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**UNITED STATES DISTRICT COURT
DISTRICT OF OREGON**

THE CHURCH OF THE HOLY LIGHT)
OF THE QUEEN, a/k/a The Santo Daime)
Church, *et al.*,)
Plaintiffs,)
)
v.)
MICHAEL B. MUKASEY, *et al.*,)
Defendants.)
_____)

CIV. NO. 08-3095-PA

**WITNESS STATEMENT OF
JERRY FRANKENHEIM, Ph.D.**

REPORT OF JERRY FRANKENHEIM, Ph.D.

December 4, 2008

I. Declaration of the author

1. I am Jerry Frankenheim, a neuroscientist and neuropharmacologist by training and profession. I obtained my B.A. in chemistry in 1964 from Queens College of the City University of New York, Flushing. I received my Ph.D. in pharmacology in 1968 from the University of Mississippi Medical Center, Jackson. I started my postdoctoral research fellowship (in behavioral pharmacology) at Downstate Medical Center, Department of Pharmacology, Brooklyn, New York (1968-1969) and finished it at the University of North Carolina School of Medicine, Department of Pharmacology, Chapel Hill (1969-1970). This entire educational experience was supported in full by scholarship, trainee, and research fellowship awards from state and federal agencies. During my postdoctoral experience, I published independent research regarding acute and chronic activity of abused drugs, and I taught in the medical schools.

2. I am currently a pharmacologist and Program Director in the Functional Neuroscience Research Branch, Division of Basic Neuroscience & Behavioral Research, National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS), Bethesda, Maryland. In this capacity, I have been responsible for initiating, planning, building, and managing several national and international research grant programs in the preclinical neuroscience and neuropharmacology of drug abuse, addiction, and their consequences, including:

a. Neurotoxicology, neuropathology, and neuro-HIV/AIDS, including spontaneous and facilitated recovery from neural insults, and interactions between drugs and other factors such as stress, aging, and mental illness (comorbidity).

b. Phencyclidine (PCP), ketamine, other glutamate antagonists, and synaptic plasticity, including pharmacologic models of psychosis.

c. Neuropharmacology and neurotoxicology of methamphetamine, MDMA ("ecstasy"), and other amphetamines.

d. LSD-like "hallucinogens."

- e. Serotonin's roles in drug actions.
- f. Neuropeptides' (e.g., hypocretin) roles in drug actions.
- g. Other "club drugs," including GHB and benzodiazepines, and newly emergent drugs of abuse.
- h. "Dietary supplements" and "natural products."
- i. Genetic vulnerability to addiction.
- j. Blood-brain barrier.

These programs, in part, include the ontogenetic (developmental) effects of drug abuse, and they include drug abuse by adolescents. I presently oversee funded grants totaling about \$15,000,000 per year. I also serve or have served on several cross-cutting workgroups at NIDA, including (partial list) Drugs and Violence, Women and Gender Research Group, Methamphetamine Addiction Treatment Think Tank, Child and Adolescent Research Group, NIDA Club Drugs Workgroup (which I chaired), Consortium on Diversity, and Comorbidity of Drug Abuse and Mental Disorders. My responsibilities include dissemination of information about, and information gained from, these programs, i.e., teaching neuroscience and neuropharmacology related to these specialized areas of drug abuse and addiction. It is in this teaching capacity that I am presently serving the U.S. Department of Justice. Since this is part of my official job responsibilities, I am receiving no extra pay for it.

3. Previous positions (after postdoctoral fellowship, in reverse chronology). Just prior to joining NIDA, in the pharmaceutical industry (Pennwalt Corporation Pharmaceutical Division, Rochester, NY), I conceived and directed a pharmacology program to discover and develop new drugs for the treatment of major depression. I adapted new test procedures, such as computerized electroencephalography, resulting in the development of a series of novel, atypical antidepressants. At Pennwalt, I discovered and developed a series of "cerebroprotective" agents to prevent the neurological sequelae of stroke, head trauma, cardiac arrest, and other conditions of ischemia or hypoxia threatening the brain. I designed a program to discover drugs to ameliorate the loss of memory in Alzheimer's disease. I discovered and developed two separate novel series of anticonvulsant drugs; one of these agents, remacemide, underwent advanced clinical trials for epilepsy, stroke, Parkinson's disease, and Huntington's chorea. Before leaving Pennwalt in 1989, I was the head of the central nervous system section, and senior principal

investigator. Prior to joining Pennwalt, I held research/teaching positions in medical schools. From 1970 to 1974, I was lecturer (equivalent, at least, to U.S. assistant professor) in pharmacology at the University of Western Australia School of Medicine, Perth, and responsible for obtaining research grants, for supervising Ph.D. thesis research, and for increasing the quality of medical and dental education in Western Australia. I have listed my publications (1968-present) separately, in my résumé.

4. Other activities directly relevant to this case. I wrote a special report at the request of the Dept. of Energy (DOE) concerning the possible emergence in individuals of hallucinogenic drug flashbacks, and how to guard against the possibility of an accident caused by a flashback. The DOE (Nuclear Safety) and the Environmental Protection Agency used my recommendations to guide policy regarding the handling of nuclear material by individuals who may have used hallucinogenic drugs. I have not served as an expert witness, paid or unpaid, at any time in the past four years.

II. Ayahuasca

5. Scope of report. I discuss ayahuasca's pharmacological mechanisms and effects, including toxicology. The complexity and variability of ayahuasca's drug components, the complexity and variability of their pharmacokinetics (i.e., how the body handles a drug (metabolism, excretion, drug-drug interactions, bioavailability, etc.)) and pharmacology (i.e., how a drug affects the body), the complexity and variability of the human pharmacological responses to ayahuasca, and the variability inherent in predicting threshold dosages (acute and chronic) for undesired or toxic responses in humans all make it extremely difficult, and not presently possible, to predict a "safe" dosage for ayahuasca. Given that a psychosis-like, visionary effect (section 7.e.) is sought by the user of ayahuasca, it must be questioned whether any dosage of ayahuasca is safe. After extensive research, I am not aware of any scientifically-established benefits of the use of this drug. However, I present here the known risks and the gaps in our knowledge of the consequences of ayahuasca use. See Appendix A for a list of reference materials consulted for and cited in this report.

6. **What is ayahuasca?** Ayahuasca is a tea derived by boiling the bark of the liana *Banisteriopsis caapi* together with the leaves of various admixture plants, most frequently *Psychotria viridis*, *Psychotria carthagenensis*, or *Diplopterys cabrerana* (Naranjo, 1969; Rivier and Lindgren, 1972; McKenna, et al., 1984; Pomilio, et al., 1999). The *B. caapi* contributes harmine, harmaline, and tetrahydroharmine (THH) to the brew (Hochstein and Paradies, 1957; Rivier and Lindgren, 1972); these beta-carbolines are inhibitors of the enzyme monoamine oxidase (MAO) (Buckholtz and Boggan, 1977; Kim, et al., 1997). The admixture plants contribute the short-acting, strong hallucinogenic indoleamine *N,N*-dimethyltryptamine (DMT) (Rivier and Lindgren, 1972; Pomilio, et al., 1999). DMT alone is pharmacologically active by injection or if smoked (Strassman, et al., 1994), but DMT is not active when orally ingested due to its metabolism (deamination and oxidation) by gastrointestinal and hepatic MAO (Szára, 1957; Suzuki, et al., 1981; Callaway, et al., 1999; Riba, et al., 2003). It has been shown, however, that DMT is orally active when administered in combination with harmaline or harmine, at dosages equivalent to those in ayahuasca, in laboratory animal assays (McKenna, et al., 1984; Gable, 2007; Halberstadt, et al., 2008) and in humans (Szára, 1957; Strassman, et al., 1994; Ott, 1999). This hallucinogenic beverage, also known as daime, hoasca, caapi, yagé, natema, pinde, and other local names, with a variety of spellings, is widely used for shamanic, ritual, and “recreational” purposes by the aboriginal and mestizo people of the Amazon Basin (McKenna, et al., 1984). While many variations of this beverage have been described, and other plants may be added to the brew, a salient common denominator is the presence of DMT and harmala alkaloids, particularly harmine, harmaline, and THH (Callaway, et al., 1999; Gambelunghe, et al., 2008).

7. **Basic pharmacology of ayahuasca.** Unlike the Judeo-Christian sacramental use of small amounts of wine, the ayahuasca sacrament (typical 55-200 ml dose) is intended to be pharmacologically active (McKenna, et al., 1984; Pomilio, et al., 1999; McKenna, 2004; Gable, 2007). Thus, even in the context of religious, ritual, shamanic, or ceremonial use, ayahuasca must be considered to be a drug, even when used as a sacrament. Therefore, its basic pharmacology must be understood.

a. The classical hallucinogenic drugs are defined as drugs that produce changes in thought, mood, and perception with little memory or intellectual impairment, and produce little

stupor, narcosis, or excessive stimulation, and produce minimal autonomic side effects (Glennon, 1999). The classical hallucinogenic drugs belong to two chemical classes: indoleamines, including LSD and DMT, and phenethylamines, such as mescaline and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, called "STP" on the street). LSD usually serves as the prototype hallucinogen. Hallucinations are perceptions of stimuli that do not exist. LSD does not usually produce true hallucinations, since the user usually remains aware that the sensory distortions are drug-induced "pseudohallucinations," but this label has persisted. Hallucinogens are also called *phantastica*, psychedelics, and psychotomimetics (Glennon, 1994; Frankenheim and Lin, 2004).

b. Indoleamine hallucinogens have been shown to induce their characteristic cognitive, perceptual, and mood distortions, which are similar to many symptoms of patients with schizophrenia, by directly activating serotonin (5-hydroxytryptamine, 5-HT) receptors, particularly the 5-HT_{2A} subtype of brain serotonin receptors (formerly referred to as 5-HT₂ receptors), resulting in (1) decreased tonic activity of noradrenergic neurons (via GABAergic afferents) and facilitation of the activation of noradrenergic neurons by sensory stimuli (via glutamatergic afferents) in the locus coeruleus, and (2) enhanced glutamate release throughout the neocortex (Aghajanian and Marek, 1999). 5-HT_{2A} receptor affinity of LSD, DMT, and other indoleamines correlates with hallucinogenic potency in humans and with relevant behavioral activity in animals (Glennon, 1994; Egan, et al., 1998). Hallucinogenic compounds, including LSD and DMT, act as agonists at the 5-HT_{2A} receptor (Sanders-Bush, et al., 1988; Pierce and Peroutka, 1989; Smith, et al., 1998). Additional evidence demonstrates that the tryptamine hallucinogens can induce behavioral effects via the 5-HT_{1A} receptor (Winter, et al., 2000; Krebs-Thomson, et al., 2006). Thus, hallucinogenic activity results from activation of the 5-HT_{2A} subtype of serotonin receptors, as well as possible activation of the serotonin 5-HT_{1A} receptor by the hallucinogenic tryptamines (Callaway, et al., 1999; Blair, et al., 2000). Glennon (Glennon, 1999) further defines the classical hallucinogens as agents that bind at 5-HT_{2A} receptors.

c. DMT has been studied far less than LSD. However, the molecular structure, mechanisms, and effects of DMT have been shown to greatly overlap those of LSD. Therefore, it is reasonable and necessary to apply the knowledge gained from studies of LSD to DMT.

Some differences between these two drugs are known or are likely; I identify and account for those differences throughout this report.

d. Serotonin is a neurotransmitter (i.e., a substance, such as noradrenaline, glutamate, and gamma-aminobutyric acid (GABA), that transmits nerve impulses across a synapse). Serotonergic neuron axon terminals (where the serotonin is released into the synapses) are remarkably widely disseminated throughout the brain. Serotonin generally regulates the activity of other neurotransmitters, and so serotonin is involved in practically everything we do – learning and memory, startle reflex, mood, impulsiveness, aggression, pain, sex, sleep, hunger and thirst, body temperature, and more. However, since the hallucinogens activate only certain subtypes of serotonin receptors, the acute effects of hallucinogens are more focused than are all of the effects of serotonin. Further, the hallucinogens can pharmacologically activate these serotonin receptors more strongly than they are activated under normal physiological conditions.

e. Acutely, hallucinogens characteristically produce a psychosis-like effect, in which the subject remains cognizant of reality; rarely, however, hallucinogens can induce a florid acute psychosis. In these latter cases, it can be hard for even a physician to distinguish the psychosis produced by hallucinogen use from schizophrenia without knowing the drug use history of the patient. The hallucinogens are sometimes referred to as psychotomimetics because the mental distortions they induce mimic many symptoms of patients with psychoses. Due to the psychotomimetic effect, many physicians, especially psychiatrists, in the early years of LSD research, self-administered LSD in order to try to understand their schizophrenic patients. DMT has also been used, by injection, to produce experimental psychoses, illustrating that it is a strong, short-acting hallucinogen (Daumann, et al., 2008). One theory regarding the etiology of schizophrenia suggests that schizophrenia may be caused by the body's own, natural, endogenous DMT (or similar chemicals) in the presence of diminished MAO activity (Pomilio, et al., 1999).

f. A number of genes implicated in synaptic plasticity, glutamatergic signaling, and cytoskeletal architecture have been reported to be activated upon acute LSD administration. It has been theorized that some of these gene expression changes may contribute to long-term effects of LSD (Nichols and Sanders-Bush, 2004) and related hallucinogens, such as persistent psychosis and hallucinogen persisting perception disorder (HPPD), discussed in section **10.b**.

g. The enzyme MAO degrades both DMT and serotonin (Suzuki, et al., 1981). The harmine and harmaline in ayahuasca function primarily as reversible inhibitors of MAO. Their presence in the brew increases the efficacy and duration of the DMT action, allows oral efficacy of the DMT, and increases central and peripheral serotonergic activity (Callaway, et al., 1999; Halberstadt, et al., 2008). The THH possibly contributes neuroactivity by slightly inhibiting the reuptake of serotonin at presynaptic sites, like other 1-methyl-tetrahydro-beta-carbolines (Airaksinen, et al., 1980), and also by slightly inhibiting MAO. Concentrations of serotonin increase in the body when both its metabolism by MAO and presynaptic reuptake are simultaneously blocked by THH. Thus, both actions of THH increase central and peripheral serotonergic activity while facilitating the activity of DMT (Callaway, et al., 1999).

h. In addition to their inhibiting MAO, both harmine and harmaline acting alone (i.e., without the presence of DMT) have been shown to be hallucinogenic in humans (PENNES and HOCH, 1957; Naranjo, 1969; Slotkin, et al., 1970). Glennon classifies harmaline as a classical hallucinogen based on harmaline's reported effects in man and based on his own results in rats (Grella, et al., 1998; Glennon, 1999). The Glennon group demonstrated, in rats, that DOM-stimulus generalization occurs to harmaline, and vice versa, suggesting that similarities exist between the stimulus properties of the two agents (DOM is used as a prototypical hallucinogen by the Glennon laboratory). They also demonstrated that, like the indoleamine hallucinogens, harmaline binds at 5-HT_{2A} (and at 5-HT_{2C}) receptors. These results are not unexpected, because these beta-carbolines have an indoleamine moiety embedded within their tricyclic structures.

i. **DMT is a strong hallucinogen, like LSD.** Both LSD and DMT are indoleamine hallucinogens. Both activate the 5-HT_{2A} receptor, and their potency in binding to this receptor parallels their hallucinogenic potency in humans and in animal models. LSD is the most potent hallucinogen known, with a typical oral dose of 100 micrograms. Potency refers to the amount of the drug required to achieve a certain level of effect. Some other hallucinogens are as powerful (i.e., as efficacious and strong – referring to the level of effect the drug is capable of reaching), but not as potent, as LSD (mescaline is at least as powerful); i.e., other hallucinogens are capable of exerting effects that are as profound as those of LSD, though at a higher dose (e.g., 200-400 milligrams of mescaline) (Frankenheim and Lin, 2004). The difference between potency and strength can be illustrated by the analgesics: morphine is a strong analgesic, and is

useful vs. severe surgical and cancer pain; aspirin, a weak-moderate analgesic, can never reach the level of pain relief that morphine can, no matter how high a dose of aspirin is administered. Ayahuasca has been tested in human subjects experienced with LSD but not experienced with ayahuasca (Riba, et al., 2003). Subjects given ayahuasca reported the same psychological and somatic effects, qualitatively and quantitatively, as those of LSD; in fact, the objective rating scales used in this study were developed using LSD as a prototype. Thus, while the doses of DMT (oral 0.6 and 0.85 mg of DMT/kg of body weight) administered in the ayahuasca tea in this study are higher than typical doses of LSD (as with mescaline and all other hallucinogens), DMT has been proven to be a powerful hallucinogen, like LSD. It is therefore valid to predict that the consequences of DMT usage are similar to the consequences of use of the better characterized hallucinogens like LSD.

j. The complex pharmacology of ayahuasca is partly explained by the fact that serotonin, DMT, and the harmala alkaloids all have similar chemical structures (Callaway, et al., 1999).

8. **Basic toxicology of ayahuasca.** Despite extensive research, I have found no laboratory animal studies in the scientific literature regarding short or long-term toxicology of ayahuasca. This lack of studies is perhaps due to the variability of ayahuasca, discussed below. However, it is possible to predict the toxicology of ayahuasca based on scientific evidence about its active components.

a. Generally, toxicity of drugs is determined by statistically estimating the acute dose that kills 50% of the laboratory animal subjects, the LD50 (median lethal dose). This criterion of single-dose acute lethality is a very limited estimate of human toxicity. In the context of human toxicology, it is more relevant to estimate the dosage, acutely or with repeated dosing, that may have a lasting adverse health effect in just a single, or just a few, humans, under various circumstances. Therefore, in this report, I primarily discuss the circumstances that may prove detrimental to the health of individual users of ayahuasca.

b. A toxic dose of a drug is usually compared with a beneficially efficacious dose to determine the risk/benefit ratio of the drug in a given therapeutic situation. However, possible benefits of ayahuasca have not been recognized by the U.S. Food and Drug Administration (FDA) or the medical community at large, so such an analysis is not feasible at this time.

c. The LD50 of DMT (alone) in mice is reported as 47 mg/kg injected intraperitoneally (Shinoda, et al., 1974) and 32 mg/kg intravenously (U.S. Army Armament Research & Development Command, 2008). The lethality of DMT in combination with MAO and serotonin reuptake inhibitors is unknown.

d. Medical case reports (Balikova, 2002; Brush, et al., 2004; Sklerov, et al., 2005; Gable, 2007; Frison, et al., 2008) (please also see the affidavit of Theodore M. King, Jr., M.D.) confirm the acute toxicity in man (including death) of the harmala alkaloids combined with substances such as 5-methoxy-*N,N*-dimethyltryptamine (Callaway and Grob, 1998; Brush, et al., 2004; Sklerov, et al., 2005) (affidavit of Dr. King). 5-MeO-DMT is a longer acting (Krebs-Thomson, et al., 2006) analog of DMT. There are case reports also of harmala alkaloids alone being acutely toxic in man (e.g., seizure, hallucinations) (Frison, et al., 2008).

9. Variation in ayahuasca components. Substantial variation in the quantities of active pharmacological constituents of ayahuasca occurs due to the diversity in the particular plants selected for harvesting; the amount of each plant selected; the ages of the plants; climate, soil, light, and other environmental conditions affecting plant growth; methods of harvesting and preparation; and other factors (McKenna, et al., 1984; Riba, et al., 2003; Gable, 2007). Further, many of the admixture plants used remain uncharacterized botanically or chemically (McKenna, et al., 1984).

a. DMT has been reported as ranging from 0.1% to 0.66% dry weight in *P. viridis* leaves (Callaway, et al., 2005). The DMT in leaf samples from a single *P. viridis* plant has been shown to vary from approximately 3 mg/g to 9.5 mg/g dry weight in the course of one day. The concentrations of the beta-carboline alkaloids in *B. caapi* have been reported as ranging from 0.05% to 1.95% dry weight (McKenna, et al., 1984; Gable, 2007). The content of DMT, harmine, harmaline, and THH varied widely in assayed ayahuasca teas (Riba, et al., 2003; Gable, 2007).

b. The other occasional additives to ayahuasca contribute alkaloids such as nicotine, scopolamine, and atropine (Pomilio, et al., 1999) that can enhance the toxicity of the tea.

c. Stored plant material, such as ayahuasca, is also subject to contamination with bacteria, fungi, and other environmental infestations, causing risk of infection, especially to users whose immune systems are weakened by old age, malnutrition, cancer chemotherapy, bone

marrow transplantation, AIDS, and other disorders and procedures. These immunocompromised individuals are susceptible to infections that healthy immune systems usually conquer.

d. The documented variability and the lack of standardization of ayahuasca distinguish this drug from any medication recognized by the medical community at large in the U.S., the FDA, or the U.S. Pharmacopeia (USP). There are substantial risks, many of which are detailed below, involved in ingestion of powerful drugs, such as those present in ayahuasca, in unknown and varying amounts.

10. Variation in responses to hallucinogens

a. Short-term effects

i. **The psychological effects of hallucinogens are unpredictable.** They depend on the amount ingested and the user's personality, mood, expectations, and surroundings. Sensations and feelings are affected more dramatically than somatic signs. The user may feel several different emotions (including euphoria) at once, or swing rapidly from one emotion to another. Visual delusions, distortions, and pseudohallucinations usually occur. Colors, sounds, odors, and other sensations appear intensified, and pseudohallucinations of movements, forms, and events may follow. The user's perceptions of time and self are distorted, including feelings of time slowing, one's body changing shape (e.g., arms very long), and out of body experience. Sensations may seem to cross over (synesthesia), giving the user the feeling of hearing colors and seeing sounds. Old memories may be vividly recalled. Anxiety often occurs while using hallucinogens, and some users experience terrifying thoughts, nightmarish feelings, despair, and fears of insanity, death, and losing control.

ii. The somatic effects of LSD are mainly sympathetic and relatively slight. They include dilated pupils, hyperthermia, increased heart rate and blood pressure, sweating, loss of appetite, restlessness, dry mouth, dizziness, and tremors (Frankenheim and Lin, 2004).

iii. The nonlinear kinetics of DMT elimination (discussed in section 11.a.iii) and the persistence of MAO inhibition after ayahuasca ingestion (Riba, et al., 2003) make the effects of large or quickly-repeated ("stacked") ayahuasca dosages especially unpredictable, in the direction of greater-than-expected effects.

iv. The psychological effects of hallucinogens also depend on whether or not the user is psychiatrically well (see section 11.a.v).

v. **Risk of accidental injury and death.** Fatal accidents have occurred during LSD use. This is a potential problem with the use of any psychoactive substance, especially one that causes cognitive and perceptual changes, pseudohallucinations and hallucinations, and may alter judgment. Based on what is known about other hallucinogenic drugs, the potential for accidental injury and death does exist for users of ayahuasca. One must also consider that these effects may only become apparent under conditions in which the limits of an individual's capabilities are approached, e.g., driving at night with adverse weather.

b. **Long-term effects.** There are two long-term disorders associated with LSD – persistent psychosis and hallucinogen persisting perception disorder (HPPD) (Abraham, et al., 1996). While acute, short-lived adverse reactions to hallucinogens are often fairly benign, the chronic, unremitting outcomes (post-LSD psychoses and HPPD) carry a poor prognosis. These long-term consequences appear to be rare, though this has not been thoroughly studied (Halpern and Pope, Jr., 2003). Given the frequent, repeated use of ayahuasca, which differs from the typical sparse and limited use of LSD and most other hallucinogens, the risk of a long-term outcome following the use of ayahuasca is substantial.

i. **Persistent psychoses.** Post-LSD psychoses are unpredictable, and sometimes follow a single dose, but are more common in people with prior psychopathology. Post-LSD psychoses resemble schizoaffective disorders, and are frequently accompanied by visual disturbances (Abraham, et al., 1996). The extent of this problem with the other hallucinogens is not known. Thus, individuals with previous and current psychiatric diagnoses and/or family histories that suggest vulnerability to development of mental disorders, particularly those characterized by psychosis, are at risk for adverse psychiatric consequences from the use of hallucinogens including ayahuasca.

ii. **Hallucinogen persisting perception disorder (HPPD).** In the 1950s, flashbacks (spontaneous, disturbing recurrences of aspects of LSD experiences, long after the use of LSD has stopped) began to be reported, sometimes months after LSD use. Abraham et al. (Abraham, et al., 1996) demonstrated that this syndrome is typically persistent and stable, rather than paroxysmal, and presents primarily with visual disturbances, including geometric pseudohallucinations, false motion in the peripheral fields, halos, flashes of color, trails behind moving objects, and afterimages. Thus the term flashback has been supplanted by HPPD. The visual distractions are increased by several factors, including stress, darkness, and marijuana, and

decreased by benzodiazepines. It is very difficult to predict who is vulnerable to HPPD. Though there are no data documenting the presence or absence of these persistent psychophysical changes related to the use of ayahuasca, this is likely due to the relative lack of knowledge regarding ayahuasca, compared to the knowledge about LSD.

c. The variability of the human responses to hallucinogenic substances is compounded by the variable content of psychoactive alkaloids in ayahuasca.

11. Studies of ayahuasca in humans. What we know of ayahuasca effects in man is limited because most studies of ayahuasca in humans (i.e., clinical studies) were conducted in experienced users of hallucinogens. Studies of ayahuasca in other populations are limited by ethical considerations. Thus, conclusions should not be extrapolated to the general American public. There are two types of clinical studies of ayahuasca – (1) those in which the ayahuasca is acutely administered by physician researchers and (2) those in which chronic ayahuasca users (by self-administration) are surveyed, examined, and interviewed by researchers.

a. Ayahuasca administered by researchers

i. In experienced users of hallucinogens without a history of regular use of ayahuasca, acute ayahuasca induced feelings of increased activation, euphoria and well being, perceptual modifications, changes in thought content, and increased emotional instability (Riba, et al., 2003). Subjective effects in humans are generally measured, as they were in this study, by means of visual analog scales and standardized self-report questionnaires. Diastolic blood pressure showed a significant increase (Riba, et al., 2003).

ii. The time course of ayahuasca's acute effects is short, relative to the time courses of other hallucinogens (Strassman, 1994; Riba, et al., 2003). After oral administration, the initial effects of ayahuasca appear between 30 and 45 minutes, peak between 90 and 120 minutes, and are over three hours after ayahuasca administration (Riba, et al., 2003; Riba, et al., 2004). By contrast, LSD's effects typically begin to clear after 8-12 hours. The time course of ayahuasca's effects follows the time course of the DMT levels detected in the plasma; the time courses of the harmala alkaloids in the plasma are much longer (Riba, et al., 2003).

iii. **“Stacking” may disproportionately increase the effects of increasing doses of ayahuasca.** In a two-dose clinical study of ayahuasca, the pharmacokinetic analysis indicated relatively greater DMT bioavailability following the high dose, probably related to the

higher amounts of harmala alkaloids in the higher dose of ayahuasca, leading to more effective MAO inhibition. This is evidence of a nonlinear increment of DMT levels in the body following ingestion of increasing doses of ayahuasca (Riba, et al., 2003). In other words, increasing the ayahuasca dose (for example, doubling it, or, for another example, “stacking” doses (i.e., taking a second dose before the effects of the first dose have completely waned)) may yield a greater-than-expected amount of DMT in the brain and greater-than-expected consequences.

iv. In the ayahuasca sample used by Riba (Riba, et al., 2003), harmine was the main MAO-inhibiting alkaloid. The observed psychoactivity (described above) was coincident with plasma DMT levels, but the levels of circulating harmine were negligible. This result and the observed lack of a clear-cut systemic MAO inhibitor effect suggest that the harmine’s MAO inhibiting effect, allowing DMT’s activity, took place in the gastrointestinal tract and liver, preventing “first pass” metabolism (i.e., metabolism in the gut and liver, before the drug reaches the systemic circulation) of DMT.

v. There are a few studies of hallucinogens administered to psychiatrically ill patients. Most of these studies demonstrated that schizophrenic patients who had LSD acutely administered to them worsened, usually with an exacerbation of their pre-existing characteristic symptoms (Strassman, 1994).

vi. A few clinical studies of ayahuasca included female subjects (e.g., (Riba, et al., 2003)), but were unable to determine gender differences.

b. **Survey studies.** The second type of clinical study involves the retrospective survey of ayahuasca users; ayahuasca is not administered as part of the study design.

i. One such study (Halpern, et al., 2008) found 19 of the 32 study subjects met lifetime criteria for a psychiatric disorder, and 24 of the 32 subjects had drug or alcohol abuse or dependence histories. The possibility that people with psychiatric and drug use disorders may seek to use ayahuasca, even within a church setting, is a concern because, as detailed in this report, these populations are particularly vulnerable to many of the risks of ayahuasca use.

ii. Some ayahuasca-church members did not volunteer for the Halpern study (Halpern, et al., 2008), so the sample of volunteers may be skewed towards church members who are in better health than the non-volunteers. The Halpern study (Halpern, et al., 2008) also did

not survey the much larger number (110, according to the study) of potential subjects who had left this church.

iii. A previous study, with members of the Uniao do Vegetal church, was reported by Grob et al. (Grob, et al., 1996). These researchers reported frequencies of ayahuasca use as often as several times per week, which is quite different from the typically sparse and limited use of LSD and other classical hallucinogens (**10.b.**); this raises concerns of adverse effects from ayahuasca that are not often observed with other hallucinogens, including all of the concerns raised in sections **8.**, **10.**, **11.a.v.**, and **12.** Though this study found “no evidence of personality or cognitive deterioration,” and “high functional status,” it also found that their matched control subjects (with no prior history of ayahuasca ingestion) had “significantly higher yearly incomes than” the ayahuasca users, possibly indicating subtle deficits related to ayahuasca use, though this disparity may have been due to an artifact caused by the methods the researchers used to recruit the control subjects. Other findings of this study (Grob, et al., 1996) are in line with the findings reported by Halpern et al. (Halpern, et al., 2008).

12. Specific risks of human ayahuasca use. I have already discussed the risks of hallucinogen-induced persistent psychosis (**10.b.i.**), exacerbation of schizophrenia (**11.a.v.**), HPPD (**10.b.ii.**), and accidental injury and death (**10.a.v.**), which can be associated with hallucinogen use in general. The following refer more specifically to ayahuasca.

a. Central serotonin syndrome. The inhibition of MAO induced by the beta-carbolines in ayahuasca can allow large amounts of serotonin to accumulate in serotonergic synapses in the central nervous system. Excessive accumulation of serotonin can result in the central serotonin syndrome, which includes confusion, disorientation, hyperthermia, hypertension, tremor, myoclonus, hyperreflexia, and possible death (see figure 1 on page 21) (Mills, 1997). The central serotonin syndrome occurs infrequently after any single drug, but combining ayahuasca (containing (1) MAO inhibitors, (2) DMT, which, like serotonin, is a direct agonist at serotonin receptors, and (3) THH, which may inhibit the reuptake of serotonin at presynaptic sites) with, for example, most antidepressants, dextromethorphan (which inhibits serotonin reuptake, and is a common ingredient of over-the-counter cough and cold remedies), methylenedioxymethamphetamine (MDMA, “ecstasy,” which releases serotonin), buspirone (an

antianxiety medication that works by stimulating serotonin type 1A receptors), LSD, or L-tryptophan (which is a precursor of serotonin, and is found in many foods) is risky.

i. In some cases, the serotonin syndrome is produced by a combination of agents that promote serotonergic effects when at least one of these agents (i.e., the MAO inhibitor or the serotonin agonist) is taken at a high dosage. In other cases, a toxic and potentially fatal interaction can occur between MAO inhibitors and tricyclic or selective serotonin reuptake inhibitor (SSRI) antidepressants given at therapeutic dosages (Lejoyeux, et al., 1995; Callaway and Grob, 1998).

ii. The “irreversible” MAO inhibitors (e.g., phenelzine (Nardil®) and tranylcypromine (Parnate ®)) used to treat depression and other disorders are strongly associated with instances of severe serotonin syndrome. “Irreversible” MAO inhibitors bind covalently (a strong, permanent chemical bond) to MAO, thus inactivating MAO until sufficient new functional MAO has been produced by the body (several weeks). Though the harmala alkaloids are “reversible” inhibitors of MAO, which means that they do not bind permanently to the MAO and that their acute effects wane in parallel with their sojourn in the body, their sojourn in the human body lasts much longer than that of the DMT (Riba, et al., 2003), and they are certainly capable of participating in the serotonin syndrome when ayahuasca is combined with agents like an SSRI (Callaway and Grob, 1998); beyond this fact, it is not known how extensive and persistent is the MAO inhibition produced by ayahuasca, especially when taken frequently over many years, sometimes more than once during the lengthy ceremonies, and it is not known how such inhibition may interact with the serotonin agonist and reuptake properties of the tea itself, as well as any medications and other substances with similar effects used by those who then ingest the tea. The range of individual differences in these parameters is also unknown. Typically, there are large individual differences in metabolism and pharmacokinetics of drugs. Such data would be useful in estimation of the probability of many of the adverse interactions of ayahuasca with medications and with drugs of abuse. It must also be noted that certain reversible MAO inhibitor antidepressant medications (moclobemide and toloxatone) are also associated with the central serotonin syndrome (Sun-Edelstein, et al., 2008).

iii. The nonlinear kinetics of DMT elimination (11.a.iii) may also contribute to the risk of the serotonin syndrome (and other risks).

b. **Hypertensive crisis (“cheese effect”).** MAO inhibitors, including those in ayahuasca, inhibit not only the metabolism of serotonin and DMT; they also can inhibit metabolism of other monoamines, including melatonin, epinephrine, norepinephrine, dopamine, and dietary amines such as tyramine and L-dopa. With MAO inhibited, consumption of foods containing tyramine can lead to a hypertensive crisis (so-called “cheese effect”). Hypertensive crises can result in stroke or cardiac arrhythmia. The amounts of MAO inhibitor and MAO substrate required to cause a toxic interaction exhibit great individual variation and depend on the degree of inhibition, which in turn depends on dosages and on the selectivity (MAO-A or MAO-B) of the MAO inhibitor. Thus, a significant risk associated with the use of MAO inhibitors is the potential for interactions with many over-the-counter and prescription medications, illicit drugs, many foods, and certain “dietary supplements” (e.g., St. John's wort).

i. Due to the serious risk of hypertensive crisis, PDRhealth™, the consumer Web portal of the Physicians' Desk Reference (PDR®), states: “Most important fact about Nardil [irreversible, non-selective inhibitor of MAO-A and MAO-B]: Avoid the following foods, beverages, and medications while taking Nardil and for 2 weeks after stopping it: beer (including alcohol-free or reduced-alcohol beer); caffeine (in excessive amounts); cheese (except for cottage cheese and cream cheese); chocolate (in excessive amounts); dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna); fava (broad) beans; liver; meat extract; pickled herring; pickled, fermented, aged, or smoked meat, fish, or dairy products; sauerkraut; spoiled or improperly stored meat, fish, or dairy products; wine (including alcohol-free or reduced-alcohol wine); yeast extract (including large amounts of brewer's yeast); yogurt; *medications to avoid:* amphetamines [either prescribed (for such indications as attention deficit-hyperactivity disorder, weight control, depression, or narcolepsy) or abused]; appetite suppressants such as diethylpropion; antidepressants and related medications such as amitriptyline, bupropion, carbamazepine, citalopram, cyclobenzaprine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine; asthma inhalants such as albuterol; cold and cough preparations including those with dextromethorphan; L-tryptophan-containing products; nasal decongestants in tablet, drop, or spray form such as pseudoephedrine; sinus medications such as Sinutab; stimulants such as epinephrine and methylphenidate. Taking Nardil with any of the above foods, beverages, or medications can cause serious, potentially fatal, high blood pressure” (PDRHealth, 2008). Since, in the context of religious use, ayahuasca

may be taken repeatedly at short intervals, similar risks apply to ayahuasca, though its MAO inhibitors are reversible.

ii. People often are not aware of the nature of the drugs they are prescribed or they buy over-the-counter, especially elderly or mentally challenged people, and are probably even less aware of the amine content of their foods and their dietary supplements, so providing a list of forbidden foods and drugs (some of which may be necessary for their health) to users of ayahuasca is not sufficient. Nardil itself (and similar agents) is used only in very carefully selected (by their physician) patients because of its numerous potentially lethal drug and food interactions; it is used as a last resort, when other antidepressants have failed.

c. **Use by women of child-bearing age.** Though the extents to which the drugs in ayahuasca cross the placental barrier and concentrate in the fetal brain are not known, it has been demonstrated that harmaline can elevate dopamine and serotonin levels (as expected from an MAO inhibitor) in the brains of rat fetuses 2-4 hours after the mother is injected with the drug, indicating that harmaline (or an active metabolite of harmaline) crosses the placental barrier to affect the fetal brain (Okonmah, et al., 1988). There are no data on how the collection of drugs in ayahuasca may affect the developing brain (or other organs/systems under development) as well as potential effects on pregnant women themselves.

d. **Use by young people**

i. Apparently, church ceremonial use of ayahuasca can begin as early as age 13 in the U.S. (Halpern, et al., 2008). Ritual use of ayahuasca, at least within the context of the Brazilian ayahuasca churches, often starts during late childhood or early adolescence (Doering-Silveira, et al., 2005), typically within rites of initiation (Grob, et al., 1996). Ayahuasca use by young people is a special concern because, as with other drugs, the effects of hallucinogens on the developing brain are relatively unknown, and what little we do know indicates greater vulnerability to adverse consequences. Further, though it was once thought that human brain development was largely complete by the onset of puberty, it is now known that the brain continues to develop throughout adolescence and into young adulthood. The higher-order association cortices develop later than primary sensorimotor cortices, with the dorsolateral prefrontal cortex still developing during the latest stages of adolescence. The later changes result in neural signals transmitting more rapidly, permitting greater capacity for complex, higher-order (i.e., executive) reasoning and processing (e.g., delay of gratification, performance of complex

tasks, planning, engaging in behavior guided by long-term goals) in adulthood. It is possible that frequent use of a strong hallucinogen such as ayahuasca may interfere with the brain's normal development.

ii. Because the adolescent brain circuitry is not fully developed yet for executive reasoning, adolescents tolerate greater risks than do mature adults; adolescents often think of themselves as somewhat invincible. Therefore, adolescents, especially those in late adolescence, are more likely than adults to engage in risky behavior, and may not appreciate the risks of combining ayahuasca with drugs and foods that interact dangerously with ayahuasca, and also may not appreciate the risks of driving, having unprotected sex, and abusing other substances under the influence of ayahuasca. Even young adults, over age 18, are vulnerable to these risks. Young people may be particularly vulnerable also to hallucinogen-triggered persistent psychoses and to drug addiction (see section 12.f.ii.).

e. **Use by the elderly.** Because older people are more likely to have poor liver, kidney, or heart function, or other diseases that could increase the likelihood of untoward effects, use of ayahuasca by the elderly is a particular concern.

f. Potential for addiction

i. Given the ritually repeated use of ayahuasca over months and years (Halpern, et al., 2008), up to several times per week (Grob, et al., 1996), there is risk that ayahuasca can produce addiction. Addiction is defined as a chronic, relapsing brain disease characterized by compulsive drug seeking and use despite harmful consequences. It is considered a brain disease because repeated drug use can change brain structure and function. Drug-induced brain changes can be persistent, and can lead to the harmful behaviors seen in people who abuse drugs (NIDA, 2008).

ii. People initiate and continue non-medical use (i.e., abuse) of drugs for a variety of reasons, including their desire to feel satisfied, euphoric, confident, or powerful; to feel better when they might otherwise feel low, anxious, or stressed; to satisfy their curiosity; to respond to peer pressure; and so on. About 10-20% of people who repeatedly abuse drugs such as heroin and other opiates, cocaine, methamphetamine, PCP, inhalants, ethanol (alcohol), other central nervous system depressants (e.g., sedatives), cannabis (marijuana), and tobacco become addicted to these drugs. People escalate (or do not escalate) from abuse to addiction due to many vulnerability (or resiliency) factors including genetic factors, gender, his or her developmental

stage, the surrounding social environment (e.g., conditions at home, at school, and in the neighborhood), the nature of the drugs that are abused, drug withdrawal signs (i.e., drug dependence) and symptoms, etc.; adolescents and individuals with mental disorders are at greater risk of drug abuse and addiction than the general population (NIDA, 2008).

iii. It often takes many years, and many unfortunate examples, to determine that a specific drug is addicting. For example, the psychostimulants (e.g., cocaine, methamphetamine) were, until recent decades, thought by many not to be addicting because they do not produce overt, somatic withdrawal signs, but it is now clear that they are as addicting as heroin and ethanol. It has even more recently been established that cannabis is addicting (see, e.g. (Swift, et al., 2008)). It has not yet been determined if certain widely-abused drugs, such as MDMA, are addicting.

iv. Many users of hallucinogens believe that their drug experiences have a mystical, perception-expanding, epiphanous character (though lasting benefits, if any, of the drug experiences have not been scientifically demonstrated) (Frankenheim and Lin, 2004).

Ayahuasca's perceptual, cognitive, and euphoric effects create a significant potential for abuse. Though the classic hallucinogens are not known to produce addiction or dependence, this drug class does not consist of drugs that are all exactly alike, but rather comprises a somewhat heterogeneous group of drugs (Glennon, 1999), which may vary in addictiveness. Thus, further studies of DMT and the harmala alkaloids regarding their propensity to produce addiction under a variety of conditions, including a history of repeated self-administration of these drugs, are needed before conclusions can be made. It was demonstrated that rhesus monkeys will self-administer DMT after they have been exposed repeatedly to (and learned to self-administer) another serotonergic drug, MDMA (Fantegrossi, et al., 2004).

v. Thus, there is risk that ayahuasca can produce drug addiction, particularly when ritually repeated over months or years, at least in a few people. Mentally ill and adolescent individuals are particularly at risk for addiction to ayahuasca, as they are for addiction to other substances.

g. **Non-compliance with established medical therapies.** The Halpern et al. (2008) study of ayahuasca-church members found a history of psychiatric and substance use disorders. It is a concern that ayahuasca users with psychiatric and substance use disorders may choose to forego conventional, established medical therapies.

13. Conclusions about the pharmacology and toxicology of ayahuasca.

a. The sacramental use of ayahuasca results in pharmacological effects from the ayahuasca, and can result in toxicological effects. The complexity and variability of (1) ayahuasca's drug components, (2) their metabolism, excretion, drug-drug interactions, bioavailability, pharmacology, and toxicology, and (3) human pharmacological and toxicological responses to ayahuasca, as well as the variability inherent in predicting threshold dosages (acute and chronic) for undesired or toxic responses in humans, all make it impossible to determine or predict a "safe" dosage for ayahuasca. Since a psychosis-like effect, similar to schizophrenia, is sought by the user of ayahuasca, it is doubtful that any dosage of ayahuasca is safe. There remain many gaps in our knowledge of the consequences of ayahuasca use. No benefits of the use of this drug are scientifically established, while many risks, some severe, are substantiated or are reasonably predicted. These risks include persistent psychosis and HPPD, the central serotonin syndrome and other interactions involving MAO inhibition, *in utero* effects, accidents, and more.

b. Even if, in the future, certain benefits of ayahuasca were to be shown scientifically, it would remain to be demonstrated that these benefits outweigh the considerable risks of ayahuasca use.

Central Serotonin Syndrome

- Cognitive / Behavioral
 - Confusion / disorientation 54%
 - Agitation / irritability 35%
 - Coma 28%
 - Anxiety 16%
 - Hypomania / seizures / hallucinations 15%
 - Neuromuscular
 - Myoclonus 57%
 - Hyperreflexia 50%
 - Muscle rigidity / tremor 49%
 - Hyperactivity / restlessness 42%
 - Ataxia 38%
 - Autonomic
 - Hyperthermia / diaphoresis 46%
 - Sinus tachycardia 41%
 - Hypertension 33%
 - Tachypnea / mydriasis 27%
- (Mills KC (1997) *Crit Care Clin* 13:763-83)

Figure 1. The central serotonin syndrome. The percentages refer to the frequency with which these specific signs and symptoms were reported in 127 published cases of serotonin syndrome.

Myoclonus is a sudden twitching of muscles or parts of muscles, without any rhythm or pattern, occurring in various brain disorders.

Sinus tachycardia is a simple tachycardia with origin in the sinus node with gradual onset and termination.

III. Dr. Frankenheim's statement regarding Dr. Cozzi's declaration

14. Before getting into a discussion of Dr. Cozzi's specific statements, it is important to note that like Dr. Halpern (section IV.), Dr. Cozzi has received funds from the plaintiffs.

15. Dr. Cozzi entitles the third section of his declaration, starting on page 2, "Is daime toxic?" Posing the question in this way oversimplifies the issues at hand. It is only to be expected that there are "no reports in the medical literature of overt toxicity resulting [from] Daime use," because it would be extremely difficult and arduous to systematically examine such a complex and variable collection of chemicals, with differing actions, and synergistic interactions, that constitutes ayahuasca (please see sections 6., 8., and 9.). Further, the toxicity of the harmala alkaloids largely depends on their interactions with foods, other drugs, endogenous amines, and other factors, which would also need to be systematically varied in toxicology studies. Besides, scientists generally need some reason to do a study (along with the agreement of a funding agency), and I am not aware of any reason that such complex, expensive studies would be initiated. Ayahuasca has only recently become popular in Europe and North America. This should not be taken to mean that there is no toxicity.

16. The limitations of the survey studies cited by Dr. Cozzi (page 3) have been detailed in my expert report (11.b.); they include limitations due to the retrospective nature of such studies, unintended subject selection bias, small sample sizes, etc.

17. Dr. Cozzi asserts that the vomiting caused by ayahuasca ingestion "makes it virtually impossible for a human ... to consume enough daime tea to experience toxicity" (page 3). This is an unreliable way to limit the absorption of ayahuasca, and it is problematic for four reasons:

a. Vomiting may be inadvertently prevented by the previous ingestion of many common medications, such as anticholinergics (e.g., scopolamine and atropine, which additionally may also be present in the ayahuasca), phenothiazines (e.g., promethazine), butyrophenones (e.g., droperidol), benzamides (e.g., metoclopramide), propofol, dexamethasone, tandospirone, midazolam, and serotonin antagonists (e.g., ondansetron, granisetron, and ramosetron).

- b. People vary in their propensity to vomit.
- c. Vomiting can be harmful because it can lead to aspiration pneumonia, dehydration, malnutrition, and metabolic disturbances such as alkalosis, hyponatremia, hypochloremia, and hypokalemia; these outcomes are life-threatening. While these detrimental outcomes are unlikely in cases of isolated instances of vomiting, they are more likely in ayahuasca users who have additional episodes of vomiting due to gastrointestinal tract disorders, cancer chemotherapy, other drugs that can induce vomiting, pregnancy, etc. Certain populations, such as the elderly, are more vulnerable to the adverse outcomes.
- d. Ayahuasca also usually induces both sweating and diarrhea, which worsen many of the life-threatening outcomes (e.g., dehydration, malnutrition, and metabolic complications) of vomiting.

18. Dr. Cozzi's final section, "drug control policy," presents similar problems in application to the case at hand.

- a. While I am not directly involved in determining drug control policy or regulations, my NIDA colleagues and I often provide scientific advice to agencies (DEA, FDA, ONDCP, Partnership for a Drug-Free America, and many others (see also section 4.)) that do determine drug control policy or provide other public services related to drug abuse prevention. I have also often given public lectures regarding the science of addiction, and am regarded as an expert in defining "drug abuse" and "addiction."
- b. Dr. Cozzi's reasoning is circular on the issue of drug scheduling (p. 4). He writes that ayahuasca "has little or no abuse potential." However, drug abuse, in the context of drug scheduling, is not defined solely by scientific criteria; it is defined primarily by society and its laws. Thus, ayahuasca use is "abuse" because society in the U.S. has decided it is, and tobacco use by adults is not drug abuse if society says it is not. The latter situation appears to be changing as U.S. society disfavors tobacco use. As to whether ayahuasca use will continue to be considered abuse is the matter currently before the court, at least in the context of ayahuasca churches. Another factor in drug scheduling is medical usage. If medical research finds ayahuasca (or at least a standardized version of ayahuasca) to be a useful, advantageous, and relatively safe medication, it might be rescheduled. The processes of scheduling are ongoing and

dynamic; for example, I participated in FDA hearings to determine the scheduling of gamma-hydroxybutyrate (GHB); GHB is now dually scheduled as a schedule 1 and 3 drug.

19. In the same paragraph on p. 4, Dr. Cozzi suggests that ayahuasca has little or no abuse potential because it is inconvenient to prepare and not palatable. However, this has not prevented its abuse (McKenna, et al., 1984; Grob, et al., 1996). Further, it can be sold already prepared for users, or its preparation can be considered to be enjoyable, and its taste can be masked, and users may consider the vomiting (as with mescaline abuse) to be a small price to pay, or even to be a positive experience, as in the ayahuasca churches. Drug abusers do go to great length and expense for their drug “recreation.” Also, if ayahuasca use is addicting (see section 12.f.), addicted users will go to even greater lengths. For example, sticking a needle into one’s own veins chronically is inconvenient and unpleasant, yet many addicting drugs (heroin, cocaine, methamphetamine) are abused in that manner (and some also routinely induce vomiting); in fact, some addicts find the act of skin popping rewarding in itself (i.e., without injecting a drug).

IV. Dr. Frankenheim’s statement regarding Dr. Halpern’s (2008) declaration

20. Dr. Halpern (like Dr. Cozzi) has received funds from the plaintiffs.

21. In his introduction (p. 2), Dr. Halpern makes statements that may be misinterpreted. Though Dr. Halpern’s statement that the mechanisms of action of the harmala alkaloids are somewhat “similar to FDA-approved” MAO inhibitor prescription medications is technically true, that assertion fails to take into account several important factors: (1) A physician’s prescription and maintenance of care are needed for the FDA-approved medications, (2) they are considered to be medications of last resort because of their risks, including the possibility of adverse drug-drug and drug-food interactions with amines (such as DMT), (3) only one MAO inhibitor, at a known dosage, is prescribed, as opposed to an unreliable, varying plant source containing several MAO inhibitors along with DMT, and (4) the MAO inhibitors in ayahuasca have actions and effects besides MAO inhibition, which entail further risk.

22. Dr. Halpern's statement (p. 2) that "there are no known reports of chronic adverse reactions" to the harmala alkaloids is similarly misleading. The lack of reports is likely due to the present limited use of these drugs. Given, for example, the belated establishing of the chronic toxicity of tobacco, or the relatively recent description of fetal alcohol syndrome, or the delays in the discovery of the teratogenicity of thalidomide, or the unexpected emergence of cardiac thrombotic events from the use of the selective cyclooxygenase (COX)-2 inhibitor rofecoxib (Vioxx®), it is easy to understand that findings of chronic adverse reactions may require a great deal of time, use of the offending drug by large numbers of people, and particularly astute physicians.

23. Halpern et al. (Halpern, et al., 2008) acknowledge that "conclusions should not be extrapolated to hallucinogen abusers of the general public." They state that "further research is warranted with blinded raters, matched comparison groups, and other measures to overcome present study limitations." While studies such as this (Halpern, et al., 2008) are useful, they can not take the place of the series of well-controlled, rigorous, prospective, multi-population studies mandated for modern medical drug development and safety monitoring.

24. On page 4 of his declaration, Dr. Halpern states that the consumption of daime "as a sacrament is literally then the non-drug use of DMT." Yet DMT is, by definition, a drug. The broadest definition of a drug is a substance other than food intended to affect the function of the body. A narrower definition is that a drug is a medication. Only the narrowest definition, that a drug is an abused, illicit, or addicting substance, is pejorative. As I detail above (section II.7.), ayahuasca, even as used in a religious context, has to be regarded as a drug, because a pharmacological effect is intended and apparently achieved.

25. Dr. Halpern's discussion of peyote (on p. 5) is inapplicable to this case. The example of peyote in the Native American Church (NAC) is not a valid precedent for ayahuasca, given the presence of variable amounts of the potentially dangerous MAO inhibiting drugs in ayahuasca, while peyote contains only one principle drug – mescaline. This difference renders any comparison between the two substances useless.

26. Drs. Halpern and Pope's review of the literature (Halpern and Pope, Jr., 1999), cited on p. 7, does not put concerns regarding ayahuasca to rest. Their review is limited to "residual neuropsychological toxicity." Halpern and Pope concluded, in this review, that "interpretation of the studies is limited by various confounding variables . . . At present, the literature tentatively suggests that there are few, if any, long-term neuropsychological deficits attributable to hallucinogen use. To better resolve this issue, however, it will be important to study larger samples of chronic, frequent hallucinogen users who have not often used other types of drugs," and that "hallucinogens might have subtle neurotoxic effects not detectable with smaller samples or with individuals with lesser exposure," and that "the existing literature essentially fails to illuminate which potentially confounding variables would form the basis for exclusion in an 'ideal' study and which neuropsychological tests would be the most sensitive." I agree with this assessment. Further, even if such deficits are indeed rare (though whether or not they are truly rare has yet to be established, as detailed above (section 10.b.)), these long-term consequences are very serious. Given the frequent, often weekly, repeated use of ayahuasca over several years (Halpern, et al., 2008), which differs from the typical sparse, limited use of LSD and most other hallucinogens, the risk of a long-term outcome following the use of ayahuasca is considerable. The review of Halpern and Pope (Halpern and Pope, Jr., 1999) covers hallucinogens generally, with only one cited study (Grob, et al., 1996) addressing ayahuasca. Finally, it may be questioned whether even rare, but serious, untoward consequences are tolerable, since no benefits of ayahuasca have been scientifically demonstrated.

27. Though Dr. Halpern (on p. 8) describes the religious leaders in ayahuasca churches as overseeing participants' ayahuasca use, analogous functions are usually performed by qualified medical practitioners (medical doctors, doctors of osteopathy, etc.) in the U.S., with important, complementary roles usually played by qualified nurses, physicians' assistants, pharmacists, etc. These professionals all undergo many years of intensive, formal, and challenging university and hospital study, which, along with their clinical practice, is overseen by several layers of supervision, insurance, licensing, authority, and law. For brevity, I will refer to this broad convention as the "medical model" in the U.S. Many nations of the world follow a similar model. Therefore, it needs to be questioned whether the South American traditions involving active doses of ayahuasca should now be condoned in the U.S., insofar as they involve and

encourage the use of a dangerous, powerful, illicit collection of substances, and insofar as they may, for some individuals, in some instances, substitute for the medical model. Is the “extensive training” of an ayahuasca-church leader as adequate for (1) diagnosing and treating diseases, or as adequate for (2) denying the ayahuasca sacrament to individuals most likely to suffer the adverse consequences of the use of this drug, or as adequate for (3) permitting the use of this powerful drug to some individuals, or as adequate for (4) making referrals to medical specialists – all without the medical model oversight, and possibly without medical records – as is the training of a conventional physician?

28. In his conclusion, Dr. Halpern states that “daime is not a recreational drug by any definition and is not likely to ever be a concern to the goals of drug enforcement ...” (p. 9). However, Dennis Jon McKenna, Ph.D., an expert in Amazonian ethnomedicine with at least 8 publications regarding ayahuasca, writes that “the recreational and religious use of ayahuasca in the United States, as well as ‘ayahuasca tourism’ in the Amazon, is increasing” (McKenna, 2004). Further concerns with ayahuasca tourism are cited by Grob et al. (Grob, et al., 1996) (page 87). Dr. Halpern himself states that “popular interest in DMT is reemerging in the United States in part because sacramental ayahuasca use is no longer exclusive to the traditional shamanic practices of the surviving indigenous peoples of the Amazon Basin. For example, Columbia, Peru, and Brazil now have a number of “eco-tour” operations that intentionally make available an ayahuasca experience as part of a travel package for those seeking “spiritual awakening” and/or have adventurous curiosity about the Amazon” (Halpern, 2004). The internet also has abundant information about how to buy the components and prepare ayahuasca tea (e.g., http://www.a1b2c3.com/drugs/aya_01.htm).

29. Dr. Halpern states (p. 9) that “absent direct evidence that the daime is a serious health risk, ... there appears to be no scientific or medically valid reason to prohibit its ingestion ...” However, (1) in the medical model described above, the onus is on the appropriate scientific and medical institutions to demonstrate positive reasons to introduce a drug into society (i.e., a favorable benefit to risk ratio and advantages over current therapies), rather than to demonstrate an apparent lack of reasons to prohibit the introduction of the drug, and (2) my report details several such serious health risks.

V. Dr. Frankenheim's comments regarding documents produced by Plaintiffs

30. Attached as Appendix B is "Practical Guidelines." While the lists of prohibited foods and drugs are extensive, they are not complete. A more complete list is provided in this report (12.b.i.), but the main point is that extensive training (not just a simple listing) by a physician and other medically-qualified personnel needs to be provided to patients who require MAO inhibitors, and these patients must be carefully selected as needing such medications and being able to comply with difficult dietary, dietary supplement, and pharmaceutical restrictions. Please also see 12.b.ii.

31. Attached as Appendix C is entitled "Prescription Drugs Having Possible Interactions with the Tea."

a. Legend 3 states "If the drug [referring to certain antidepressant medications] is being taken in small or medium dosages the risk of interaction with the tea is less significant and the tea can be administered. In all cases the participant must be closely watched and assisted." However, (1) some patients may be unable to determine the relative dosages of their medications, (2) many patients take multiple prescription drugs, along with non-prescription drugs, and herbal preparations, which greatly complicates this issue, (3) the risks are the serotonin syndrome, which is difficult even for a physician to diagnose quickly, and hypertension, which can not be seen by the unaided eye, so it is unlikely that the watchers and assistants can provide adequate care in a crisis, and (4) if the watchers and assistants are not medically-qualified, it appears they are given a task outside their qualifications.

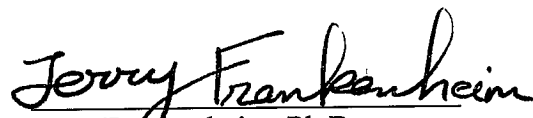
b. Buspirone (which has numerous brand-names) is a serotonin receptor agonist that has been associated with the serotonin syndrome (12.a.). Buspirone differs from other anxiolytics in this respect, but, in exhibit 8, it has the same legend, number 1 ("The presence of these substances in the body together with the tea is not risky") as the other anxiolytics. This may be an error in the exhibit; if so, confidence in the usefulness of the list is diminished.

c. The interactions of ayahuasca with drugs that inhibit vomiting (supposed to limit ayahuasca toxicity; see section 17.a.) appear not to have been taken into account. Even when

such a drug is listed (e.g., prochlorperazine), the legend (number 4 in this case) refers to a problem other than inhibition of vomiting.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

DATED: December 4, 2008


Jerry Frankenheim, Ph.D.