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 Aoxaca, 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 of 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. 5/31/14

Maja Lisa Lundborg-Gray, MD, FAAEM, FACEP

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Watertown, NY 13601
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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. Encompases 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

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section
Washington, D.C. 20537

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.

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

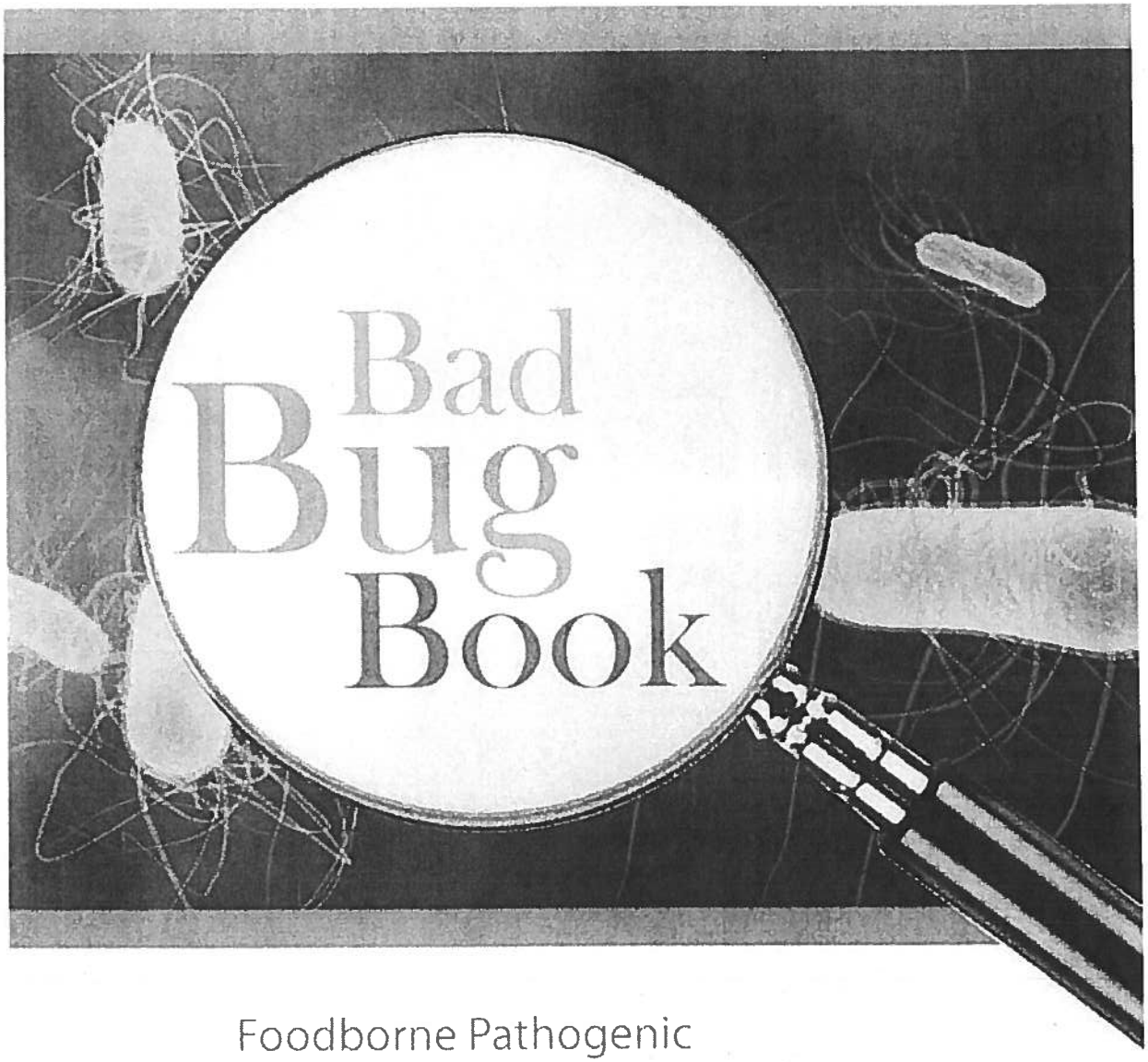
Kratom has been abused as a recreational drug around the world. In low doses, Kratom works as a stimulant and in high doses as a sedative. In low doses (10 grams) kratom induces mild euphoria and reduces fatigue, and generally does not interfere with ordinary activities. With strong doses (20-50 grams)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



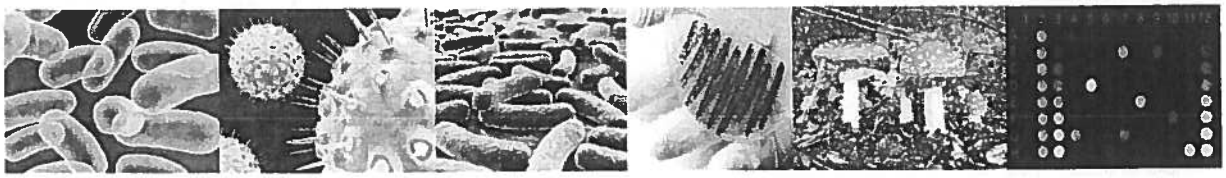
Foodborne Pathogenic Microorganisms and Natural Toxins Handbook

FDA

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 Clitocybe or Inocybe spp.	Generally, complete recovery within approximately 2 h
Inebriation or hallucinations without drowsiness or sleep	Psilocybin from Psilocybe, Paneolus, Gymnopilus, Conocybe, or Pluteus 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 Amanita muscaria or A. pantherina	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 *Amanita phalloides* and its relatives; *Galerina autumnalis* and its relatives; or *Lepiota josserandii* 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 *Gyromitra esculenta* 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.	*Giardia lamblia*
1 to several weeks	Abdominal pain, diarrhea, constipation, headache, drowsiness, ulcers, variable; often asymptomatic.	*Entamoeba histolytica*
3-6 months	Nervousness, insomnia, hunger pangs, anorexia, weight loss, abdominal pain, sometimes gastroenteritis.	*Taenia saginata, T. solium*
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.	*Clostridium botulinum* and its neurotoxins
More than 72 h	Numbness, weakness of legs, spastic paralysis, impairment of vision, blindness, coma.	Organic mercury

EXHIBIT 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
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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 dietar 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]

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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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Links on this page:

1. /ICECI/EnforcementActions/WarningLetters/2012/ucm302162.htm
2. /ICECI/EnforcementActions/WarningLetters/2012/ucm302261.htm
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- State & Local Officials
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Links on this page:

1. /ICECI/EnforcementActions/WarningLetters/2012/ucm302162.htm
2. /ICECI/EnforcementActions/WarningLetters/2012/ucm302261.htm
3. /ICECI/EnforcementActions/WarningLetters/2012/ucm302211.htm
4. /ICECI/EnforcementActions/WarningLetters/2012/ucm302202.htm
5. /ICECI/EnforcementActions/WarningLetters/2012/ucm302160.htm
6. /ICECI/EnforcementActions/WarningLetters/2012/ucm302279.htm
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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 arylethylamine – 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). 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 methyliodide 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). LD_{50} 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.

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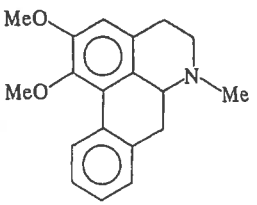
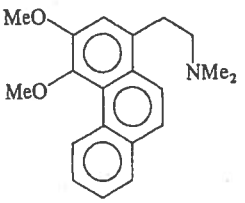


Nuciferine



Phenanthrene derivative

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. LD_{50} 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 recptors 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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A Campaign to Prevent Inhalant Abuse
Bureau of Substance Abuse Services
Massachusetts Department of Public Health

AUDIENCE: Adults Only

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,[2] 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 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 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 N_2O 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 N_2O 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 N_2O, 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 N_2O 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.oshaslc.gov/SLTC/healthguidelines/nitrousoxide]

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

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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]