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Ayahuasca: Risks to Public Health and Safety

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I. Ayahuasca

This document describes the risks of ayahuasca to public health and safety by identifying its adverse effects and any other relevant available information. Because ayahuasca is a concoction (described below) and there is no unified and standardized formula for its preparation, evaluation of its adverse health risks is challenging. In addition, there are a limited number of relevant and well-controlled scientific studies that evaluate the safety and pharmacological effects of ayahuasca, and, of the studies that exist, each study uses a different concoction of ayahuasca. Therefore, in this document the risks of ayahuasca and its main constituents (N,N-dimethyltryptamine (DMT) and the β-carbolines) alone and in combination with each other and/or other substances, to the extent possible, have been evaluated. Using this approach, a more comprehensive evaluation of ayahuasca can be achieved.

A. Background

Ayahuasca is a tea made from brewing a mixture of plants that typically contains the known psychoactive substance, DMT and β-carboline alkaloids such as harmine, harmaline, or tetrahydroharmine (Rivier and Lindgren, 1972; Ott, 1996, 1999; DEA, 2001, 2005; McKenna, 2004; Callaway, 2005; Herraiz *et al.*, 2010; Barbosa *et al.*, 2012; Dominguez-Clave *et al.*, 2016). The plants *Psychotria viridis* (which contains DMT) and *Banisteriopsis caapi* (which contains the β-carboline alkaloids − harmine, harmaline, tetrahydroharmine, *etc.*) are the most common plants used in the ayahuasca admixture. However, other plants such as *Peganum harmala* (*P. harmala*), *Diplopterys cabrerana*, and *Psychotria carthagenensis* that also contain these substances (DMT or β-carboline alkaloids) have also been used.

There is no standard ayahuasca preparation. Ayahuasca is a concoction that can be prepared differently depending upon the individual or organization. Variabilities in ayahuasca admixtures can also be attributed to factors such as the cultivation, harvesting, botanical and cooking processes, the species and regional source of plants, and the amount of the plants used (regional variants) (Rivier and Lindgren, 1972; McKenna *et al.*, 1984, 2004; Liwszyc *et al.*, 1992; Ott, 1996; Callaway, 2005; Gaujac *et al.*, 2012; Lanero *et al.*, 2015; Dominguez-Clave *et al.*, 2016; Santos *et al.*, 2017; da Motta *et al.*, 2018). For these reasons, variations in the concentrations of the typical active constituents (DMT, β-carboline alkaloids, *etc.*) in each ayahuasca concoction as

well as other psychoactive constituents are expected. Besides the common components usually found in ayahuasca brews as described above, other psychoactive substances such as nicotine, cocaine, atropine, scopolamine, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), 5-OH-DMT (bufotenine) and caffeine have been found in brews of ayahuasca (Ott, 1993, 1999; Balíková, 2002; Mckenna, 2004; Warren, 2004; Sklerov *et al.*, 2005).

Ayahuasca is used by indigenous tribes around the world and by members of modern syncretic religious groups abroad and in the United States (Rivier and Lindgren, 1972; Grob *et al.*, 1996; Mckenna, 2004; Doering-Silveira *et al.*, 2005; Trichter, 2010; Dominguez-Clave *et al.*, 2016). Its use has also been reported in drug tourism industries (De Rios, 1994; Winkelman, 2005; Trichter, 2010; Bauer, 2018). The frequency of use of ayahuasca by the syncretic religious groups differs (Grob *et al.*, 1996; Mckenna, 2004; Doering-Silveira *et al.,* 2005; Dominguez-Clave *et al.*, 2016). According to published reports, ayahuasca is used from two times per month to several times per week by church members (Rivier and Lindgren, 1972; Grob, 1996; Gable, 2007). Participants in these ceremonies normally consume 50 - 200 millimeters (ml) of ayahuasca per session (Rivier and Lindgren, 1972; Callaway, 2005; Gable, 2007; McKenna *et al.*, 1984, 2004; Callaway and Grob, 1996). For example, in a ceremony, only one dose (~ 50 - 200 milliliters) of the brew may be ingested by a participant; however, other participants may consume several doses (over different sessions) during the course of the same ceremony which may last from four to 12 hours. In addition to the amount of ayahuasca ingested, the manner of consumption of ayahuasca can also vary between or within groups. In some ceremonies, ayahuasca has been reported to be consumed by the participant while singing and dancing, while in other ceremonies, the users remain seated in a relaxed position (Rivier and Lindgren, 1972; Barbosa *et al.*, 2016). The manner of ayahuasca use in drug tourism industries seems diverse. These manners and frequencies of consumption play a role in the pharmacological effects of ayahuasca.

B. Control Status of Ayahuasca

DMT was controlled as a schedule I substance when the Controlled Substances Act (CSA) was enacted in 1970. Substances in schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. Because ayahuasca contains DMT, the manufacture, possession, *etc.* of ayahuasca is illegal under the CSA unless exempted. Any person who handles (manufacture, distribute, import, export, engage in research, or possess) DMT, including DMT found in ayahuasca preparations (unless exempted), in a manner not authorized by the CSA is unlawful and those in unlawful possession of any quantity of this substance may be subject to prosecution pursuant to the CSA.

II. Pharmacological Effects of Ayahuasca and Its Constituents

The pharmacology of ayahuasca is based on the individual constituents of the ayahuasca brew (DMT, β-caboline, *etc.*) as well as the interactions of those constituents with each other and with exogenous (*e.g.,* foods and medications) or endogenous substances in the human body. Thus, because ayahuasca is a concoction or admixture of substances, knowledge about the pharmacological effects of ayahuasca comes from studies on the effects of ayahuasca as well as the primary constituents of the admixture - DMT and β-carboline substances (Mckenna, 2004; Strassman *et al.*, 1996; Freedland and Mansbach, 1999). In this section, scientific reports concerning the pharmacological effects of DMT and β-carbolines (the common constituents that make ayahuasca), and also those of ayahuasca were reviewed and are described. Information taken into account and described in this report was obtained from studies in animals and humans. Human studies include both clinical studies and long-term epidemiological studies which rely on self-reported drug use. Occasionally, preclinical laboratory studies evaluated DMT and β-carbolines, the constituents of ayahuasca. In those studies, the effects of DMT and β-carbolines were extrapolated to humans.

Overview of Ayahausca's pharmacological effects

Ayahuasca has been reported to produce visual and auditory hallucinations such as dreams with complex scenes like near-death experiences, modifications of external stimuli like music, and altered states in subjects (Rivier and Lindgren, 1972; Callaway *et al.*, 1999; Riba *et al.* 2001, 2003; Dos Santos and Strassman, 2011). Adverse health effects (*see* Section III) such as hyperthermia, cardiotoxicity, ataxia, seizures, and coma have been reported for ayahuasca (Callaway *et al.*, 1999; Riba *et al.* 2001, 2003; Dos Santos and Strassman, 2011; Szmulewicz *et al.*, 2015). The DMT, a schedule I hallucinogen, in the ayahuasca admixture, is reported to be responsible for the subjective effects (such as visual hallucinations and illusions, distortions of spatial perception and body image, disturbances of thought and speech, and euphoria) of ayahuasca. β-carboline alkaloids, also commonly found in ayahuasca preparations, are monoamine oxidase (MAO) inhibitors that protect DMT from degradation in the liver and the gut so that DMT in systemic circulation can cross the blood-brain barrier to exert its effects on the central nervous system (Ott, 1999; McKenna *et al.*, 1984).

DMT

DMT, one of the main psychoactive ingredients in the ayahuasca admixture, has been identified in the leaves of the *Psychotria viridis*, *Diplopterys cabrerana*, and *Psychotria carthagenensis* plants (Rivier and Lindgren, 1972; McKenna *et al.*, 1984; Riba *et al.*, 2003; McKenna, 2004; Gaujac *et al.*, 2012; McKenna and Riba, 2017). DMT is also a naturally occurring (*i.e.*, endogenous) substance found in the central nervous system (CNS) of living organisms (*e.g.*, rodents and humans) but its functional role as an endogenous substance has not yet been elucidated (Christian *et al.*, 1976, 1977; Smythies *et al.*, 1979; Barker *et al.*, 2012; Carbonaro and Gatch, 2016). Although the role of endogenous DMT in the body is not clear, it has been reported to interact with a

variety of biological systems (serotonin, glutamate, dopamine, acetylcholine, sigma-1, and trace-amine receptors) (Fantegrossi *et al*., 2008; Araújo *et al*., 2015; Carbonaro and Gatch, 2016).

As mentioned above, DMT has been found in small concentrations in rodents and humans (Christian *et al.*, 1976, 1977; Smythies *et al.*, 1979; Barker *et al.*, 2012; Carbonaro and Gatch, 2016). However, endogenous concentrations of DMT in human urine or blood samples are reported to be substantially lower than the concentrations of DMT in individuals (urine or blood samples) after being given a psychoactive dose of DMT (0.7 mg/kg intramuscular (*i.m.*)). This suggests that endogenous concentrations of DMT are not likely to be primarily responsible for the psychedelic effects of exogenous DMT (Mandel, 1974; Wyatt *et al.*, 1974; Gillin *et al.*, 1976; Gillin and Wyatt, 1976; Barker *et al.*, 2012).

Considerable evidence indicates that DMT is responsible for the hallucinogenic effects of ayahuasca (Boszormeny and Szára, 1958; Strassman *et al.*, 1994; Nichols, 2004; Cakic *et al.*, 2010; Tittarelli *et al.*, 2015). This is because DMT, on its own, has been demonstrated to produce hallucinogenic effects in humans that are similar to effects observed in individuals after ingesting ayahuasca. The most predominant effects reported in a survey[1] of lifetime recreational DMT users were meaningful or insightful experiences, spiritual experiences, euphoria, intense visual hallucinations, bad taste or coughing, psychospiritual distress, and anxiety (Cakic *et al.*, 2010). Similarly, results from several well-controlled clinical studies (described below) show that DMT (0.05 – 0.4 mg/kg) produces effects like those reported in the above mentioned survey study (Szára, 1956; Boszormenyi and Szára, 1958; Gillin and Wyatt, 1976; Gillin *et al.*, 1976; Strassman *et al.*, 1994; Strassman and Qualls, 1994; Gouzoulis-Mayfrank *et al.*, 2005, 2006). In a clinical study by Szára (1956) of 30 healthy individuals, the effects reported following the intramuscular administration of DMT (0.7 and 1.0 mg/kg) were found to be similar to those produced by the schedule I hallucinogens mescaline and lysergic acid diethylamide (LSD) (Szára, 1956; Wyatt *et al.*, 1974). The psychoactive effects of DMT described in this and in another subsequent study were visual hallucinations and illusions, distortions of spatial perception and body image, disturbances of thought and speech, anxiety, disturbances in mood and perception, loosened associations, and euphoria (Szára, 1956; Boszormenyi and Szára, 1958). In comparison, LSD and mescaline have been reported to produce many of these same effects (Isbell *et al.*, 1956; Szára, 1956). In a double-blind, randomized study of intravenously (*i.v.*) administered DMT (0.2 and 0.4 mg/kg), subjects experienced visual hallucinations, bodily dissociation, extreme shifts in mood, and auditory hallucinations (Strassman et *al.*, 1994). In yet another clinical study using 15 healthy volunteers, DMT (0.15 – 0.3 mg/kg, *i.v.*) produced powerful alterations of visual and auditory perception, illusions,

[1] 121 lifetime DMT users were recruited and answered a self-administered online questionnaire regarding patterns of drug use, subjective effects and attitudes towards DMT and other drug use.

abnormal somatic sensations, paranoid ideation, visual and auditory hallucinations, and positive formal thought disorder (*i.e.*, loosening of associations, derailment and distractibility) (Gouzoulis-Mayfrank *et al.*, 2005, 2006). In addition, DMT has been demonstrated to induce psychosis in an individual with no psychiatric history (Paterson *et al.*, 2015). Ayahuasca has also been shown to produce psychoactive effects similar to those observed following the administration of DMT. In a clinical study using ayahuasca, 28 individuals were recruited to participate in an authentic ayahuasca ceremony and were assessed before and after the ceremony (Barbosa *et al.*, 2005). Recruited individuals predominately experienced visual phenomena, numinousness (described as a mixture of terror and fascination, which results from the sense of a superior and powerful presence), peacefulness, insight, alterations in self-body image, and a distressing reaction (described by Barbosa et al., (2005) as an overwhelming affliction due to an experience of "being imposed" an ideation of a "prophecy" of an imminent personal tragedy; the prophecy was attributed to a supposed "superior self," which was a previously expected spiritual latency; idiosyncratically considered as part of the superior self, the ritual events were interpreted as an irrefutable confirmation of the prophecy). Thus, studies show that the effects of DMT are like those of LSD and mescaline which are also like the ones experienced by those who ingest ayahuasca. Hence, there is evidence that the hallucinogenic effects of ayahuasca are mediated by DMT.

Further support of DMT's role in the hallucinogenic effect of ayahuasca is that DMT, similar to classical hallucinogens LSD and mescaline, produces its effects through activation of the serotonin receptor (5-HT) (Glennon *et al.*, 1980, 1994; Titeler *et al.*, 1988; Pierce and Peroutka, 1989; Sadzot *et al.*, 1989; Nichols and Sanders-Bush, 2001; Nichols, 2004; Tittarelli *et al.*, 2015; Winstock *et al*., 2014). Many other schedule I hallucinogens such as 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-bromoamphetamine (DOB), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-ethylamphetamine (DOET), 5-methoxy-diisopropyltryptamine (5-MeO-DiPT, foxy methoxy), psilocin, 5-methoxy-dimethyltryptamine (5-MeO-DMT) are believed to produce hallucinogenic effects through activation of serotonin receptors, specifically the 5-HT_{2A} receptor (Glennon *et al.*, 1980, 1994; Titeler *et al.*, 1988; Pierce and Peroutka, 1989; Sadzot *et al.*, 1989; Nichols and Sanders-Bush, 2001; Nichols, 2004; Tittarelli *et al.*, 2015). Hence, DMT belongs to the same class of schedule I substances that produce its hallucinogenic effects via the serotonin receptor.

DMT is orally inactive if ingested alone, but if ingested in the presence of an MAO inhibitor, such as a β-carboline (another ingredient found in ayahuasca preparations), it is orally active (McKenna, 2004; Haroz and Greenberg, 2005; Titarelli *et al.*, 2015; Domingues-Clave *et al.*, 2016). DMT is also psychoactive when taken by other routes of administration such as by inhalation (via smoking), intravenous, intramuscular, and subcutaneous routes. Using these other routes of administration, co-administration of a MAO inhibitor is not necessary for DMT to be psychoactive. Routes of administration of DMT for recreational use has been reported to include oral ingestion and inhalation (smoking and vaporizing) (Mckenna, 2004; Cakic *et al.*, 2010; Tittarelli *et*

al., 2015; Carbonaro and Gatch, 2016). Not including its use in ayahuasca, smoking is the most common method of administering DMT (Winstock *et al.*, 2014; Lawn *et al.*, 2017).

For a drug to be psychoactive, it needs to 1) reach the brain in sufficient concentrations and 2) produce an effect. The pharmacokinetic properties[2] of a given substance influence the ease and extent, and thus, the amount of that substance that can reach the brain to produce its effects. For DMT, the route of administration along with the co-administration of other substances highly influences its pharmacokinetic properties. Thus, the doses of DMT that are required for experiencing psychoactive effects are dependent upon, for one, the route of administration because the route of administration is one of the factors that influence the pharmacokinetics of a drug and ultimately the amount of drug that can reach the brain to exert its effects (Katzung, 1992). Smoking and inhalation routes of administration increase the bioavailability (the amount of substance that enters the circulatory system when administered and is able to have an active effect in the body) of consumed substances compared to oral consumption (Lanero *et al.*, 2015). Some other factors that can affect the pharmacokinetics of a drug include genetic disposition, food consumption, drug interactions, and medical history. Table 1 lists reported doses of DMT that have been found to be psychoactive by different routes of administration.

Measurements that are reflective of the pharmacokinetic properties of a given substance include onset and duration of its effects and peak effect. Generally, the effects of DMT (*see* Table 2) begin almost immediately, peak within minutes, and usually completely resolve within 30 to 60 minutes (Szára, 1956; Gillin and Wyatt, 1976; Gillin *et al.*, 1976; Wyatt *et al.*, 1974; Mandel, 1974; Strassman and Qualls, 1994; Strassman *et al.*, 1994, 1996; Barker *et al.*, 2012; Tittarelli *et al.*, 2015; Carbonaro and Gatch, 2016).

Table 1: Psychoactive Doses of DMT* are Dependent on the Route of Administration

Route of Administration	Minimum Effective Dose	Minimum Effective Dose by Weight
oral†	~30 mg	0.3 mg/kg
intramuscular	60 – 100 mg	0.2 mg/kg
subcutaneous	60 – 100 mg	
smoked	60 – 100 mg; 40 – 50 mg freebase	
inhalation	15 – 60 mg; 40 – 50 mg freebase	0.4 mg/kg freebase
intravenous	4 – 30 mg	0.2 mg/kg

*Wyatt *et al.*, 1974; Gillin *et al.*, 1976; Strassman *et al.*, 1996; Shulgin and Shulgin, 1997; Ott, 1999; Gable, 2007; Szára, 2007; Tittarelli *et al.*, 2015; Carbonaro and Gatch, 2016
†ingested as ayahuasca; effective dose with a MAO inhibitor

β-Carbolines

β-Carbolines, the other common ingredients in ayahuasca, have been identified

[2] Pharmacokinetics is used to describe the absorption, distribution, metabolism and elimination of a substance in the body.

in the vine *Banisteriopsis caapi* (*B. caapi*) which is one of the plants frequently identified in ayahuasca concoctions (Rivier and Lindgren, 1972; McKenna *et al.*, 1984; Callaway, 2005; Frison *et al.*, 2008; Gaujac *et al.*, 2012). β-carbolines have also been identified in the seeds of the *Peganum harmala* (*P. harmala*) plant (Rivier and Lindgren, 1972; Ott, 1996; Frison *et al.*, 2008; Gaujac *et al.*, 2012). Small concentrations (nanograms) of β-carbolines have also been found in food, notably meats or foods that are cooked at higher than typical cooking conditions (Lavita *et al.*, 2016).

The use of β-carbolines alone as recreational substances is not well recognized. However, one can find in the scientific literature cases where β-carbolines (seeds or plants that contain β-carbolines) have been used for homeopathic purposes or as an herbal medicine (Ben Salah *et al.*, 1986; Frison *et al.*, 2008; Yuruktumen *et al.*, 2008). In these circumstances, it was reported that the ingestion of β-carbolines (*i.e., P. harmala*) produced adverse or toxic health effects (*see* Section III).

As explained previously, β-carbolines are MAO inhibitors, but β-carbolines have a wide range of other pharmacological effects besides its MAO inhibitor effects (McKenna *et al.*, 1984; McKenna and Towers, 1984; Ott, 1999; Khan *et al.*, 2001; Mckenna, 2004; Herraiz *et al.*, 2010; Lavita *et al.*, 2016). For example, studies show that β-carbolines are cytotoxic to tumor cell lines suggesting their potential anti-tumor or anti-cancer effects (Lamchouri *et al.*, 2000, 2002, 2013). There are also claims that β-carbolines may be useful therapeutic agents for the treatment of asthma, diarrhea, diabetes, hypertension, jaundice, syphilis, fever, hysteria, malaria, neuralgia, parkinsonism, rheumatism, colic, asthma and eye complaints (Lamchouri *et al.*, 2000, 2002, 2013; Khan *et al.*, 2013; Cakic *et al.*, 2016; Dos Santos *et al.*, 2016; Sanches *et al.*, 2016). There have been some positive results for using β-carbolines in the treatment of hypothermia and as an anti-parasitic agent in animals (Khan *et al.*, 2013). However, there are not enough scientifically valid and reliable data or well-controlled studies to support all of these therapeutic claims. On the contrary, the proposed use of β-carbolines as an experimental model of toxicity in animals to induce and study essential tremor (a neurological movement disorder characterized by involuntary tremor of the arms, head, and/or voice) and its potential use as an anti-cancer agent demonstrate their cytotoxic effects (Lamchouri *et al.*, 2000, 2002, 2013; Handforth, 2012; Lavita *et al.*, 2016).

Ayahuasca

A number of published studies describe the subjective effects of ayahuasca in humans. In clinical studies, ayahuasca preparations have been shown to produce psychoactive effects similar to those observed following the administration of DMT (Rivier and Lindgren, 1972; Grob *et al.*, 1996; Callaway *et al.*, 1999; Riba *et al.*, 2001, 2003; Barbosa *et al.*, 2005; Fabregas *et al.*, 2010; Schenberg *et al.*, 2015; Soler *et al.*, 2016). Similar effects were also reported by ayahuasca users in a large, international, self-selecting online survey (Lawn *et al.*, 2017). Some of these studies are described below.

In a controlled clinical study of non-religious users, 20 healthy volunteers with a history of drinking ayahuasca in non-religious settings reported experiencing changes in

their state of consciousness, visual perceptions, heightened sensitivity, alterations in time and space, increased imagination, introspection and emotional arousal after drinking ayahuasca tea (donated by the União do Vegetal church; *see* Table 3 for details) (Schenberg *et al.*, 2015). Riba *et al.* (2001) reported similar results in a study of six healthy male volunteers with prior ayahuasca experiences. Oral administration of ayahuasca (donated by the Daime church; *see* Table 3 for details), similar to DMT, produced visual and auditory hallucinations such as dreams with complex scenes like near-death experiences, modifications of external stimuli like music, and altered states in subjects. Ayahuasca also induced introspective states such as reflections on personal issues and insights into person concerns, intense emotions, and emotional memories.

The pharmacokinetic properties of ayahuasca (*see* Table 2), which contains a mixture of drugs, are more complex than DMT alone because the pharmacokinetic properties of one drug in a mixture can affect the pharmacokinetic properties of another drug in a mixture and each substance in this mixture can vary in their pharmacokinetic activities (also *see* Section I). Thus, the number and amount of psychoactive substances in the ayahuasca brew that reaches the brain to exert effects vary. Like DMT, there are studies in which the pharmacokinetic parameters (*i.e.*, onset of effects, duration of effects, concentrations in biological samples) of ayahuasca in humans have been evaluated and described (Strassman and Qualls, 1994; Strassman et *al.*, 1994; Grob *et al.*, 1996; Riba *et al.*, 2001, 2003; McKenna, 2004; Cakic *et al.*, 2010; Carbonaro and Gatch, 2016; Domingues-Clave *et al.*, 2016). Ayahuasca taken in a ceremonial setting is usually consumed orally over several hours. Studies show that the onset of ayahuasca hallucinations usually begins around 30 to 60 minutes after ingestion, peaks between 1.5 and 2 hours and last for 3 to 4 hours. Similarly, a large, international, self-selecting online survey of ayahuasca users reported that the median duration of effect was 6 hours and the time to peak effects was 1 hour (Lawn *et al*., 2017). Studies also show that, like DMT, the intensity of the effects of ayahuasca are dependent upon the dose of DMT in the ayahuasca admixture (Riba *et al.*, 2001, 2003; Domingues-Clave *et al.*, 2016). Hence, it is anticipated that ayahuasca admixtures that have high doses of DMT will produce more intense pharmacological effects than admixtures that have lower doses of DMT. Thus, the pharmacokinetic properties of ayahuasca, like DMT, can be affected by many factors including the psychoactive constituents, the amount of those constituents, and the route of administration.

Table 2: Pharmacokinetic parameters of DMT and Ayahuasca (Based on clinical studies)

Pharmacokinetic parameter	DMT (*i.v.*)*†	DMT (oral) ¥	DMT (smoked)§	Ayahuasca (oral) †‡
Onset of effects	2 min	none	2 – 5 min	20 – 60 minutes
Peak effects	3 – 10 min	none	within 5 min	1 – 2 hrs
Duration of effects	30 – 60 min		20 - 60 min	2 – 4 hrs

*Strassman and Qualls, 1994

†Gable *et al.*, 2007

‡Rivier and Lindgren, 1972; Riba *et al.*, 2001, 2003; Yrita *et al.*, 2002

¥Riba *et al.*, 2015 (30 mg DMT extracted from *Mimosa tenuiflora* w/o MAO inhibitor; only one participant experienced subjective effects which was rated 1 out of the highest intensity of 10)

§Haroz and Greenberg, 2005; Winstock *et al.*, 2014; Paterson *et al.*, 2015

Conclusion

Overall, ayahuasca exhibits a pharmacological profile similar to that of DMT although other psychoactive constituents like β-carbolines in the ayahuasca brew may have a contributory role. Ayahuasca, similar to DMT and other schedule I hallucinogenic substances, has been reported to produce hallucinogenic effects (visual and auditory hallucinations), spiritual experiences, euphoria, psychospiritual distress, alterations of visual and auditory perception, illusions, and abnormal somatic sensations. The hallucinogenic effects of DMT and ayahuasca are believed to be primarily through activation of the serotonin receptor. Evidence shows that the pharmacokinetic properties (*i.e.*, absorption, distribution, metabolism and elimination) of ayahuasca are affected by the route of administration (*see* Table 2). While β-carbolines are also significant ingredients in ayahuasca, how β-carbolines contribute to the ayahuasca experience, beyond their effects as MAO inhibitors, is not clear. Other psychoactive constituents in the ayahuasca brew may also play a role in the overall effects of ayahuasca. Thus, the overall physical, subjective, and psychological effects of ayahuasca depend upon many factors including those that affect the pharmacokinetics (e.g., route of administration, genetic disposition, and food consumption) of all the active substances in the ayahuasca brew.

III. Risks of Ayahuasca and its Constituents to Public Health and Safety

As mentioned previously, ayahuasca is an admixture of substances, so knowledge about the risks of ayahuasca to public health and safety comes from studying the effects of ayahuasca as well as the individual substances in the admixture such as DMT and β-carboline substances (Mckenna, 1996, 2004; Strassman *et al.*, 1996; Freedland and Mansbach, 1999). In this section, scientific reports concerning the risks or adverse health effects of DMT and β-carboline substances (the common constituents of ayahuasca) and ayahuasca are reviewed and described, including their physical, psychological and societal adverse effects, if available. Information was obtained from laboratory-controlled studies which include *in vitro* and *in vivo* animal studies, clinical studies (of which many were not well-controlled) and clinical case reports (reports of the diagnosis, prognosis, results, and treatment of individuals who reported to the emergency department after ingesting harmful substances). Long-term epidemiological studies of DMT and ayahuasca in humans relying on self-reported drug use is also taken into account and described here. Occasionally, *in vivo* or *in vitro* laboratory studies that used ayahuasca's constituents, DMT and β-carbolines, in determining the health risks and safety of these substances on individuals are also reviewed and described in this section. From these studies, the overall risks of ayahuasca to public health and safety can be extrapolated from the risks of DMT and β-carbolines.

A. Overview

Based upon the existing information, ayahuasca presents a significant risk to public health and safety. As discussed previously, the route of administration of a substance highly influences the amount of that substance that reaches the brain to

exert its effects. In religious ceremonies, ayahuasca is typically ingested like a tea. This manner of consumption of ayahuasca can limit the amount of psychoactive or toxic substances including DMT that may reach the brain and, subsequently, produce adverse health effects. However, there is no standard ayahuasca preparation. As mentioned previously, the variations in the preparation, cultivation, and consumption of ayahuasca as well as its constituents affect the amount of toxic substances and psychoactive substances in each ayahuasca concoction and will differ with each preparation. Thus, what psychoactive or toxic substances reach the brain after ingesting ayahuasca and the concentrations of those substances are unknown and will vary depending upon to the preparer. Consequently, despite claims that ayahuasca is safe, the use of ayahuasca has been associated with moderate cardiotoxicity, neurotoxicity, psychopathology, transient disorientation, anxiety, coma and death.

B. Adverse Health Effects

As detailed below in this section, data from poison control centers and anecdotal information (*i.e.,* case and media reports) indicate that users have experienced adverse health effects following the administration of β-carbolines, DMT or ayahuasca. Clinical reports also indicate that ayahuasca, DMT, and β-carboline substances have produced adverse health effects and individuals have presented at emergency departments (EDs) following exposure to these substances or infusions that contain these substances. Furthermore, preclinical pharmacology studies show that ayahuasca or its psychoactive components, DMT and β-carbolines, have the potential to produce mild to severe adverse health effects.

Poison control data

Poison control data indicate that individuals are using ayahuasca or DMT and adverse health effects are being reported (Heise and Brooks, 2016; DEA, 2017). According to the American Association of Poison Control Centers (AAPCC) [3, 4] data as reported by Heise and Brooks (2016), there were 538 human exposure calls related to ayahuasca botanical products between September 1, 2005 and September 1, 2015.

[3] The AAPCC is a non-profit, national organization that represents the poison centers of the United States. Poison centers receive calls from individuals who come into contact with dangerous or potentially dangerous substances or health care facilities (*i.e.*, doctors and nurses) that want information related to poisoning cases and offer free, confidential, expert medical advice through Poison Help Line and online services.

[4] AAPCC (http://www.aapcc.org) maintains the national database of information logged by the country's poison centers (PCs). Case records in this database are from self-reported calls. They reflect only information provided when the public or healthcare professionals report on actual or potential exposure to substance (e.g. an ingestion, inhalation, or topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

Exposure calls refer to actual or potential human exposure to ayahuasca (*e.g.,* inhalation, ingestion, topical exposure). Over the ten-year period, the exposure calls increased annually until they peaked in 2012. Subsequently, there was a gradual reduction in calls in the following two successive years. Forty-eight percent (258) of the patients related to these calls were treated and released, 17% (92) of patients required admission to the intensive care unit (ICU)/critical care unit, and 11% (58) required treatment in a semi-intensive care unit/ non-critical care unit (Heise and Brooks, 2016; De Pablo *et al.*, 2017). Six percent (33) were medically cleared and admitted to a psychiatric unit and 18% (97) were lost to follow-up or not reported. Of the total number or exposure cases, mechanical ventilation treatment (*i.e.*, intubation) was provided on 5% (28) of the exposure cases. Respiratory (7) and cardiac arrest (4) were each reported in 1% of the exposure cases. Heise and Brooks (2016) also reported that 7% (41) of exposure calls relevant to ayahuasca were noted to have major[5] clinical manifestations and 55% (296) were noted to have moderate[6] clinical manifestations. The clinical effects most reported included hallucinations, agitation, tachycardia, confusion, hypertension, mydriasis, and vomiting. The most severe effects reported by these authors included seizures, respiratory arrest, and cardiac arrest.

An independent analysis of AAPCC data that was procured by the DEA also identified exposure calls related to ayahuasca or DMT (recreational use) (DEA, 2018). According to this review of all exposures to ayahuasca or DMT registered with the AAPCC between September 2012 and December 2017, poison centers throughout the United States received at least 341 exposure calls regarding ayahuasca and 122 exposure calls regarding DMT. A majority of the calls (286, 84%) regarding ayahuasca came from health care facilities, but the exposure site (267, 78%) was most often at the caller's residence. Of the total number of exposure calls regarding ayahuasca, 196 (57%) involved only ayahuasca; 81 (24%) involved two substance (one being ayahuasca), 35 (10%) involved three substances, and 29 (9%) involved more than 3 substances. The adverse health effects most often affiliated with exposure calls related to ayahuasca included cardiotoxicity (tachycardia and hypertension), hallucinations/ delusions, agitation, confusion, drowsiness/ lethargy, mydriasis, elevated creatine phosphokinase (CPK) levels, nausea and vomiting supporting theories that the clinical effects of ayahuasca mirror those of DMT. In comparison, the adverse health effects most often affiliated with exposure calls related to DMT included cardiotoxicity (tachycardia and hypertension), hallucinations/ delusions, agitation, confusion mydriasis and elevated CPK levels. Respiratory (6, 2%) and cardiac (3, 1%) arrest were also reported for

[5] The patient exhibited symptoms as a result of the exposure which are life-threatening or resulted in significant residual disability or disfigurement.

[6] The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability of disfigurement.

exposure calls associated with ayahuasca. The medical outcomes of the exposure cases (ayahuasca) were 54 (16%) with minor[7] effects, 200 (59%) with moderate effects[6], and 27 (8%) with major effects (*see* footnote 5 above). Like reported with Heise and Brooks (2016), in 5% of the 341 cases involving ayahuasca, patients were treated with intubation (17) or a ventilator (16). Sixty-five (19%) of the calls led to admissions to critical care units and 49 (14%) to admissions to noncritical care units. However, for the majority of the calls (163, 48%), patients were treated/evaluated and released.

These analyses of poison control data demonstrate that individuals are using ayahuasca or DMT and adverse health effects are being reported following exposure to DMT or ayahuasca containing products. It should be noted that there was no drug testing that verified the use of ayahuasca or the use or involvement of other drugs for these exposure calls. Nonetheless, AAPCC data provides useful information regarding poisoning trends in the United States.

Clinical studies and case reports reported by medical staff or scientific researchers

Clinical reports indicate that ayahuasca, DMT, and β-carboline substances have produced adverse health effects and individuals have presented at emergency departments (EDs) following exposure to these substances or infusions that contain these substances. Adverse health effects include feeling-unwell, anxiety, hallucinations, cardiovascular toxicity, tremor, mania and psychotic symptoms. Listed below are the adverse health effects reported in clinical studies (*i.e.*, controlled studies) or case reports ((incidents of adverse effects as described by medical staff or scientific researchers) after the ingestion of DMT, β-carbolines, or ayahuasca.

Adverse health effects have been associated with the administration of DMT (Strassman and Qualls, 1994). In a double-blind, randomized study of 11 experienced hallucinogen users, DMT (0.2 and 0.4 mg/kg, *i.v.*) administration increased pupil diameter, heart rate, and mean arterial blood pressure. These effects peaked at about 2 minutes which paralleled with the time course of the peak psychedelic effects. Higher doses produced significant visual hallucinations and auditory distortions. Transient anxiety was common but was usually replaced by euphoria.

Adverse health effects have been associated with the administration of β-carbolines (Ben Salah *et al.*, 1986; Frison *et al.*, 2008; Yuruktumen *et al.*, 2008). Ben Salah *et al.* (1986) described the case of a 27-year-old female who was prescribed *Peganum Harmala* seeds to treat a medical condition. Following ingestion, the individual experienced a severe headache, tingling of the extremities, visual and audio disturbances, visual hallucination, and abdominal pain with vomiting. After several hours, all the symptoms resolved. The substance that the individual ingested was

[7] The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement.

analytically determined to contain *P. harmala* which contain β-carbolines. Frison *et al.* (2008) described the case of a 25-year-old male who was admitted to the ED after ingesting a "rue" he made from seeds purchased from the Internet. This individual presented to the ED experiencing psychomotor agitation, visual hallucinations, diffuse tremors, ataxia and vomit. He was unable to stand upright, and exhibited nystagmus, tremor, and a lack of coordination. A toxicological screen of the individual's urine identified the β-carbolines: tetrahydroharmine, harmaline, and harmine. Laboratory analysis of the seed infusion also identified these substances. Blood samples for routine drugs as well as DMT and 5-MeO-DMT were negative. The patient was successfully treated and discharged the day after. Yuruktumen *et al.* (2008) described the case of a 41-year-old female who presented at the emergency department after drinking a hot infusion of 100 grams *P. harmala* seeds (10 – 20 times the recommended dose) in water. The patient was unconscious and had hypertension, tachycardia, tachypnea, and elevation of kidney and liver markers. After supportive treatment all of the patients improved. Balíková (2002) described an incident in which 30 individuals aged from 20 – 50 experienced intoxications after participating in a meditation session and drinking an herbal preparation containing an "Amazonian psychoactive agents" later identified as harmine, atropine, and scopolamine. The individuals experienced hallucinations, aggression, agitation, amnesia, mydriasis, dry skin, tachycardia, hyperthermia, hypotension, collapse, coma and respiratory depression. All patients recovered with supportive treatment which in severe cases included mechanical ventilation.

Adverse health effects have been associated with the administration of ayahuasca (Grob, 1996; Callaway *et al.*, 1999; Riba *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2005; Callaway and Dos Santos, 2013; Dos Santos, 2013a, b; Schenberg *et al.*, 2015; De Pablo Márquez, 2017). Nausea and vomiting have been commonly reported after ingesting ayahuasca in non-clinical settings (Grob, 1998; Callaway *et al.*, 1999; Riba *et al.*, 2001; Callaway and Dos Santos, 2013a, b). However, in studies of ayahuasca performed in clinical settings, nausea and vomiting are seldom reported (Gouzoulis-Mayfrank *et al.*, 2005; Dos Santos, 2013a, b; Schenberg *et al.*, 2015). Other adverse health effects associated with the consumption of ayahuasca as reported by users include transient disorientation and anxiety (Riba *et al.*, 2001).

The risk of developing or exacerbating the onset of psychiatric disorders in relation to the consumption of ayahuasca has been described (De Pablo Márquez, 2017*).* A 36-year-old male with previous history of suffering from manic and psychotic symptoms related to the consumption of cannabis reported to the emergency department for behavioral alterations related to the recreational use of ayahuasca. The patient was reported to be hyperactive and insomniac with feeling of well-being and euphoria. A drug test was negative for other drugs of abuse like cocaine, amphetamine, cannabis, and heroin. The author suggested that the risk of developing psychiatric disorders in relation to the use of ayahuasca increases in individuals with a personal and family history of mental illness or psychosis. A different author disputed this causal relationship in this case because DMT and other substances like ketamine, MDMA, and LSD were not measured in biological specimens from this patient; however, this author

did agree that individuals with a personal or family history of any psychotic illness or non-psychotic mania should avoid the ingestion of hallucinogens (Dos Santos *et al.*, 2017).

Adverse effects of ayahuasca reported in the media

In addition, to the clinical reports that implicate ayahuasca in the manifestations of adverse health effects, Dos Santos *et al.* (2013a) and Bauer (2018) reported a number of media reports that were associated with the use of ayahuasca. These media reports show that under the influence of ayahuasca, individuals can be a harmed by others or vulnerable to accidents due to the loss of the perception of reality. For example, an 18-year-old man allegedly died from an ayahuasca overdose during an ayahuasca ritual in Peru. The shaman buried the individual to hide the death. A 33-year-old man suffered convulsions and died after his third ayahuasca ritual. A 40-year-old Swedish man was hospitalized in a coma after taking ayahuasca in Peru. An 18-year-old man drowned after participating in an ayahuasca event. A 39-year-old French man was found dead in a room with many bottles of ayahuasca. A 43-year-old female allegedly died from a heart attack during an ayahuasca ceremony. A 19-year-old male was found dead on the side of the road after feeling unwell at a ceremony. A criminal investigation found that a Shaman had arranged for the 19-year-old man to be taken to the hospital because of feeling unwell during the ceremony but the individual died on route to the hospital and was left on the side of the road. A 35-year-old female felt ill during a ceremony and died. A 41-year-old female was found dead in an ayahuasca ceremony room. These authors stated that these media reports were poorly described and did not confirm that ayahuasca played a causal or contributing role indicating that correlation is not causation. However, the fact that ayahuasca may have played a role in these events is noteworthy.

C. Acute Toxicity

Acute toxicity tests or LD_{50} tests can provide preliminary information on the toxic nature of a substance. LD_{50} values are a way to assess the acute toxicity of a substance. Essentially, the LD_{50} is the median lethal dose or amount of substance that can be expected to cause death in half (*i.e.*, 50%) of a particular animal species, usually rats or mice. In short, it is a way to assess the possible toxicity of a substance to humans. Because there is no standard formulation for ayahuasca and the adverse effects of ayahuasca match those of DMT, this toxicity data is extrapolated from the LD_{50} of DMT. In addition, while the acute toxicity data from β-carbolines substances are important and are described below in animals, its contribution to the toxic effects of ayahuasca is unclear so acute toxicity data for ayahuasca will be primarily limited to data obtained for DMT. Acute toxicity data show that the LD_{50} of oral DMT in humans is estimated to be 8 mg/kg or 560 mg (for a 70 kg human) which is more than 15 to 50 times the dose of ayahuasca taken during a religious ritual (Gable, 2007; Pic-Taylor *et al.*, 2015). The basis for this extrapolation is described below.

DMT – Acute Toxicity

The LD_{50} for DMT in humans (560 mg for a 70 kg human) has been calculated from the LD_{50} in rodents (Gable, 2007; Pic-Taylor *et al.*, 2015). In mice, the LD_{50} of DMT is reported to be 32 mg/kg by intravenous injection (Gable, 2007). If humans are twenty times more sensitive to the effects of drugs than mice then the LD_{50} in humans for intravenous DMT would calculate to be 1.6 mg/kg (*i.e.,* 32 ÷ 20 = 1.6) or 112 mg DMT. Taking into consideration that the doses reported to be "highly" psychoactive are 0.4 mg/kg DMT by intravenous administration and 2.0 mg/kg DMT by oral administration (which is a ratio of 1 (intravenous administration) to 5 (oral)), then the LD_{50} of oral DMT in humans would be calculated to be 8 mg/kg (*i.e.,* 1.6 x 5 = 8) or 560 mg for a 70 kg individual which is more than 15 to 50 times the dose of DMT (~27 mg; *see* Table 1) in ayahuasca taken during a religious ceremony. A preclinical study in rats supports these findings that the lethal oral dose of DMT (via ayahuasca ingestion) was more than 15 to 50 times the dose of ayahuasca taken during a religious ceremony (Pic-Taylor *et al.*, 2015).

β-Carbolines – Acute Toxicity

The LD_{50} of an aqueous extract of *P. harmala* seeds (contains harmine, harmaline, tetrahydroharmine, and other alkaloids) in rats was measured to be 2 g/kg (Gable, 2007; Frison *et al.*, 2008; Lamchouri *et al.*, 2000). Besides LD_{50} data from animal studies, cytotoxicity studies in cell lines show that β-carbolines in the aqueous extract of *P. harmala* seeds are cytotoxic to tumor cell lines (Lamchouri *et al.*, 2000, 2002, 2013). Concentrations of 60 µg/ ml (or 60,000 ng/ ml) of the *P. harmala* seed extract caused 100% cell death to tumor cells (Lamchouri *et al.*, 2000, 2002, 2013).

Ayahuasca – Acute Toxicity

As stated previously, Gable (2007) calculated that more than 20 times the amount of ayahuasca typically used in ceremonial settings would be necessary before ayahuasca reached its lethal dose in humans. Thus, for this and other reasons, supporters of ayahuasca claim that the amount of DMT in ayahuasca preparations used in religious ceremonies is relatively safe. Other reasons that some authors support the claims of safety of ayahuasca include its method of preparation, route of administration, and use in a controlled and monitored setting (Grob *et al.*, 1996; Gable, 2007; Barbosa *et al.*, 2012; Dos Santos *et al.*, 2013a, b; Bouso *et al.*, 2015).

The amount of DMT or other psychoactive substances in the ayahuasca preparation that could reach the central nervous system (CNS) to exert a psychoactive effect is dependent upon several different factors including its route of administration. While it is true that oral ingestions of ayahuasca will limit the CNS DMT concentrations compared to smoking and inhalation routes of administration, there is no standard formulation for ayahuasca; thus, the amount of DMT or B-carbolines in any preparation could be toxic. Therefore, the use of ayahuasca in a religious ceremony or for recreational purposes could result in amounts of DMT that approach the LD_{50} dose and, consequently, may lead to DMT intoxications and/or extreme psychoactive effects.

Table 3: Alkaloid Content of the Main Psychoactive Substances in Ayahuasca or DMT Preparations

Sample Origin	DMT	THH	HRL	HRA	Reference
Religious ceremonies:					
Santo Daime (200ml)	106 mg	278 mg		298 mg	Liwszyc *et al.*, 1992
Santo Daime	41 mg	44 mg	5 mg	56 mg	Don *et al.*, 1998
Santo Daime[§]	106 mg	144 mg	12 mg	180 mg	Riba *et al.*, 2001, 2003
Brazilian	82 mg **(mean)**	154 mg	12 mg	93 mg	Lanero *et al.*, 2015
Peru	60 mg	160 mg	41 mg	467 mg	McKenna *et al.*, 1984
spiritual group	75 mg **(mean)**	89 mg	11 mg	98 mg	Kuyper *et al.*, 2016
spiritual group	43 mg **(mean)**	31 mg	5 mg	21 mg	Kuyper *et al.*, 2016
Culina Indians (Peru)	26 mg	14 mg		34 mg	Rivier & Lindgren, 1972
Sharanahua Indians	20 mg	20 mg	2 mg	36 mg	Rivier & Lindgren, 1972
Clinical studies:					
União do Vegetal	36 mg				Callaway *et al.*, 1999
União do Vegetal	91 mg	356 mg	49 mg	300 mg	Schenberg *et al.*, 2015
Brazilian Daime	39 mg	54 mg	6 mg	67 mg	Riba *et al.*, 2001, 2003
Brazilian Daime	57 mg	77 mg	7 mg	96 mg	Riba *et al.*, 2001, 2003
Brazilian Daime	70 mg				Riba *et al.*, 2001
União do Vegetal	29 mg	128 mg	24 mg	204 mg	Callaway *et al.*, 1996
Brazilian Daime	42 mg	49 mg	4 mg	60 mg	Yrita *et al.*, 2002
Brazilian Daime	60 mg	70 mg	5 mg	68 mg	Yrita *et al.*, 2002
not stated	49 mg[†] (0.7 mg/kg)				Wyatt *et al.*, 1974
synthetic	49 mg[†] (0.7 mg/kg)				Szára *et al.*, 1956
synthetic	77 mg[†] (1.1 mg/kg)				Szára *et al.*, 1956
synthetic	28 mg[†] (0.2 mg/kg)				Strassman *et al.*, 1994
synthetic	24 mg[†] (0.4 mg/kg)				Strassman *et al.*, 1994
Law enforcement seizures:					
Sample 1	820 mg/g	--	--	--	Lanero *et al.*, 2015
Sample 2	--	--	160 mg/g	120 mg/g	Lanero *et al.*, 2015
Sample 3	20 mg/g	--	--	--	Lanero *et al.*, 2015
Exhibit 4.1	0.67 mg/kg (80 mg[‡])				DEA seizure
Exhibit 4.2	0.40 mg/kg (48 mg[‡])				DEA seizure
Exhibit 4.3	0.84 mg/kg (101 mg[‡])				DEA seizure
Exhibit 4a	0.27 mg/kg (32 mg[‡])				DEA seizure
Exhibit 5a	0.81 mg/kg (97 mg[‡])				DEA seizure
Exhibit 5b	0.56 mg/kg (68 mg[‡])				DEA seizure
Exhibit 5c	0.55 mg/kg (66 mg[‡])				DEA seizure
Exhibit 11	0.18 mg/kg (22 mg[‡])				DEA seizure
Exhibit 12a	0.69 mg/kg (83 mg[‡])				DEA seizure
Exhibit 12b	0.60 mg/kg (72 mg[‡])				DEA seizure
Exhibit 13	0.65 mg/kg (78 mg[‡])				DEA seizure
Exhibit 14	0.51 mg/kg (61mg[‡])				DEA seizure

THH = tetrahydroharmine, HRL = harmaline, HRA = harmine;
[†]calculated based upon a 70 kg individual; [‡]calculated based on 120 ml dose; [§]calculated based on 200 ml dose

Indeed, evidence shows that the concentrations of the alkaloids, DMT and the β-carbolines (harmine, harmaline, tetrahydroharmine) in religious/ceremonial and seized recreational ayahuasca preparations vary widely (*see* Table 3). Concentrations of active

ingredients vary depending upon the amount ingested, the preparation method, and the frequency and manner of consumption (Rivier and Lindgren, 1972; McKenna *et al.*, 1984, 2004; Callaway, 2005; Gaujac *et al.*, 2012; Lanero *et al.*, 2015; Dominguez-Clave *et al.*, 2016; Santos *et al.*, 2017). Consequently, the amounts of DMT and β-carbolines can approach unsafe doses because there is no standard ayahuasca preparation.

In addition to the variations in alkaloid content, ayahuasca preparations are confounded by the unpredictable and unknown composition of these products as well as the frequency of their use (Rivier and Lindgren, 1972; Ott, 1993; Warren, 2004; Sklerov et al, 2005). As mentioned previously, other psychoactive substances such as nicotine, cocaine, atropine, scopolamine, and caffeine that have psychoactivity have been found in brews of ayahuasca and may play a role in its pharmacological effects (Ott, 1993; Warren, 2004; Sklerov et al, 2005). In addition, the consumption of ayahuasca differs amongst participants (Rivier and Lindgren, 1972; Grob, 1996; Gable, 2007). Whereas some ceremonial participants consume only one dose, others consume many more. Thus, the use of any ayahuasca preparation, because of its unknown composition and frequency of utilization, can result in overdoses and intoxications (Grob *et al.*, 1996; Dos Santos, 2013a; Lanero *et al.*, 2015; De Pablo, 2017).

D. Psychological and Physical Dependence

Drugs of abuse can pose serious health risks to the user and the general public through the development of tolerance (Katzung, 1992; Jaffe, 1993). The development of tolerance means that more drug than the initial dose is needed to produce the desired or psychoactive effect. This increased dose could be troublesome because a high dose can result in more severe adverse health effects linked to activation of biological systems that may not have been affected by the necessary psychoactive dose (*i.e.*, visual and auditory hallucinations) of the drug (Jaffe, 1993; Nichols 2004). Although tolerance to hallucinogen substances is rare, it has been observed. For example, daily administration of LSD to individuals has resulted in a complete loss of sensitivity to the effects of the drug on the fourth day of administration (Cholden *et al.*, 1955; Isbell *et al.*, 1956; Nichols, 2004). Regarding DMT, Strassman *et al.* (1996) and Wyatt *et al.* (1974) both concluded from clinical studies that there was no evidence of tolerance to the effects of DMT. Although, there is no definitive evidence that the use of ayahuasca (which DMT is a common ingredient) leads to psychological or physical dependence in those cases, it still is possible that the repetitive nature of using ayahuasca could lead to tolerance and/or dependence (Strassman *et al.*, 1996; Fabregas *et al.*, 2010). For example, there is evidence of changes in the brain with long-term use of ayahuasca. In long-term users of ayahuasca, there were significant or measureable changes in brain structure (Bouso *et al.*, 2015; McKenna and Riba, 2017). Structural changes induced by the repeated use of psychedelic drugs including ayahuasca could support personality traits of religiousness, transpersonal feelings and spirituality but causation could not be established. In addition, if these structural changes are correlated negatively (psychopathology) or positively (positive effects on personality) to the psychology of individuals is questionable. Therefore, these results should be

extrapolated to the American public with caution since many clinical studies with DMT or ayahuasca are limited to experienced users of hallucinogens because of the ethical concerns of testing ayahuasca or DMT in healthy individuals.

E. Neurotoxicity

Preclinical studies demonstrate that β-carbolines have neurotoxic effects (Freedland *et al.*, 1999; Handforth, 2012; Lavita *et al.*, 2016). The administration of an extract of *B. Caapi* (contains β-carbolines) in animals caused tremors (clonic and tonic motor movements) in these animals (Freedland *et al.*, 1999). These tremors have been linked to a known medical condition in humans called essential tremor (ET). ET is one of the most common neurological disorders in the world, and it is described as a syndrome characterized by involuntary tremor of the arms, head, and/or voice. ET affects elderly people but it can also affect young adults and children. Genetic factors, environmental and food exposures, and age have all been proposed to contribute to the development of ET. Based on this information, β-carbolines induced tremor in animals has been used as a preclinical model of ET (Handforth, 2012; Lavita *et al.*, 2016). Thus, it can by hypothesized that β-carbolines in ayahuasca may produce neurotoxic effects.

F. Cardiotoxicity

The ingestion of DMT or ayahuasca has been associated with moderate elevations in cardiovascular parameters in humans (Callaway *et al.*, 1999; Riba *et al.*2001, 2003; Carbonaro and Gatch, 2016). In a double blind clinical study, the oral administration of ayahuasca (0.85 mg/kg) to 18 experienced healthy psychedelic users caused a significant increase in diastolic blood pressure (Riba *et al.*, 2001, 2003). The dose that increased diastolic blood pressure also produced subjective effects in these individuals. However, the increase in cardiovascular functions was reported to be milder than that reported for substances that cause stimulant effects such as amphetamine or 3,4-methylenedioxymethamphetamine (MDMA). Mild effects on cardiac function was also reported by Strassman *and Qualls* (1994) in a double-blind, randomized study of DMT (0.2 and 0.4 mg/kg) in 12 experienced hallucinogen users. In these individuals, the increased pupil diameter, heart rate, mean arterial blood pressure all peaked at about 2 minutes after intravenous administration of DMT which correlated with the time that users reported experiencing subjective effects. A review of the scientific literature by Carbonaro and Gatch (2016) also found that DMT induced moderate cardiovascular effects when administered intravenously in large doses. These data demonstrate that the acute administration of ayahuasca or DMT produces moderate elevations of cardiac function. Thus, individuals with preexisting health conditions, like heart disease, may be at higher risk of adverse outcome from the consumption of ayahuasca than healthy individuals (Dos Santos *et al.*, 2013a, b).

Repeated administration of ayahuasca in animals also produced cardiotoxic effects (Favaro *et al.*, 2015; Pitol *et al.*, 2015). Preclinical studies demonstrate the chronic or long-term use of DMT can have mild cardiovascular effects, but does not affect memory or anxiety (Favaro *et al.*, 2015). Furthermore, in rats treated for 14 days

with ayahuasca, the structure of the aorta was altered (thickening of the walls of the aorta relative to the lumen diameter) compared to controls suggesting vascular remodeling (Pitol *et al.*, 2015). Thickening of the walls of the aorta is an indication that ayahuasca may induce hypertensive effects of hypertension.

G. Psychopathology

Psychotic manifestations have been reported after the use of DMT or ayahuasca (Dos Santos and Strassman, 2011; Szmulewicz *et al.*; 2015; Paterson *et al.*, 2015; Bilhimer *et al*., 2018). These psychotic episodes can persist after the expected or desired effects of ayahuasca have subsided. There is also a possibility that DMT and ayahuasca can trigger a psychotic break in individuals who are susceptible (via environmental or genetic factors) to psychosis or have underlying mental health conditions (Dos Santos and Strassman, 2011). In fact, in the past, DMT, LSD, ketamine, and phencyclidine (PCP), were proposed to be used to induce psychosis in animals for further study of the cause of schizophrenia and other experimental research (Gouzoulis-Mayfrank *et al.*, 2005, 2006; Szára, 2007). However, it is no longer globally accepted that hallucinogens are the sole cause of mental disorders like schizophrenia; but, it is still believed that psychedelics play a role in psychotic symptoms and psychiatric disorders (Szára, 2007; Krebs and Johansen 2013; Johansen and Krebs, 2015). Although the occurrence of psychosis from ayahuasca is low, the consequences or health outcomes of developing psychosis can be severe (Gable, 2007; Dos Santos and Strassman, 2011; De Pablo Márquez, 2017).

The following case reports document incidents of psychopathology associated with the use of ayahuasca:

Dos Santos and Strassman (2011) described the case of an individual who experienced psychotic paranoid episodes after ingesting ayahuasca. This individual had intense hallucinations that led him to believe that he should kill himself (suicidal ideation) and so the individual attempted to cut himself with a sharp object. These symptoms persisted for two to three weeks after ingesting ayahuasca and resolved after treatment with an antipsychotic drug.

Szmulewicz *et al.* (2015) described the case of a 30-year-old male who was admitted to a psychiatric hospital after having an acute psychotic episode after participating in a four-day ritual of ayahuasca consumption. The subject had a family history of bipolar disorder and a previous history of hypomanic episodes. Two days after the last consumption of ayahuasca, the individual began having mystical and paranoid delusional ideas, auditory hallucinations, racing thoughts, disorganized behavior, elevated energy, and euphoria. Successful treatment of the psychotic episode was immediately followed by a depressive episode.

De Pablo Márquez and Gómez-Luengo (2017) described the case of a 36-year-old male with a history of mental health issues who presented to the emergency department (ED) with behavioral alterations related to the recreational use of ayahuasca. The individual was reported to be experiencing hyperactivity, insomnia, and

a feeling of well-being. At the hospital, the following symptoms were observed: extra-familiarity that was inadequate at times, unable to concentrate, increased perception, and mystical content conversation. The patient reported experimental use of cocaine, LSD, and ayahuasca. A toxicological analysis of the patient's urine was negative for cocaine, cannabis, amphetamines, and heroin. The patient was admitted to the hospital and treated with antipsychotic drugs.

Bilhimer *et al.* (2018) described the case of a 25-year-old male with a history of schizophrenia who presented to the ED under mental health arrest for displaying altered mental status. Prior to being arrested, the individual was at home causing a disturbance that led to neighbors to call the police. Police arrived on the scene and found the individual fighting with a cat. The individual was bleeding from lacerations obtained from the cat's claws. The individual was, subsequently, subdued and restrained by the police and transported to the hospital. The individual admitted drinking a hallucinogenic tea containing ayahuasca purchased from the Internet. A toxicology screen of the individual's urine detected high concentrations of DMT (~20,000 ng/mL). The individual eventually was discharged four days later after all symptoms had subsided.

H. Developmental/Reproductive Toxicity

Ayahuasca has been shown to be highly toxic to reproducing/pregnant rats and their fetuses in a study that evaluated the effects of repeated administration of normal and high doses of ayahuasca to pregnant rats (da Motta *et al.*, 2018). Rats were given doses of ayahuasca (prepared by a União do Vegetal (UDV) group in the Federal District of Brazil) that corresponded to one to eight fold the dose taken by individuals participating in a religious ceremony. Nearly half the rats died that were given four or eight fold doses whereas the other surviving half suffered kidney damage. In addition, rats given the eight fold doses experienced delayed intrauterine growth, embryo deaths, and increased fetal anomalies. Rats given the two fold showed signs of neuronal damage. The authors from this study concluded that women of child-bearing-age should be cautioned over the use of ayahuasca. In contrast, a similar study by Oliveira *et al.* (2010) did not find any preclinical signs of maternal of fetal toxicity, except a deficit in maternal weight gain, in rats given up to ten times the human dose (prepared by a religious group in the state of São Paulo). There are no plausible reasons to explain the different outcomes except that the ayahuasca was prepared by two different groups.

I. Mortality

Ayahuasca or DMT containing products have been implicated in the fatality of an individual as reported in the medical literature. Sklerov *et al.* (2005) reported the death of a 25-year-old male who ingested an ayahuasca-like preparation containing 5-MeO-DMT. The individual ingested an "herbal tonic" thought to be ayahuasca which was later determined to contain "ooasca" (an American tree bark) during a camping trip. A few hours later the individual also ingested some tryptamines and went to sleep. The

following morning he was found dead. A toxicology screen of the individual's blood and urine samples identified DMT, 5-MeO-DMT, tetrahydroharmine, harmaline, and harmine. The medical examiner ruled that the cause of death was hallucinogenic amine intoxication. However, other researchers have challenged this finding by the medical examiner because they argue that the high levels of 5-MeO-DMT detected in the decedent could not have come from natural sources (*i.e.*, ayahuasca) but instead may have come from synthetic sources (Callaway *et al.*, 2006).

J. Other Adverse Health Effects of Ayahuasca (Co-ingestions)

Interactions of ayahuasca with medications (*e.g.*, tricyclic antidepressants/ serotonin reuptake inhibitor – Zoloft, Prozac, Paxil, trazodone,) and dietary supplements (*e.g.*, St John's-wort and ginseng) are poorly understood, thus, there could be detrimental consequences from combining ayahuasca (which contain MAO inhibitors) with these substances (Dos Santos, 2013a; Malcolm and Lee, 2017). The combination of these substances with an MAO inhibitor can lead to a condition, known as the "serotonin syndrome" which is characterized by altered mental status, hyper-reflexia, and autonomic instability and can possibly lead to death in extreme cases (Calloway and Grob, 1998; Dos Santos, 2013). Ayahuasca, in combination with serotonin-selective reuptake inhibitors (SSRIs), could be deadly due to the blockade of two essential pathways in serotonin disposal mechanisms: 1) specific metabolism of serotonin by MAO and 2) reuptake of serotonin into the presynaptic neuron, respectively. Dietary supplements can also increase the concentrations of serotonin in the body leading to serotonin toxicity.

It would be over simplistic to believe that only those treated with SSRIs are at particular risk if they consume ayahuasca. Individuals suffering from asthma, emphysema, or chronic obstructive pulmonary disease (COPD) and treated with bronchodilators and those individuals who are treated with an array of cardiovascular medications are also at risk if they consume ayahuasca brews containing MAO-inhibitors during treatment or 8 to 10 weeks before and after treatment with these drugs. MAO inhibitors can also interact with seizure medications through unknown mechanisms, increasing side effects.

MAO-inhibitors can be also prescribed as medication themselves (*e.g.,* isocarboxazid, phenelzine, selegiline, and tranylcypromine) for the treatment of depression, Parkinson's disease, panic disorders, personality disorders, agoraphobia, social phobia, anxiety, bulimia, post-traumatic stress disorder, etc. (Herraiz *et al.*, 2010; Khan *et al.*, 2013; Song *et al.*, 2013; Finberg, 2014; Dos Santos *et al.*, 2016). The combination of MAO inhibitors for the treatment of these diseases plus the additional intake of MAO inhibitors from ayahuasca brews may have additive effects leading to potential toxic consequences.

Interactions of MAO inhibitor with certain foods can also be dangerous (Simpson and De Leon, 1989; Calloway and Grob, 1998; Callingham, 1993; Garcia and Santos, 2017; Gillman, 2017; Malcolm and Lee, 2017). Restricted foods that should not be

consumed with MAO inhibitors include aged cheeses, yogurt, cured meats, beef or chicken liver, anchovies, cavier, *etc.* This is because MAO inhibitors inhibit monoamine oxidase which decrease the breakdown of tyramine from ingested foods, thus increasing the level of tyramine in the body. Excessive tyramine can elevate blood pressure and cause a hypertensive crisis. Thus, it is important that individuals that ingest foods with tyramine be cautious of the foods they ingest if ayahuasca will also be consumed.

Given that millions of individuals worldwide are currently undergoing treatment with SSRIs, bronchodilators, cardiovascular medications, and their active metabolites or take dietary supplements, the potential for incurring a dangerous life threatening event is not insignificant.

K. Conclusion

There is no approval of ayahuasca for use as a drug under the Food and Drug Administration, the regulatory agency with the Department of Health and Human Services that is responsible for ensuring that drugs sold in the United States are both safe and effective. One of the common ingredients of ayahuasca, DMT, is a schedule I hallucinogen which means that it has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. The other common ingredient, a β-carboline also has no currently accepted medical use in treatment in the United States.

The risks of ayahuasca to public health and safety as presented in this section come from various sources and collectively suggest that ayahuasca presents a significant risk to public health and safety and to the health and well-being of individuals. First, clinical case reports show that the ingestion of DMT or ayahuasca has been associated with moderate cardiotoxicity, neurotoxicity, psychopathology, transient disorientation, anxiety, coma and death (Callaway *et al.*, 1999; Riba *et al.*2001, 2003; Dos Santos and Strassman, 2011; Szmulewicz *et al.*; 2015; Carbonaro and Gatch, 2016). Poison control data confirm that individuals are using ayahuasca and experiencing harm (Heise and Brooks, 2016; DEA, 2018). Second, data show that co-ingestions of ayahuasca with other chemicals can have serious consequences to those with preexisting health conditions. Third, preclinical data show that β-carbolines, which have also been reported to produce neurotoxic effects, may contribute to the toxicity of ayahuasca although its role is unclear (Freedland *et al.*, 1999; Lamchouri *et al.*, 2000, 2002, 2013; Handforth, 2012; Lavita *et al.*, 2016). Additionally, preclinical studies data show that ayahuasca is highly toxic to reproducing/pregnant rat and their fetuses. Thus, the use of ayahuasca in women of child bearing age is strongly cautioned. Finally, there is no standard ayahuasca preparation. Ayahuasca is a concoction that can be prepared differently depending upon the individual or organization.

As mentioned above, there is no ''universal'' definition of what is or what is not ayahuasca. The brewing of several different botanicals results in a concoction that is known as "ayahuasca." Thus, many active ingredients (controlled or uncontrolled) including coca, DMT, scopolamine, atropine, nicotine and β-carbolines, and other

alkaloids have been found when the varieties of brews have been analyzed and evidence show that some of these constituents can cause harm. Some of these constituents found in these brews can also have serious consequences to those with preexisting health conditions. For example, ayahuasca concoctions have been found to contain scopolamine and atropine which could produce serious cardiac effects in normal healthy adults and death to those with pre-existing or unrecognized cardiac problems such as high blood pressure, tachycardia, congestive heart failure, or silent ischemia, *etc.* (Balíková, 2002). In one case of a fatality, nicotine was found to be the main ingredient in the ayahuasca concoction (Warren, 2004).

Gable (2007) suggested that the use of ayahuasca in a religious context is safe because the lethal dose of DMT in ayahuasca preparations was calculated to be greater than 20 times the amount that is used in ayahuasca ceremonies or rituals and the oral ingestions of such large amounts of ayahuasca are not likely realistic. However, as stated previously, there is no universal brew that is ayahuasca. In fact, differences in ayahuasca brews are expected. Ayahuasca is a concoction that can be prepared differently depending upon the individual or organization. Variabilities in ayahuasca admixtures can also be attributed to factors such as the cultivation, harvesting, botanical and cooking processes, the species and regional source of plants, and the amount of the plants (regional variants) (McKenna *et al.*, 1984, 2004; Ott, 1996; Callaway, 2005; Gaujac *et al.*, 2012; Lanero *et al.*, 2015; Dominguez-Clave *et al.*, 2016; Santos *et al.*, 2017; da Motta *et al*., 2018). For these reasons, variations in the concentrations and identification of the active constituents (DMT, β-carboline alkaloids, *etc.*) in each ayahuasca concoction as well as other psychoactive constituents are expected.

There is growing concern that ayahuasca is being used for recreational purposes and drug tourism industries (De Rios, 1994; Winkelman, 2005; Cakic *et al*., 2010; Trichter, 2010; Bauer, 2018). For these reasons, there is growing concern that the use of ayahuasca in the United States, including its use as a recreational substance, is expanding and will continue to expand. Indeed poison control data indicate that more individuals are using ayahuasca and are seeking help from its adverse effects (Heise and Brooks, 2016). It should be noted that a survey of lifetime recreational DMT users (n=121), 54.5% of the users believed the use of DMT to be safe, 38% quite safe, and 6.6% moderately safe indicating that that perceived risk of using DMT is low (Cakic *et al*., 2010).

Ayahuasca supporters assert that the use of ayahuasca is beneficial and safe, but this is based upon limited information. There are claims in the medical and scientific literature that ayahuasca may be beneficial in the treatment of substance abuse disorders, anxiety, and depression based upon preliminary clinical studies (Dominguez-Clave *et al.*, 2016; Sanches *et al.*, 2016; Davic *et al.*, 2017). There are also claims that ayahuasca have may have positive effects on psychosocial problems. Consequently, to endorse its potential medical use, some publications suggest that the administration of ayahuasca is safe (Doering-Silveira *et al.*, 2005; Gable *et al.*, 2007; Dos Santos, 2013a, b; Barbosa *et al.*, 2012; Barbosa *et al.*, 2016; Dominguez-Clave *et al.*, 2016). However, all

of these claims are based on limited published studies and are complicated by many factors. These factors include limited population diversity, difficulty in finding appropriate individuals for controls, small sample size, and establishing the cause and effect relationship especially since for some individuals the results may be linked to the religious surroundings. Although ayahuasca has been alleged to have beneficial psychological effects, there are not enough well-controlled studies to support this claim. More well-controlled clinical studies are needed to assess it full therapeutic potential and to increase and diversify the study population. More studies are also needed to link the positive or negative findings specifically to ayahuasca and not the context in which ayahuasca was used and to evaluate the long term or persisting effects of ayahuasca and its constituents and the effects of ayahuasca and its constituents on mental health (McKenna, 2004; Frecska *et al.*, 2016a, b; Nunes *et al.*, 2016; Malcolm and Lee, 2017). Until these studies are completed and the outcomes are analyzed, it cannot be stated that ayahuasca is safe.

In summary, the adverse health effects reported from ayahuasca administration, the lack of current scientifically valid and reliable data on the mechanisms involved in DMT's and the harmala alkaloid's neuropharmacological effects, the lack of a reliable and standard definition of ayahuasca, the variability in both the manufacturing technique and composition, and the differences in the routes of administration of ayahuasca brews all lead to the only logical and credible conclusion that can be drawn: Ayahuasca is not safe and is a threat to human health.

IV. References

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