the DEA that the federal government will treat certain chemicals as analogs provides both fair notice and sufficient deterrence to all but the most foolhardy individuals. Even though the DEA cannot issue legally binding interpretations of the Federal Analog Act, the mere threat of enforcement, coupled with the virtually unlimited legal resources of the federal government, ensures that few individuals will run the risk of losing an expensive legal battle against the federal government.¹⁴⁰ Any attorney could give a similar--and perhaps more objective--legal analysis, but such analysis carries significantly more weight when issued by an agency with the power of acting upon its analysis. Indeed, some courts *1114 have indicated that they will give special weight to an agency's nonbinding opinion in deciding whether a defendant knew that he was distributing a controlled substance analog.¹⁴¹ One disadvantage, however, is the possibility that the DEA might overextend its authority and capture as many chemicals as possible, whether or not the chemical properly falls under the Federal Analog Act. For example, in 2002, the DEA issued an opinion that *Salvia divinorum* fell within the orbit of the Federal Analog Act.¹⁴² However, this is demonstrably untrue, as the chemical structure of *Salvia divinorum* does not bear any resemblance to any of the twenty-three categories of drugs listed on

Schedule I or II.¹⁴³ Thus, to provide checks and balances, a refined definition of what constitutes a “substantially similar” structure is needed to provide a counter to the federal government's ability to issue nonbinding legal opinions at will.

Finally, the DEA should hold nonbinding preliminary hearings and allow citizens to challenge potential controlled substance analogs. Although this approach concededly adds to transaction costs, there are twin benefits to treating potential analogs procedurally as if they were officially listed drugs. First, this provides ample notice as to whether the DEA considers the drug to be a potential analog. Second, it also provides an important opportunity to set the stage for possible medical and psychotherapeutic uses of the drug. A scientist is much more likely to proceed with research if he has obtained the equivalent of a “no-action” letter from the DEA.

***1115 Conclusion**

The alphabet soup of designer drugs that exploded onto the drug scene in the 1980s presented an amorphous and fluid threat that provoked a shock and awe campaign from Congress in response. However, the twenty years since the passage of the Federal Analog Act have shown us three important insights.

First, the threat is not as amorphous and unpredictable as it may have appeared at first glance. Rather, the name “designer drug” is something of a misnomer--“designed and copied drug” is probably a more accurate description. If there is a copy, there is a source; if there is a source, we know where the next copy will arise.

Second, the standards of the Federal Analog Act have failed to blossom into a satisfactory set of precedents that maximize proper notice and deterrence of criminal activity, minimize deterrence of legitimate research, and minimize information costs. In addition, the Federal Analog Act's implementation of a pure standards-based model presents several unresolved and perplexing problems. A comparison of the use of rules versus standards in the controlled substances area suggests that a mixture of rules and standards provides a compelling solution that addresses many of the current problems found in the Federal Analog Act.

Third, the backlash from the widespread recreational use of phenylethylamines has begun to subside, sparking new interest in the potential of well-known psychoactive agents like MDMA and psilocybin, as well as other undiscovered agents that may hold great potential for medical and psychotherapeutic applications.

The power to predict designer drug trends comes with the power to define the contours of the Federal Analog Act and make it into a cost-effective and precise weapon that selectively targets criminal activity while minimizing collateral damage to medical research and innocent actors. The current standards-based model of the Federal Analog Act--which suffers from both theoretical and

practical problems--is long overdue for a dose of change. Adding rules into the brew to cook up a rules-standards hybrid may be the best remedy available.

Footnotes

- d1 B.S., 2004, Yale University; J.D. Candidate, 2008, University of Pennsylvania Law School. I would like to thank the Senior Editors of the University of Pennsylvania Law Review for their invaluable commentary and help, and the Associate Editors for all their help. I am particularly grateful to Evan Chyun and Aretae Ortiz for their sound advice and superhuman editing skills, and to Erica Lai and Christopher Fromherz for their resourcefulness in dealing with a labyrinth of strange and exotic sources. I would also like to thank the Yale Chemical Engineering faculty and graduate students for their impossible patience in putting up with my experiments in the laboratory. I bear sole responsibility for all errors.
- 1 For a more detailed description of the incident, see Claudia Wallis, *Surprising Clue to Parkinson's*, *Time*, Apr. 8, 1985, at 61, 61-62.
- 2 *Id.* at 61.
- 3 *Id.*
- 4 *Id.*
- 5 See Halle L. Weingarten, *1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP): One Designer Drug and Serendipity*, 33 *J. Forensic Sci.* 588, 588-59 (1988).
- 6 *Id.*
- 7 See Anthony Trevor et al., *Pharmacology and Toxicology of MPTP: A Neurotoxic By-Product of Illicit Designer Drug Chemistry*, in *Cocaine, Marijuana, Designer Drugs: Chemistry, Pharmacology, and Behavior* 187, 188 (Kinfe K. Redda et al. eds., 1989) ("MPTP represents a side product formed through inadequate control of temperature and/or acidity....").
- 8 See Weingarten, *supra* note 5, at 590-92 (describing the isolation of MPTP and its neurodegenerative effects on dopamine-producing neurons); see also Neal Castagnoli, Jr. & Kay P. Castagnoli, *Metabolic Bioactivation Reactions Potentially Related to Drug Toxicities*, in 173 *NIDA Research Monograph* 85, 91-94 (Rao S. Rapaka et al. eds., 1997), available at http://www.nida.nih.gov/pdf/Monographs/Monograph173/085-105_Castagnoli.pdf (discussing the biochemistry of MPTP's effects).
- 9 Weingarten, *supra* at note 5, at 588. Some five hundred people may have ultimately ingested the toxin-laced narcotic. Shari Roan, *Designer Drug Roulette*, *S. Fla. Sun-Sentinel*, Nov. 7, 1985, at 1.E.
- 10 See Walter Borges, *Designer Drug Sales Questioned*, *Dallas Morning News*, Nov. 20, 1985, at 31A (describing a citizen movement to "counter the sales of legal designer drugs" near a local high school); Daniel L. Lungren, *Letter, The Rapid Spread of Synthetic Narcotics*, *L.A. Times*, Oct. 5, 1985, at A2 (outlining Congressman Lungren's response to "[t]he rapid spread of the problem of synthetic narcotics"); Bill Romano, *Shootings Laid to "Drug Explosion,"* *San Jose Mercury News*, Nov. 23, 1985 (describing an "explosion of PCP, LSD and designer drugs" in San Jose).
- 11 See Lester Grinspoon & James B. Bakalar, *A Drug Bill's Bad Side Effects*, *N.Y. Times*, Apr. 28, 1986, at A25 (citing numerous deaths and injuries from heroin analogs as the impetus for the then-proposed Federal Analog Act); Philip Shenon, *U.S. To Back Penalties for New Drug Threat*, *N.Y. Times*, July 11, 1985, at A13 (quoting Attorney General Edwin Meese, who announced the new federal legislation and called synthetics a "dangerous phenomenon in the illicit drug market").
- 12 *Controlled Substance Analogue Enforcement Act of 1986*, Pub. L. No. 99-570, §1203, 100 Stat. 3207, 3213-14.
- 13 See *United States v. Turcotte*, 405 F.3d 515, 518 (7th Cir. 2005) (calling the Federal Analog Act "Congress's attempt to adapt the nation's controlled substances laws to the dizzying pace of innovations in drug technology"); *United States v. Forbes*, 806 F. Supp. 232, 238 (D. Colo. 1992) ("Congress declared that the purpose of the statute is to attack underground chemists who tinker with the molecules of controlled substances to create new drugs that are not yet illegal.").
- 14 Nick Ravo, "Designer Drugs" Head for Florida, Chiles Fears, *Miami Herald*, Aug. 8, 1985, at 3PB.

- 15 According to Alexander Shulgin, the number of known psychedelics will rise exponentially over the next century. See Drake Bennett, *Dr. Ecstasy*, N.Y. Times Mag., Jan. 30, 2005, available at <http://www.nytimes.com/2005/01/30/magazine/30ECSTASY.html> (“At the beginning of the 20th century, there were only two psychedelic compounds known to Western science: cannabis and mescaline. A little over 50 years later—with LSD, psilocybin, psilocin, 3,4,5-trimethoxyamphetamine (TMA), several compounds based on dimethyltryptamine (DMT) and various other isomers—the number was up to almost 20. By 2000, there were well over 200. So you see, the growth is exponential.... [By 2050] we may have well over [2000].” (internal quotation marks omitted) (quoting Shulgin)). Since the vast majority of these drugs will most likely be permutations of existing drugs, see *infra* Part I.B (explaining the rarity of new structures and the method of discovering new drugs by permutation), the Federal Analog Act could potentially prohibit thousands of drugs under its broad reach.
- 16 See *id.* (“[T]here’s obviously been a significant shift at the regulatory agencies and the Institutional Review Boards. There are studies being approved that wouldn’t have been approved 10 years ago. And there are studies being proposed that wouldn’t have been proposed 10 years ago” (internal quotation marks omitted) (quoting Mark A.R. Kleiman, director of the Drug Policy Analysis Program at UCLA)); Roxanne Khamsi, *Magic Mushrooms Really Cause “Spiritual” Experiences*, *NewScientist*, July 11, 2006, <http://www.newscientist.com/article.ns?id=dn9522> (describing how psilocybin—the hallucinogenic component in “magic mushrooms”—is beginning to spark interest in medical circles after being “ignored” by the scientific community for about forty years); Christopher Newton, *FDA OKs Clinical Testing of Ecstasy*, *WashingtonPost.com*, Nov. 6, 2001, http://www.washingtonpost.com/wp-srv/aponline/20011106/aponline215233_000.htm (remarking that recent approval by the Food and Drug Administration to test MDMA, commonly known as “Ecstasy,” on human subjects “marks a shift for the agency, which has virtually banned the drug from researchers for more than a decade”).
- 17 See Khamsi, *supra* note 16 (reporting the results of a recent study conducted at Johns Hopkins University School of Medicine, which found that more than a third of the volunteers in a double-blind psilocybin study described their encounter with the hallucinogen as “the single most spiritually significant experience in their lifetimes”).
- 18 The Act defines a “controlled substance analogue” as a substance,
(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or
(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.
21 U.S.C. § 802(32)(A) (2000). While § 802(32)(A)(ii), the “effect” prong of the Federal Analog Act, is also an interesting topic, it does not implicate the same concerns as the first prong and is beyond the scope of this Comment.
- 19 See *United States v. Forbes*, 806 F. Supp. 232, 235 (D. Colo. 1992) (describing the legislative history of the Federal Analog Act).
- 20 21 U.S.C. § 802(32)(A).
- 21 See *supra* note 18 (explaining and providing the text of the Federal Analog Act’s definition of “controlled substance analog”).
- 22 See U.S. DEA, *Drug Scheduling*, <http://www.dea.gov/pubs/scheduling.html> (last visited Feb. 15, 2008) (providing a list of drugs in Schedules I through V).
- 23 U.S. DEA, *Drug Enforcement Administration: A Tradition of Excellence 1973-2003*, at 13 (2003), available at http://www.dea.gov/pubs/history/history_part1.pdf (quoting President Richard Nixon’s 1973 declaration).
- 24 *Id.*
- 25 See *id.* at 9 (“[The Controlled Substances Act of 1970], along with its implementing regulations, established a single system of control for both narcotic and psychotropic drugs for the first time in U.S. history.”).
- 26 See *id.* at 13-14 (describing the founding of the DEA and its *raison d’être*).
- 27 See generally *id.* at 3-42 (describing the DEA’s global operations in the early 1970s).

- 28 See Donald A. Cooper, DEA, Future Synthetic Drugs of Abuse, [http:// designer-drug.com/synth/index.html](http://designer-drug.com/synth/index.html) (last visited Feb. 15, 2008) (“[S]everal fentanyl derivatives have such high potencies that the quantities required to be synthesized are trivial. For instance, carfentanil is approximately 400 times as potent as heroin and has an extremely favorable therapeutic index. Hence, an easy week’s work for two chemists could provide 10 kilograms of carfentanil which would be equivalent to 40 metric tons of pure heroin.” (citations omitted)).
- 29 See *id.* (“The Drug Enforcement Administration (DEA) has noted that the designer drug terminology tends to cast a somewhat glamorous aura onto the concept, and as a result, the DEA feels that it would be wise to refer to these compounds in some other manner and suggests the use of the term Controlled Substance Analogs.”).
- 30 See Robert Seidenberg, Letter to the Editor, Dangers of Prescribing Mind-Bending Drugs, *N.Y. Times*, May 9, 1986, at A34 (“[D]rugs dispensed in the office and those on the ‘street’ have very much in common.”).
- 31 See Albert Hofmann, LSD: My Problem Child 12 (1980) (“In 1938, I produced the twenty-fifth substance in this series of lysergic acid derivatives: lysergic acid diethylamide, abbreviated LSD-25 (Lysergsäure-diäthylamid) for laboratory use.”).
- 32 *Id.* at 31; see also Paul Anacker & Edward J. Imwinkelried, The Confusing World of the Controlled Substance Analogue (CSA) Criminal Defense, 42 *Crim. L. Bull.* 744, 744 (2006) (describing chemists’ efforts “to slightly modify the chemical structure of prohibited substances to create a new substance that technically differs from the controlled substance”).
- 33 Although Hofmann ultimately produced hundreds of lysergic acid analogs, he found that LSD-25 was still by far the most potent compound. See Hofmann, *supra* note 31, at 32-33 (describing the search that yielded compounds such as LA-111 and LAE-32, which were psychoactive but considerably weaker than LSD-25).
- 34 Bennett, *supra* note 15.
- 35 See Roland W. Freudenmann et al., The Origin of MDMA (Ecstasy) Revisited: The True Story Reconstructed from the Original Documents, 101 *Addiction* 1241, 1242-45 (2006) (explaining the history of Merck’s discovery of MDMA as part of a project to evade patents on a clotting agent).
- 36 See Cong. Budget Office, Research and Development in the Pharmaceutical Industry 2 (2006), available at [http:// www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf](http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf) (“A recent, widely circulated estimate put the average cost of developing an innovative new drug at more than \$800 million, including expenditures on failed projects and the value of forgone alternative investments.”).
- 37 Cooper, *supra* note 28.
- 38 See Trevor et al., *supra* note 7, at 188 (discussing how the two “entrepreneurs” copied the chemical blueprints for producing MPPP out of a university library); Carl Wilkinson, The Next Big High?, *Observer*, Apr. 21, 2002, available at [http:// observer.guardian.co.uk/drugs/story/0,11908,686710,00.html](http://observer.guardian.co.uk/drugs/story/0,11908,686710,00.html) (“[I]t is felt by many pharmacologists that the creation of new substances from scratch has become far less likely simply through the exhaustion of possibilities. What is more likely is for a previously discovered substance, created through bona fide medical research, to be uncovered in an obscure academic journal and recreated in an underground lab....”). Shulgin observed that [t]he raw material for such technologic predictions is available in the scientific literature. In every issue of the journals in the fields of pharmacology, medicinal chemistry, the botanical sciences, and biochemistry, articles appear that advertise the isolation, synthesis, or evaluation of materials which have some pharmacologic action. Any article describing a new family of compounds (“Potential Centrally Active Stimulants Evaluated in Experimental Animals,” for example) will encourage an unknown number of synthetic repetitions by underground researchers and manufacturers (with immediate pharmacologic evaluation in man). Alexander T. Shulgin, *Drugs of Abuse in the Future*, 8 *Clinical Toxicology* 405, 406 (1975).
- 39 The process of researching a synthetic path to a target chemical is remarkably similar to doing legal research with Westlaw or LexisNexis. A curious chemist need only access an online science database, draw a diagram of his target chemical structure, gather a number of citations to chemical journals, and explore the proven synthetic methods blazed by previous chemists. Compounds that emerged as problematic “designer drugs” were not only reported in research journals, but also often came with explicit synthesis instructions.

- 40 See *infra* notes 69-70 and accompanying text (providing an informal survey of DEA Microgram Bulletins throughout the last five years). Between 2003 and 2007, nearly all reported “new designer drugs” were actually discovered a number of years earlier by academic and pharmaceutical researchers. The only exceptions were certain exotic plants with hallucinogenic properties, such as *Salvia divinorum*, and *Mitragyna speciosa*, which would not have fallen under the Federal Analog Act because of the wholly unique chemical structures of their psychoactive components. A survey of the case law stretching back to the enactment of the Federal Analog Act suggests that truly novel designer drugs have not appeared in at least two decades. See *infra* notes 98-106 (listing the analog cases and the chemicals that have appeared in them).
- 41 See U.S. Dep’t of Justice, DEA, Drugs of Abuse 2-3 (2005 ed.), available at <http://www.usdoj.gov/dea/pubs/abuse/doa-p.pdf> (describing the procedural requirements for formally prohibiting a chemical as a controlled substance).
- 42 See 21 U.S.C. § 812(b) (2000) (setting out the criteria and procedures for placing a drug on a controlled substances schedule).
- 43 See *id.* (providing the various factors considered in scheduling a suspected controlled substance); Amanda Kay, *The Agony of Ecstasy: Reconsidering the Punitive Approach to United States Drug Policy*, 29 *Fordham Urb. L.J.* 2133, 2163-66 (2002) (outlining the four-year period from the time that the DEA published a notification of its intention to control MDMA to when MDMA was actually placed on the schedule); Brian Rubens, *Common Law Versus Regulatory Fraud: Parsing the Intent Requirement of the Felony Penalty Provision of the Food, Drug, and Cosmetic Act*, 72 *U. Chi. L. Rev.* 1501, 1501 (2005) (describing the scheduling process as “long and involved”).
- 44 Many countries follow a pure rules approach. See generally Agence française de sécurité sanitaire des produits de santé, Réglementation, <http://afssaps.sante.fr/htm/10/pharma/pharma8.htm> (last visited Feb. 15, 2008) (France); Betäubungsmittelgesetz (BtMG), <http://www.eve-rave.net/abfahrer/recht.sp?text=1> (last visited Feb. 15, 2008) (Germany); *Wet van 13 juli 2002 tot wijziging van de Opiumwet*, Stb. 2002, 520, translation at http://www.cannabisbureau.nl/pdf/Opiumwet_EN_29nov2004.pdf (Netherlands); Erowid.org, Thailand Law, http://www.erowid.org/psychoactives/law/countries/law_thailand.shtml (last visited Feb. 15, 2008) (Thailand).
- 45 See, e.g., Ark. Code Ann. § 5-64-414(a)(1) (2005); Cal. Health & Safety Code § 11401(b) (West 2007); Controlled Substances Act 1984 § 4(2), available at http://www.austlii.edu.au/au/legis/sa/consol_act/csa1984242/s4.html; Controlled Drugs and Substances Act 1996 S.C., Ch. 19 (Canada) (defining an analog broadly as “a substance that, in relation to a controlled substance, has a substantially similar chemical structure” irrespective of the pharmacological properties of the substance in question); Wilkinson, *supra* note 38 (noting that the United Kingdom has no analog statute but a blanket prohibition on “hallucinogens”).
- 46 See *United States v. Turcotte*, 405 F.3d 515, 522-23 (7th Cir. 2005).
- 47 Under the Federal Analog Act and many other state analog statutes, a controlled substance analog must have both a “substantially similar” structure and a “substantially similar” pharmacological effect. See Colo. Rev. Stat. § 12-22-303(7.5)(a) (2007); D.C. Code Ann. § 48-902.14(b) (LexisNexis 2004); Guam Code Ann. tit. 9, §67.100(5)(i) (2007); Ind. Code Ann. 35-48-1-9.3(a) (West 2004); Kan. Stat. Ann. §65-4101(bb)(1) (2001) (mirroring the Federal Analog Act in Kansas); La. Rev. Stat. Ann. § 40:961(8) (2001); Mich. Comp. Laws Ann. § 333.7104(3) (West 1999).
- 48 Technically, neither model implies any intrinsic breadth of coverage. It is possible, for instance, for a rules-based model to list a vast number of prohibited substances that cut through a wider swath than a standards-based model, and vice versa. In practice, however, the number of potentially banned analogs far exceeds the number of explicitly scheduled chemicals in every jurisdiction.
- 49 The majority of cases find a conjunctive reading between 21 U.S.C. §802(32)(A)(i) and 21 U.S.C. § 802(32)(A)(ii). See *Turcotte*, 405 F.3d at 518 (“The majority of these courts base their rulings largely on the absurd results that might obtain under a disjunctive reading, noting that alcohol and caffeine could be criminalized as controlled substance analogues based solely on the fact that, in concentrated form, they might have depressant or stimulant effects similar to illegal drugs.”); see also *United States v. Hodge*, 321 F.3d 429, 432-39 (3d Cir. 2003) (analyzing the statute and overturning a conviction based on a trial court’s finding that a mixture of “wax-and-flour” qualified as a controlled substance analog of crack cocaine); *United States v. Forbes*, 806 F. Supp. 232, 234-36 (D. Colo. 1992) (reading the structural prong and the effect prong conjunctively).
- 50 See Mohsen Imanshahidi & Hossein Hosseinzadeh, *The Pharmacological Effects of Salvia Species on the Central Nervous System*, 20 *Phytotherapy Res.*, 427, 431 (2006).

- 51 Under Illinois law, an analog is a substance which is intended for human consumption, other than a controlled substance, that has a chemical structure substantially similar to that of a controlled substance in Schedule I or II, or that was specifically designed to produce an effect substantially similar to that of a controlled substance in Schedule I or II. Examples of chemical classes in which controlled substance analogs are found include, but are not limited to, the following: phenethylamines, N-substituted piperidines, morphinans, ecgonines, quinazolinones, substituted indoles, and arylcycloalkylamines.
Ill. Comp. Stat. Ann. 570/401 (West 2007); see also Fla. Stat. Ann. § 893.02(2) (West 2000) (defining an analog under Florida law to be “a structural derivative of a parent compound that is a controlled substance”). Illinois treats the analog as equivalent to its predecessor: “a controlled substance analog shall be treated in the same manner as the controlled substance to which it is substantially similar.” Ill. Comp. Stat. Ann. 570/401.
- 52 See Louis Kaplow, *Rules Versus Standards: An Economic Analysis*, 42 *Duke L.J.* 557, 560 (1992) (“[T]he only distinction between rules and standards is the extent to which efforts to give content to the law are undertaken before or after individuals act.”).
- 53 See *infra* note 88 (discussing the chemical structure of MDBU in depth).
- 54 Russell B. Korobkin, *Behavior Analysis and Legal Form: Rules vs. Standards Revisited*, 79 *Or. L. Rev.* 23, 33 (2000) (“[R]ules will be relatively cheaper... in areas of law where identical disputes arise frequently.... In high-frequency disputes, standards are relatively less efficient because adjudicators must match the same facts to legal consequences over and over, effectively reinventing the wheel every time.” (footnote omitted)).
- 55 See *id.* at 48 (“When the law is determined on a case-by-case basis after disputes arise rather than prospectively, adjudicators’ evaluations about what an individual should have done are likely to be tainted by information about the results of the individual’s actions.”).
- 56 See *United States v. Roberts*, 363 F.3d 118, 124 n.3 (2d Cir. 2004) (“It is perhaps unfortunate that Congress did not opt to list known controlled substance analogues itself, and then to delegate to an appropriate designee... the authority to expand that list as necessary, but rather left the determination of what qualifies as a controlled substance analogue to the courts and to informal legislative or administrative commentary.”); *United States v. Lusk*, No. A05-052, 2005 WL 2704988, at *2 (D. Alaska Oct. 5, 2005) (“Congress did not choose to list known controlled substance analogue [sic] themselves. Rather, it left the determination of what qualifies as a controlled substance analogue to legislative or administrative commentary (and to the courts).”).
- 57 See Kaplow, *supra* note 52, at 608 (“Legislatures may be better equipped to draw upon technical expertise than courts.”).
- 58 The saga of medical marijuana provides interesting insights into the practical difficulties encountered with challenging Schedule I status, although this topic is beyond the scope of this Comment.
- 59 See *supra* text accompanying note 43 (recounting the long regulatory litigation surrounding doctors’ efforts to stop the DEA from officially listing MDMA as a Schedule I drug).
- 60 See *Evers v. Dwyer*, 358 U.S. 202, 203 (1958) (“[T]he question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.” (internal quotation marks omitted) (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 320 U.S. 270, 273 (1941))). But see *N.H. Hemp Council, Inc. v. Marshall*, 203 F.3d 1, 4-5 (1st Cir. 2000) (noting that while “federal courts are disinclined to provide either injunctive or declaratory relief to foreclose federal criminal prosecutions in the absence of a reasonably clear and specific threat of prosecution,” the DEA’s conduct in promulgating agency rules classifying medical marijuana as a controlled substance and threatening prosecution of medical marijuana provided a sufficient threat of federal prosecution).
- 61 See, e.g., *Gettman v. DEA*, 290 F.3d 430, 433-36 (D.C. Cir. 2002) (reviewing Jon Gettman and High Times’ petition to the DEA to remove marijuana from Schedule I and holding that although any interested party could petition the DEA for a hearing, Gettman and High Times did not have Article III standing to seek appellate review); cf. *Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(-)-<<DELTA>>⁹-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Caplets From Schedule II to Schedule III*, 64 *Fed. Reg.* 35,928, 35,928-30 (July 2, 1999) (codified at 21 C.F.R. pts. 1308, 1312) (exemplifying a rare instance of the DEA moving Marinol, a synthetic marijuana substitute,

from Schedule II to Schedule III, possibly motivated by *Gonzales v. Raich*, 545 U.S. 1 (2005), which was pending in the Supreme Court at that time).

- 62 *United States v. Forbes*, 806 F. Supp. 232, 234-36 (D. Colo. 1992).
- 63 Cass R. Sunstein, *Problems with Rules*, 83 Cal. L. Rev. 953, 995 (1995).
- 64 See Kaplow, *supra* note 52, at 605 (“Because individuals tend to be less well informed concerning standards, they may bear more risk under standards....”).
- 65 See Frank L. Sapienza, *DEA, Controlled Substance Analogues* (1996), available at http://www.erowid.org/psychoactives/law/law_fed_dea_analog_intro1.pdf (attributing the decrease in analogue production and distribution in the United States in part to the Federal Analog Act).
- 66 See *supra* Part I.B (discussing the close relationship between clandestine chemists and legitimate pharmaceutical and academic researchers).
- 67 See Shulgin, *supra* note 38, at 405-07 (cautioning that an attempt to predict drug abuse trends may indirectly provide black market entrepreneurs with “an itemization of potentially interesting avenues of financially profitable drug exploration,” but also noting that “very few who are deeply invested in the preparation of illicit drugs will learn much that they do not already know or that could easily be learned from the scientific literature”). Shulgin also noted that [e]ven more disturbing, and less easily anticipated, are the novel pharmaceutical agents that may spring forth from the imagination and wit of the illicit manufacturer himself. He does not advertise the substances of his inventions, nor does he warn others of his failures. The scientific community discovers these sallies sometimes years after their success or failure.... *Id.* at 406-07. That prediction does not appear to have come to fruition.
- 68 See *id.* at 406 (“[T]echnological extrapolation [may be] valid when considering certain pharmacologic families of drugs, such as the opiates, the amphetamines, the barbiturates, and the hallucinogens.”). Clandestine chemists have proved to be resourceful in the past in adapting to diversion control, but research and development typically requires specialized experience in both theoretical chemistry and laboratory technique, coupled with sophisticated, well-equipped laboratories and expensive reagents. Consider, for example, that the illicit synthesis of LSD--a notoriously fragile molecule requiring expertise to manufacture even on a small scale--fell by ninety-five percent after the DEA arrested two of the only underground chemists capable of producing it. See Ryan Grim, *Who's Got the Acid?: These Days, Almost Nobody*, *Slate*, Apr. 1, 2004, <http://www.slate.com/id/2098109/> (exploring the reasons for the drastic decline in LSD usage); see also Seth Rosenfeld, *William Pickard's Long, Strange Trip: Suspected LSD Trail Leads from the Bay Area's Psychedelics Era to a Missile Silo in Kansas*, *S.F. Chron.*, June 10, 2001, at A1 (describing the unusual and tragic life trajectory of William Leonard Pickard, a Harvard- and Stanford-educated chemist who single-handedly produced the vast majority of the LSD consumed in the United States for both financial and ideological reasons, and funneled the profits back into legitimate research on psychoactive drugs at UCLA).
- 69 The DEA publishes the *Microgram Bulletin*, a publication that lists Intelligence Alerts about drug seizures and trends. See generally U.S. DEA, *Microgram Bulletins*, http://www.dea.gov/programs/forensicsci/microgram/bulletins_index.html (last visited Feb. 15, 2008) (indexing past issues). Recent issues have issued alerts for drugs like 2C-I, MDDMA, TMA, DOC, DOB, and DOI--each of which was discovered over fifteen years ago by Alexander Shulgin. See, e.g., 2C-I Capsules in Miami Beach, Florida, 39 *Microgram Bull.* 3, 3-4 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg0106/mg0106.pdf>; Ecstasy Combination Tablets (Containing MDMA, Methamphetamine and MDDMA) in Miami, Florida, 39 *Microgram Bull.* 148, 148-49 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg1206/mg1206.pdf>; Large Fentanyl/MDA/TMA Laboratory in Azusa, California--Possibly the “OC-80” Tablet Source, 39 *Microgram Bull.* 45, 45-47 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg0406/mg0406.pdf>; LSD Blotter Acid Mimics (Containing 2,5-Dimethoxy-4-Chloroamphetamine (DOC)) in Boca Raton, Florida, 39 *Microgram Bull.* 72, 72 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg0606/mg0606.pdf>; LSD Blotter Acid Mimics (Containing 4-Bromo-2,5-Dimethoxyamphetamine (DOB)) in Ames, Iowa, 39 *Microgram Bull.* 145, 145 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg1206/mg1206.pdf>; LSD Blotter Acid Mimics (Containing 4-Iodo-2,5-Dimethoxyamphetamine (DOI)) in Orlando and Winter Springs, Florida, 39 *Microgram Bull.* 55, 55 (2006), available at <http://www.dea.gov/programs/forensicsci/microgram/mg0506/mg0506.pdf>. Other alerts have been published for a large number of known psychoactive drugs, including 2,5-di-methoxy-4-ethylphenethylamine (2C-E), 4-chloro-2,5-dimethoxyphenethylamine (2C-C), 4-methylaminorex, 5-methoxy-alphamethyltryptamine (5-MeO-AMT), 5-MeO-MiPT, N,N-dipropyltryptamine (DPT), 2C-T-21, 2,5-dimethoxy-4-

ethylthiophenethyl-amine (2C-T-2), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-methoxymethamphetamine, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), N-methylpyrrolidone (NMP), phenylpropylmethylamine, and scopolamine. See generally 2005 Subject Index, 38 Microgram Bull. 188, 188 (2005), available at <http://www.dea.gov/programs/forensicsci/microgram/mg1205/05dec-mb.pdf> (listing issues that contained alerts for the first six of these compounds); 2004 Subject Index, 37 Microgram Bull. 218, 218, 222 (2004), available at <http://www.dea.gov/programs/forensicsci/microgram/mg1204/mg1204.pdf> (listing issues that contained alerts for the last eight of these compounds).

- 70 It is entirely possible that designer drugs—even before the last five years—would have come as no surprise, especially given that nearly all of the 1980s- and 1990s-era Federal Analog Act cases litigated previously known compounds. However, since the DEA Microgram Bulletins published before 2003 are classified and beyond the reach of a Freedom of Information Act (FOIA) request, there is no way to know if the DEA considered any pre-2003 designer drugs to be completely novel.
- 71 Consider, for example, that the N-terminal alkylation of MDMA decreases its psychoactive value, to the point where the addition of two carbon atoms makes MDMA completely inactive. See Alexander Shulgin & Anne Shulgin, *PIHKAL: A Chemical Love Story* 721 (2006) (discussing the pharmacological impact of modifying the phenylethylamine backbone).
- 72 See Hofmann, *supra* note 31, at 31 (explaining that the discovery of a novel backbone would be both rare and fortunate).
- 73 See Anacker & Imwinkelried, *supra* note 32, at 13 (noting that “[i]t seems evident that upon viewing these diagrams [of GHB and GBL], most laypersons would say these diagrams do not appear ‘substantially similar’” despite legal precedent to the contrary).
- 74 Consider, for example, that “Research Companies” operating on the Internet openly sold psychoactive phenylethylamines and tryptamines under the theory that these chemicals did not fall under the Federal Analog Act. See Press Release, DEA, *DEA Announces Arrests of Website Operators Selling Illegal Designer Drugs* (July 22, 2004), available at <http://www.dea.gov/pubs/pressrel/pr072204.html> (“The formulation of analogues is like a drug dealer’s magic trick meant to fool law enforcement. They didn’t fool us....”).
- 75 See Korobkin, *supra* note 54, at 46 (suggesting that since individuals are inclined to interpret provisions in a manner that benefits them most, uncertainty is more likely to capture individuals who unknowingly violate the law rather than overdetering individuals).
- 76 See Press Release, DEA, *supra* note 74.
- 77 See David McCandless, *Bad Trip for Online Drug Peddlers*, *Wired Mag.*, July 6, 2005, available at <http://www.wired.com/medtech/health/news/2005/07/68049?currentPage=all> (“Thanks to their novelty, most research chemicals are not specifically listed as controlled substances under U.S. drug laws. Many site operators and customers believed, erroneously, that this made the drugs legal, or at least left them in a gray area that would protect them from prosecution.”).
- 78 See Korobkin, *supra* note 54, at 46 (“The self-serving bias is less problematic in a rules regime where there is, by definition, little or no ex ante ambiguity about legal boundaries.”).
- 79 See *infra* Part II.B.3 (discussing why the Federal Analog Act’s definition of “controlled substance analog” is vague).
- 80 See *supra* Part I.B (discussing the pharmaceutical search for molecular variations that might uncover promising potential drugs).
- 81 See Robert F. Kushner & Hazel Manzano, *Obesity Pharmacology: Past, Present, and Future*, 18 *Current Opinion Gastroenterology* 213, 213 (2002) (describing fenfluramine as an appetite suppressant).
- 82 See Saeid Raofi & Susan M. Schappert, U.S. Dep’t of Health & Human Servs., *Medication Therapy in Ambulatory Medical Care: United States, 2003-04*, 6-7 (2006) (describing the use of Albuterol, a bronchodilator, in emergency health care).
- 83 See Linda P. Dvoskin et al., *Review of the Pharmacology and Clinical Profile of Bupropion, an Antidepressant and Tobacco Use Cessation Agent*, 12 *CNS Drug Revs.* 178, 192-93 (2006) (describing the promising use of the antidepressant Bupropion to stop nicotine addiction).
- 84 See *supra* note 16 (discussing these new studies).
- 85 Some of the most remarkable developments in psychoactive drugs emerged when pharmacologists and chemists bioassayed the drug themselves. See, e.g., Hofmann, *supra* note 31, at 14-20 (describing his initial discovery of LSD as a combination of intuition and

serendipity, and the resulting distribution of the new compound to other chemists in the lab to prove its astonishing potency and unique psychedelic effects); Shulgin & Shulgin, *supra* note 71, at 736-37 (describing the author's rediscovery of MDMA and his self-bioassay as the pivotal experiment that alerted him to the phenomenal entheogenic properties of the drug). Although the era of this laissez-faire attitude toward pharmaceutical development seems to have faded, it is possible that an especially daring pharmacologist or chemist could be ensnared in the course of legitimate research, despite the third prong of the Federal Analog Act.

- 86 See generally Clayton L. Smith, Note, *The Controlled Substance Analogue Enforcement Act of 1986: The Compromising of Criminalization*, 16 Am. J. Crim. L. 107, 128-33 (1988) (analyzing the Federal Analog Act and concluding that it does not present a viable void-for-vagueness constitutional challenge).
- 87 See Kaplow, *supra* note 52, at 608 (“[E]ven when rules will be less accurate in providing results that are appropriate to actual circumstances-- which they often will not be--they will tend to provide clearer notice than standards to individuals at the time they decide how to act.” (footnote omitted)).
- 88 MDBU probably induces only very weak, if any, psychoactive activity. See Shulgin & Shulgin, *supra* note 71, at 721 (“Straight chain homologues on the nitrogen atom of MDA longer than two carbons are probably not active.... All mouse assays that compared this homologous series showed a consistent decrease in action (anesthetic potency and motor activity) as the alkyl chain on the nitrogen atoms was lengthened.”).
- 89 Legality concerns over criminal statutes have typically arisen in the context of loitering. See, e.g., *City of Chicago v. Morales*, 527 U.S. 41 (1999) (plurality opinion) (striking down a municipal statute that defined “loiter[ing]” as “remain[ing] in any one place with no apparent purpose” as unconstitutionally vague under the due process clause); *Kolender v. Lawson*, 461 U.S. 352 (1983) (holding California's loitering statute unconstitutional and providing the landmark two-prong test for penal statutes to pass due process muster).
- 90 See Korobkin, *supra* note 54, at 54-55 (“As long as a body of law is viewed as embodying a community's norms, law can be used to signal a particular community norm.”).
- 91 Technically, this standard would not be a pure standard, but a rule-standard hybrid. See Kaplow, *supra* note 52, at 560-62 (drawing a distinction between a pure standard, which has no reference point, and a rule-standard hybrid, which has reference points).
- 92 See generally DEA, *Drug Scheduling*, [http:// www.dea.gov/pubs/scheduling.pdf](http://www.dea.gov/pubs/scheduling.pdf) (last visited Feb. 15, 2008) (“This document is a general reference and not a comprehensive list. This list describes the basic or parent chemical and does not describe the salts, isomers and salts of isomers, esters, ethers and derivatives which may also be controlled substances.”). This does not even describe an analog but instead serves as a basic extension of the core Controlled Substances Act. The distinction between a “derivative” and an “analog” makes the situation even more complicated. See Alexander T. Shulgin, *Controlled Substances: A Chemical and Legal Guide to Federal Drug Laws* 9 (2d ed. 1992) (describing the imprecision of federal drug scheduling).
- 93 At least one court has commented, somewhat counterintuitively, on the due process concerns of defining a chemical structure too specifically. See *One Thousand Four Hundred Sixty-Two Dollars in U.S. Currency and One 1982 Buick v. State*, 774 S.W.2d 17, 21 (Tex. App. 1989) (holding that an ordinary person would not be able to discern structural similarity from molecular weights, and therefore that such weights are unnecessary to give “a person of ordinary intelligence fair notice of the substances which are to be treated as controlled substances”); see also *infra* notes 124-125 and accompanying text (arguing that standards may provide better notice than rules in certain cases).
- 94 See Anacker & Imwinkelried, *supra* note 32, at 768-70 (noting that litigation under the Federal Analog Act presents Daubert problems because the standard of “substantially similar” is a matter of opinion, not fact).
- 95 See *id.* at 759-62 (discussing the wide variation in methods used to produce expert testimony on whether a chemical is “substantially similar” in structure to another).
- 96 See Korobkin, *supra* note 54, at 29 (“Just as a pure rule can become standard-like through unpredictable exceptions, a pure standard can become rule-like through the judicial reliance on precedent.”).
- 97 See Kaplow, *supra* note 52, at 610 (“[T]he difficulty of learning about laws promulgated by legislatures may differ from those promulgated by courts... because of the manner in which legislative enactments and judicial opinions are written, published, and indexed.”).

- 98 See *United States v. Forbes*, 806 F. Supp. 232, 233 (D. Colo. 1992) (taking note of internal dissent among the U.S. Prosecutor's office on whether alphaethyltryptamine (AET) has a chemical structure that is substantially similar to dimethyltryptamine (DMT) or diethyltryptamine (DET) and quoting a DEA memorandum as conceding that "there is a great diversity of opinion whether [AET] is controlled as an analogue under the 1986 Act").
- 99 See *United States v. Roberts*, 363 F.3d 118, 124 (2d Cir. 2004) (recognizing that the Federal Analog Act leaves the determination of whether a chemical qualifies as a controlled substance analog to the courts and "as a result, in the absence of prior court decisions the statutory and regulatory pronouncements provide no real notice").
- 100 See, e.g., *United States v. Brown*, 415 F.3d 1257, 1271 (11th Cir. 2005); *United States v. Turcotte*, 405 F.3d 515, 529 (7th Cir. 2005); *United States v. Ansaldi*, 372 F.3d 118, 123 (2d Cir. 2004); *United States v. Fisher*, 289 F.3d 1329, 1335-36 (11th Cir. 2002) (citing Placement of Gamma-Butyrolactone in List I of the Controlled Substances Act (21 U.S.C. § 802(34)), 65 Fed. Reg. 21,645-47 (Apr. 24, 2000) (codified at 21 C.F.R. § 1310.02) and Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000, Pub. L. No. 106-172, § 2(4), 5(a), 114 Stat. 7, 7, 10).
- 101 See, e.g., *United States v. Carlson*, 87 F.3d 440, 445-46 (11th Cir. 1996); *United States v. Raymer*, 941 F.2d 1031, 1046 (10th Cir. 1991); *United States v. Desurra*, 865 F.2d 651, 653 (5th Cir. 1989) (relying on the legislative history of the Federal Analog Act).
- 102 See, e.g., *United States v. Granberry*, 916 F.2d 1008, 1009 (5th Cir. 1990).
- 103 See, e.g., *Hooper v. United States*, No. 99-1287, 2000 WL 658037, at *1 (6th Cir. May 8, 2000) (methcathinone and cathinone); *United States v. Colberg*, No. 94-2173, 1995 WL 641303, at *3 n.1 (6th Cir. Oct. 31, 1995) (methcathinone and methamphetamine); *United States v. Pavlik*, No. 93-2494, 1995 WL 59227, at *1 (6th Cir. Feb. 13, 1995) (same); *United States v. Hofstatter*, 8 F.3d 316, 320 (6th Cir. 1993) (methylcathinone and methamphetamine).
- 104 See, e.g., *United States v. Nunez*, 57 F. App'x 776, 776 (9th Cir. 2003) (asserting that phenylethylamine is an analog, although the court does not specify its parent chemical); *McKinney v. United States*, No. 99-1814, 2000 WL 1010581, at *2 (8th Cir. July 24, 2000) (aminorex and 4-methylaminorex).
- 105 See *United States v. Ono*, 918 F.2d 1462, 1467 (9th Cir. 1990).
- 106 See, e.g., *United States v. Linder*, 200 F. App'x 186, 187 (4th Cir. 2006) (per curiam); *United States v. Klecker*, 348 F.3d 69, 73 (4th Cir. 2003).
- 107 *Klecker*, 348 F.3d at 73.
- 108 See Sapienza, *supra* note 65 ("[M]ost, if not all, of the substances described in 'PIHKAL' [sic] could meet the definition of controlled substance analogue."). PiHKAL is a book authored by Alexander Shulgin and Ann Shulgin that describes a compilation of 179 permutations of the phenylethylamine backbone. Shulgin & Shulgin, *supra* note 71. Of these permutations, only fourteen are currently listed as scheduled drugs by the DEA. See Erowid.org, PiHKAL: Legal Status, http://www.erowid.org/library/books_online/pihkal/pihkal_law.shtml (last modified Nov. 7, 2006) (listing the fourteen phenylethylamine variations present both in PiHKAL and on the DEA's schedule).
- 109 While the Federal Analog Act also requires "representation" or "intent" as to a substantially similar pharmacological effect, this raises the interesting scenario of a person synthesizing or distributing a chemical that is substantially similar in structure to MDMA--perhaps to fool the testing device of a purchaser--and advertising the chemical's pharmacological properties as "similar to MDMA," despite the fact that the chemical may have no pharmacological effect whatsoever.
- 110 See *supra* text accompanying note 94 (discussing the problems with expert witnesses in Federal Analog Act litigation).
- 111 The sole possible exception appears to be AET before it was scheduled. In *Forbes*, a district court struck down the application of the Federal Analog Act to AET, but this was not because AET was not an analog. See *United States v. Forbes*, 806 F. Supp. 232 (D. Colo. 1992). Rather, the district court found that even though AET might be a potential analog, there was enough disagreement among experts to strike the application of the Federal Analog Act because of vague due process concerns. *Id.* at 236-39. It appears that although *Forbes's* central holding is still good law, if the case were decided today, AET would almost certainly be found to be an analog.

- 112 At least one court has implied that as long as the core of the chemical is intact and identical to a core in a listed chemical, and the remaining elements are “substantially similar,” a substance qualifies as an analog. See *Klecker*, 348 F.3d at 73 (“‘Foxy’ and DET share the same core arrangement of atoms, known as tryptamine. Tryptamine is the core element of a number of hallucinogenic drugs.... The Court finds that the substitutions to Foxy and DET, while not identical, are substantially similar. The tryptamine core is intact and therefore identical in the two compounds, and the remaining elements are substantially similar.” (internal quotation marks omitted) (quoting *United States v. Klecker*, 228 F. Supp. 2d 720, 728 (E.D. Va. 2002))). This is an extremely broad rule, since the “core” of the chemical will generally remain intact even after heavy substitution has obliterated any pharmacological activity that the original molecule possessed. For example, this rule effectively covers all tryptamines—including serotonin, which is a major neurotransmitter naturally produced by the body. However, serotonin is completely inactive when ingested.
- 113 In *United States v. Roberts*, the government argued that a two-atom difference, standing alone, would be enough to establish substantial similarity in chemical structure. 363 F.3d 118, 124 (2d Cir. 2004). The Second Circuit rejected that theory, noting that “[i]n another case, it might well be that a one- or two-atom difference in a molecule made such a radical difference in the substance’s relevant characteristics that any similarity in two-dimensional charts would not be ‘substantial’ enough to satisfy the definition of ‘controlled substance analogue.’” *Id.* The circuit court nevertheless reversed the district court’s dismissal of the indictments: Where there is only a two-atom difference between the relatively complex molecules of a suspect substance and of a controlled substance and where, upon ingestion, the suspect substance is metabolized into the controlled substance, we believe that the chemical structure of the suspect substance is manifestly “substantially similar to the chemical structure of [the] controlled substance [analog].” *Id.* at 125 (first alteration in original).
- 114 See *People v. Rudakowski*, No. D040822, 2003 WL 21490044, at *3 (Cal. Ct. App. June 30, 2003) (upholding a conviction when the prosecution’s expert witness testified that MDMA was “substantially similar” to the controlled methamphetamine and the defendant did not call his own expert witness); *People v. Kim*, No. B145073, 2002 WL 864505, at *6 (Cal. Ct. App. May 7, 2002) (“[T]hat MDMA or Ecstasy is an analog of MDA was an objective fact the defense did not and, no doubt, could not contest.”); *People v. Silver*, 281 Cal. Rptr. 354, 355-56 (Cal. Ct. App. 1991) (upholding a lower court’s decision that MDMA is an analog of methamphetamine in a classic battle of the experts, despite defense expert testimony that “only 50 percent of the molecules were the same or similar; that it was impossible to create a molecule of MDMA from a molecule of methamphetamine”); *People v. Frantz*, 114 P.3d 34, 40 (Colo. Ct. App. 2004) (upholding a trial court’s determination that the unlisted precursor pseudoephedrine was “substantially similar” to ephedrine); *Mohamed v. State*, 843 N.E.2d 553, 556 (Ind. Ct. App. 2006) (accepting the trial court’s factual determination that cathinone’s chemical structure is substantially similar to that of the controlled drug methcathinone); *State v. Cathcart*, 589 A.2d 193, 195 (N.J. Super. Ct. App. Div. 1991) (upholding a trial court’s determination that L-cocaine is substantially similar to its prohibited isomer D-cocaine); *Porter v. State*, 806 S.W.2d 316, 321-22 (Tex. App. 1991) (upholding a trial court’s finding that N-Hydroxy-3,4-methylenedioxyamphetamine (N-Hydroxy MDA) is substantially similar to MDA); *Robinson v. State*, 783 S.W.2d 648, 653-54 (Tex. App. 1990) (upholding a trial court’s determination that 3,4-methylene-dioxymethamphetamine (MDEA or “Eve”) is an analogue of both controlled drugs MDMA and MDA); *One Thousand Four Hundred Sixty-Two Dollars in U.S. Currency and One 1982 Buick v. State*, 774 S.W.2d 17, 21 (Tex. App. 1989) (defining “substantially similar” to be equivalent to the Oxford English Dictionary’s definition of “analog” as “an organic compound with a molecular structure closely similar to another (typically differing in one atom or group)” and rejecting the use of molecular properties like valence, atomic weights, mirror images and absolute or relative atomic weights because of due process concerns).
- 115 See, e.g., 21 U.S.C. § 844(a) (2000) (requiring that the accused person knowingly or intentionally possess a controlled substance).
- 116 See *United States v. Turcotte*, 405 F.3d 515, 528 (7th Cir. 2005) (“One could represent to others (earnestly or not) that a substance has physiological effects similar to a controlled substance despite being totally ignorant of its actual chemical properties.”).
- 117 See *id.* at 527 (providing a “provisional remedy” for the paradox by imposing a scienter requirement on the Federal Analog Act but also allowing a permissive inference that the defendant satisfies the scienter requirement for the first prong if the defendant satisfies the second prong of the Federal Analog Act).
- 118 See *supra* note 49 and accompanying text (discussing the debate over the conjunctive and disjunctive interpretations of the Federal Analog Act).
- 119 See, e.g., *United States v. Desurra*, 865 F.2d 651, 653 (5th Cir. 1989) (upholding a conviction under the Controlled Substances Act because there is no requirement that the defendant know that the substance in her possession qualifies as a controlled substance analog).

- 120 See *supra* Part II (discussing the characteristics of rules versus those of standards in the context of controlled substance analog legislation).
- 121 See Korobkin, *supra* note 54, at 30 (“The legal forms of rules and standards, then, are better understood as spanning a spectrum rather than as being dichotomous variables.”); see also *id.* at 29 fig. (providing a diagram describing the spectrum between rules and standards).
- 122 See generally Colin S. Diver, *The Optimal Precision of Administrative Rules*, 93 *Yale L.J.* 65, 67 (1983) (contrasting the objectives for rulemaking, which are transparency, accessibility, and congruence).
- 123 Technically, isomers and different enantiomers may be variations on a molecule, but they still fall within the purview of the Controlled Substances Act. See 21 U.S.C. §812(c) sched. I (2000) (prohibiting “isomers, esters, ethers, salts, and salts of isomers, esters, and ethers”).
- 124 For example, consider the United Kingdom’s extraordinarily complex controlled substance legislation. See, e.g., *The Misuse of Drugs Regulations 2001*, S.I. 2001/3998 sched. 1 (U.K.), available at http://www.opsi.gov.uk/si/si2001/uksi_20013998_en.pdf.
- 125 This is discussed further in Part III.C, *infra*.
- 126 See Anacker & Imwinkelried, *supra* note 32, at 749-50 (“[D]efense critics point out that some prosecution witnesses have frankly conceded that their conclusion [about substantial similarity] is ‘a “gut level thing” ... based on intuition....” (quoting *United States v. Brown*, 415 F.3d 1257, 1267 (11th Cir. 2005))).
- 127 For example, if two highly unrelated chemicals like salvinorin A and THC were regarded as “substantially similar” in structure under a particular standard, it would be exceedingly difficult to extract information as to why the chemicals were “substantially similar.” Are they “substantially similar” because they both contain cyclical ether groups? Or is it because they both contain hydroxyl groups? Or perhaps because they both contain three signature aromatic rings? Would we infer that the large number of carboxylate groups in salvinorin A do not impact the analysis? The speculation could go on and on. The problem is that salvinorin A and THC are structurally different in so many ways that this standard would be largely meaningless for any future determination.
- 128 See Sapienza, *supra* note 65 (“[One approach involves] chemical structural parameters for different classes of substances subject to abuse and control. All substances which fell within these parameters would be considered controlled. Defining these parameters was rather difficult for the many classes of controlled substances. Additionally, this method would impose regulatory controls on thousands of substances and could negatively impact legitimate drug development.”). However, history has shown that these problems arise even under the DEA-endorsed incarnation of the Federal Analog Act. See *supra* Part II.B.3 (discussing the broad and vague interpretations of “substantially similar” structure that appellate courts have upheld).
- 129 See note 124, *supra*, for an example of the United Kingdom’s extremely convoluted analog statute using a purely rules-based, *ex ante* model.
- 130 By recognizing that “substantially similar” is essentially a proxy for policy decisions, instead of a fact-based inquiry, Congress could adjust the definition accordingly. The proposed definition assumes that a chemical is “substantially similar” to chemicals with substituted groups on the same backbone, and dissimilar to chemicals with second-degree substitutions--an assumption that appears to be compatible with the case law reviewed in notes 100-106, *supra*. However, Congress could also further expand or contract the scope of the case law as needed by either eliminating or strengthening the recursion, and by providing guidelines delineating which functional groups would fall within the definition.
- 131 See Smith, *supra* note 86, at 122.
- 132 *Id.* at 120-21 (describing Representative Lundgren’s opposition to the proposed exemption).
- 133 See Korobkin, *supra* note 54, at 29 (“[A] pure rule can become standard-like through unpredictable exceptions....”).
- 134 See European Monitoring Ctr. for Drugs and Drug Addiction, *Legal Responses to New Synthetic Drugs: 2000-2004*, at 6 tbl.1 (2004), available at http://eldd.emcdda.europa.eu/attachements.cfm/att_9942_EN_New%20Synthetic%CC20Drugs%C#eport.pdf (describing Denmark’s unusually fast official scheduling system as being capable of permanently prohibiting a new drug within ten days). Most other European countries schedule

drugs for permanent prohibition within one to two months. See *id.* Emergency scheduling is similarly speedy, usually taking place within two months. See *id.* Compare this to the United States' slower response: it took four years to permanently prohibit MDMA, and a full month to complete the emergency scheduling procedure. See Kay, *supra* note 43, at 2163-66.

- 135 A pure standards-based approach like the Federal Analog Act also suffers from this problem, to an even greater degree. One possible remedy might be to provide a less onerous mechanism for challenging the permanent scheduling of drugs, or to loosen the reins around medical research on scheduled drugs (this is unlikely to happen, however, because in the United States a Schedule I drug is by definition one that has no medical use).
- 136 See Kaplow, *supra* note 52, at 610 (“Precedents could be established in a more rule-like fashion than is usually done.”).
- 137 See *supra* Part I.B (discussing the link between legitimate pharmaceutical research and black market “designer drugs”).
- 138 See Shulgin, *supra* note 38, at 406 (suggesting that illicit chemists use this method to draw upon research to acquire targets for synthesis).
- 139 As Kaplow describes it,
[G]overnment action outside the formal lawmaking processes can provide important guidance for future behavior. For example, the government’s undertaking and publishing the results of comprehensive studies of the hazards posed by various chemicals may have a substantial effect on their use even if the results are not embodied in a regulation or formally binding in a negligence suit or other legal proceeding. If a regulatory agency undertook such an investigation, individuals might expect the agency to act on the results in setting its enforcement priorities and in adjudicating even if no rule was promulgated declaring the result to be binding. Kaplow, *supra* note 52, at 615 (footnote omitted).
- 140 See, e.g., Walter R. Rodriguez & Russell A. Allred, Synthesis of trans-4-Methyl-aminorex from Norephedrine and Potassium Cyanate, 3 *Microgram J.* 154, 155-56 (2005), available at <http://www.dea.gov/programs/forensicsci/microgram/journal071203/mj071203.pdf> (noting that the DEA believes that trans-4-methylaminorex is a potential analog of cis-4-methylaminorex under the Federal Analog Act, and that “it is virtually certain that Federal prosecution of trans-4-methylaminorex as a controlled substance analogue would be successful”). It is curious that this opinion is buried within an obscure DEA in-house technical publication instead of being easily accessible on the DEA’s frontpage. In a recent case, a chemical engineer was convicted of synthesizing and distributing trans-4-methylaminorex by a novel synthetic method that he developed himself. 4 *Methylaminorex/MDMA/Methamphetamine Laboratory in Fort Lauderdale*, 38 *Microgram Bull.* 31 (2005), available at <http://www.usdoj.gov/dea/programs/forensicsci/microgram/mg0205/mg0205.pdf>. If the defendant in that case had been aware that the DEA regarded trans-4-methylaminorex as a controlled substance analog, perhaps he would have been deterred from his conduct.
- 141 See, e.g., *United States v. Turcotte*, 405 F.3d 515, 528-29 (7th Cir. 2005) (finding on appeal that the lack of a jury instruction concerning the defendant’s scienter as to whether a chemical was a controlled substance analog would ordinarily constitute reversible error but for “DEA regulations [that] also specify that ‘GBL and 1,4-butanediol are structurally and pharmacologically similar to GHB and are often substituted for GHB. Under certain circumstances they may satisfy the definition of a controlled substance analogue.’” (quoting Placement of Gamma-Butyrolactone in List I of the Controlled Substances Act (21 U.S.C. § 802(34)), 65 Fed. Reg. 21,645 (Apr. 24, 2000) (codified at 21 C.F.R. § 1310.02)).
- 142 See U.S. Dep’t of Justice, Diversion Control Program, *Salvia Divinorum*, *ska. Maria Pastora, Salvia (Salvinorin A, Divinorin A)* (last visited Feb. 15, 2008) (search <http://www.archive.org/> for http://www.deadiversion.usdoj.gov/drugs_concern/salvia_d/summary.htm, select result from Nov. 18, 2001) (describing salvinorin A’s legal status as possibly subject to control under the Federal Analog Act “because of its functional pharmacological similarities to other CI hallucinogens like THC”).
- 143 Cf. Shulgin, *supra* note 92, at 256-58 (breaking down all of the scheduled drugs into categories based on their fundamental chemical structure). *Salvorin A*, the psychoactive component in *Salvia divinorum*, does not belong to any of the classical backbones. Cf. *Imanshahidi & Hosseinzadeh*, *supra* note 50, at 428.