Memorandum

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Subject: Review of the published literature pertaining to the safety of Kava for use in conventional foods

I. Introduction

This memorandum summarizes generally available information from the published literature and other informational sources on Kava (*Piper methysticum* G. Forster). The root is the part of the kava plant ordinarily used by consumers. The memorandum discusses kava root extract's chemistry, absorption, distribution, metabolism and excretion (ADME), and its potential mechanism(s) of action; and highlights concerns regarding its hepatotoxic and carcinogenic effects, and other adverse health effects associated with food uses of kava.

II. Literature Searches

The following primary literature databases were searched to retrieve scientific data published on kava: PubMed, ScienceDirect, Embase, ChemIDplus Advanced, Natural Medicines (formerly Natural Standard, and Natural Medicines Comprehensive Database), and Medline. The search terms used were kava, dietary intake of kava, ingestion of kava, kava hepatotoxicity, kava and anxiety, kava and CNS effects, adverse effects of kava, kava pharmacokinetics, metabolism of kava, human exposure of kava, and kava case reports. The entirety of the databases from

all the years available up to July 2020 was searched revealing more than 800 publications. In order to focus on literature most relevant to the use of kava as a "relaxation" beverage and/or as an ingredient in foods, the search was refined to identify studies related to the oral consumption of kava with greater emphasis on potential adverse effects in humans. The literature selected for this review describes some of the effects of kava on the liver, the central nervous system as well as other toxicities.

III. Background

Kava (*Piper methysticum* G. Forster), is a perennial shrub, a member of the pepper family Piperaceae, native to the geographic regions of Polynesia, Micronesia and Melanesia. Some of the common names for kava include intoxicating pepper, ava, ava pepper, awa, kava kava, kava pepper, kava root, kawa, kawa kawa, kew, rauschpfeffer, sakau, tonga, wurzelstock, and yagona.

Kava beverages have been used ceremonially and socially in the South Pacific for many centuries. Kava drinking was introduced to places like New Caledonia, the Solomon Islands, Kiribati, and New Zealand by migrants. Kava became popular in Western society as a recreational drink, a dietary supplement and used for medicinal purposes as an anxiolytic drug for anxiety and insomnia. Traditionally, kava extracts are prepared from macerated rhizome roots combined with cold water or coconut milk. Kava beverages made from fresh or dried roots of *Piper methysticum*, are consumed for their relaxant and psychoactive properties (Bilia et al. 2002). Commercially available kava formulations have been primarily ethanol, methanol or acetone extracts, standardized to specified kavalactone content.

Although there is some scientific evidence for the use of kava to treat anxiety, safety concerns over hepatotoxicity has resulted in withdrawal or ban in several European markets (France, Switzerland, Czech Republic, Spain, UK, Hungary, Portugal and Germany (up to 2015)) and Canada since 2002. FDA also issued a consumer advisory and a letter to health care professionals in 2002 expressing concern about liver damage in individuals who have ingested kava products (CFSAN, March 25, 2002). However, currently, kava is still available for sale in the U.S. as dietary supplements, promoted for relaxation to relieve stress, anxiety, and tension, as well as for sleeplessness and menopausal symptoms and in Australia and New Zealand as herbal medicine in the treatment of generalized anxiety.

In Australia, Kava has a Schedule 4 entry, and there is a regulatory limitation regarding the maximum of 250 mg kavalactones per day derived from water-based extracts of kava rhizomes and roots, with a limit per dosage of 125 mg kavalactones for any individual tablet or capsule (Therapeutic Goods Act (TGA), Oct. 2016).

The Committee on Herbal Medicinal Products (HMPC) of European Medicines Agency (EMA) concluded that based on the available data, a European Union

herbal monograph on kava cannot be established for the treatment of anxiety disorders (EMA Nov. 2017).

IV. Chemistry of Kava

Fresh kava rootstock has been reported to be comprised of about 80% water. Dried rootstock consists of about 43% starch, 20% fibers, 12% water, 3–4% proteins, 3% sugars, 3% minerals, and 3 to 20% kavalactones, depending on the age of the plant and the cultivar (He et al. 1997). More than 40 compounds have been isolated from kava, with the active components present in the lipid-soluble resin (Singh 2005).

There are three chemical classes in the kava resin:
(i) arylethylene-alpha pyrones;
(ii) chalcones and other flavanones; and
(iii) conjugated diene ketones.

The substituted 4-methoxy-5, 6-dihydro-alpha-pyrones or kava pyrones, commonly called kavalactones, possesses the highest purported pharmacological activities.

Kavalactones are concentrated mainly within the rhizomes, roots and root stems of the plant, with the highest concentration in the lateral roots, decreasing gradually towards the aerial plant structures. There are eighteen kavalactones that have been isolated and identified from kava root extract, six of which account for approximately 95–96% of the total kavalactones in the lipid resin, namely, kavain (K), 7, 8-dihydrokavain (DHK) methysticin (M), 7, 8-dihydromethysticin (DHM), yangonin (Y), and desmethoxyyangonin (DMY; 5,6-dehydrokavain) (Fu et al. 2008). In general, kavalactones have low water solubility (Côté et al. 2004). Minor constituents of kava extracts include amino acids, minerals (iron, magnesium, potassium, calcium, sodium and aluminium) and three chalcones (flavokavains A, B and C). Trace amounts of other compounds have been isolated such as alkaloids (pipermethystine, 3α, 4α-epoxy-5β-pipermethystine, and methoxy-cinnamoyl pyrolidine), flavonoids, ketones, phytosterols and aliphatic alcohols.

There are >200 kava varieties or cultivars categorized as noble cultivars, medicinal cultivars, “non-noble” or “two-day” (tudei) cultivars and wild (Wichmannii) species. Kava cultivars are established based on the chemical signature of the six kavalactones obtained from a kava sample. The chemotyping is based on the sequence of the elution of each kavalactone by HPLC and in their decreasing order of quantity. Table 1 shows the chemotype identity and reported “recreational” effects of the six main kavalactones. Hence, variations in chemical composition occur in different cultivars, plant parts, age of the plant, geographic and growth conditions (Singh et al. 2002).

Table 1:

Kavalactone	Chemotype	Reported Effects
Desmethoxyyangonin (DMY)	1	
Dihydrokavain (DHK)	2	Very sedating
Yangonin (Y)	3	
Kavain (K)	4	Euphoria or headiness
Dihydromethysticin (DHM)	5	Very sedating, long lasting
Methysticin (M)	6	

V. Biochemical Aspects of Kava

Absorption, Distribution, Metabolism, and Excretion (ADME)

Mice

Robinson et al. 2009 summarized the absorption of 6 kavalactones—K, DHK, M, DHM, Y, DMY, administered orally in a peanut oil solution to mice. Both K and DHK were rapidly absorbed from the gastrointestinal tract, the peak effect in mice being 10 minutes, as measured by a maximal electric shock test (no details provided about the test). M and DHM had a longer induction period, about 30 to 45 minutes, but also had a longer duration of action. Y and DMY were poorly absorbed from the gut peritoneum, and/or rapidly eliminated.

The pharmacokinetics of four kavalactones, K, DHK, Y, and DMY was studied in the mouse brain. Balb/c mice were administered intraperitoneally (i.p.) each of the kavalactones at a dose of 100 mg/kg, and were sacrificed at specific time intervals (5, 15, 30, and 45 min). The concentrations of these four compounds in brain was determined by GC/MS. After 5 min, DHK and K attained maximum concentrations of 64.7 and 29.3 ng/mg wet brain tissue, respectively, and were rapidly eliminated. In contrast, DMY and Y reached concentrations of 10.4 and 1.2 ng/mg wet brain tissue, respectively, and were more slowly eliminated from brain tissue. However, when crude kava resin (containing 44 mg/kg K and 18 mg/kg Y) was administered i.p. at a dose of 120 mg/kg, the brain concentrations of K and Y markedly increased (2 and 20 times, respectively) relative to the values measured from their individual injection. In contrast, DHK and DMY, after the administration of crude resin, remained similar to their levels obtained after individual i.p. injection suggesting a synergistic effect with kava resin compared with its individual constituents acting alone. The synergism in pharmacological activity appears to be due to potentiation of penetration into the brain when the compounds are administered together rather than separately. However, the mechanism by which this may occur remains unknown. Similarly, it has been reported that Y and DMY when given orally were relatively ineffective. But, in combination with other kava constituents, a marked increase in their potency was observed implying a synergistic action in the absorption of kavalactones from the intestine, when kava constituents are administered together rather than individually (Keledjian et al. 1988).

Rats

The oral pharmacokinetics of Kavain was studied in male Fischer 344 (F344) rats. Kavain (100 mg/kg) was administered either alone or with kava extract (256 mg/kg). The results revealed that K was well absorbed, with >90% of the dose excreted within 72 h, mainly in the urine. When K was co-administered with kava extract, the peak concentration of K (Cmax) in blood plasma was doubled and the area under the plasma drug concentration-time curve was tripled, demonstrating that the presence of other constituents had great impact on the ultimate pharmacokinetics of the whole herb. However, a 7-day pretreatment with kava extract had no effect on the pharmacokinetics of K administered on day 8 (Mathews et al. 2005).

The metabolism of 5 kavalactones (DHK, K, M, DHY and Y) was investigated in Wistar rats. Individual kavalactones were administered by stomach tube at a dose of 400 mg/kg (p.o). The results indicate that ~50% of the dose of DHK was found in the urine within 48 h mostly as hydroxylated metabolites, of which p-hydroxy-DHK was the most abundant and some hippuric acid (9-13% of the dose) was seen. With K, lower amounts of both hydroxylated and ring-opened urinary metabolites were found. M was poorly absorbed with very small amounts of only 2 metabolites seen. In the case of DHY and Y, relatively small amounts of urinary metabolites were formed via O-demethylation. DHK and DHY appear to be better absorbed than other compounds (Rasmussen et al. 1979).

Humans

Studies examining the metabolism of kava in humans are described below.

In vitro studies using Caco-2 cells found kavalactones to be potentially bioavailable as they all readily crossed the Caco-2 monolayers, most with more than 70% crossing within 90 min. There are two characteristics that appear to affect the permeability of the kavalactones. The first factor is the presence of the methoxy (OCH3) group at R2 and the absence of an oxygen functionality at R1. The second factor appears to be the other components present in the extract. The study suggests that the extraction method (aqueous or ethanolic) used is able to influence the total concentrations of kavalactones present in a preparation but does not markedly affect the bioavailability of these kavalactones (Matthias et al. 2007).

Duffield et al. (1989) identified human urinary metabolites of kavalactones following ingestion of aqueous kava extract prepared by the traditional method. Nine kavalactone metabolites were identified, including DHK, K, DMY, Y, tetrahydroxyangonin, 11-methoxytetrahydroyangonin, DHM, methylsticin, and dehydromethylsticin. Metabolites formed were due to the reduction of the 3, 4-double bond and /or demethylation of the 4-methoxyl group of the α-pyrone ring system. Demethylation of the 12-methoxy substituent in yangonin was also identified. In contrast to rats, no dihydroxylated or ring opened metabolites were detected. The main metabolic pathways for kavalactones in humans and rats are

hydroxylation of the C-12 in the aromatic ring, breaking and hydroxylation of the lactone ring with subsequent dehydration, reduction of the 7,8-double bond, and demethylation of the 4-methoxyl group.

Zou et al. (2005) analyzed urine samples of two human subjects (one male and one female Caucasian) after ingestion of 10 g of powdered kava root mixed in water. Analysis of the root extract showed that the total kavalactone content was 13%, which is in the typical range of the levels (3-20%) reported. 6-phenyl-3-hexen-2-one (6-PHO) was detected in the urine as a mercapturic adduct confirming the reactivity of 6-PHO with GSH observed in their *in vitro* studies. The authors suggest that 6-PHO could possibly conjugate with other nucleophiles such as protein thiols or DNA bases and potentially alkylate DNA or disrupt enzymatic and metabolic activity resulting in kava-associated hepatotoxicity.

Tarbah et al. 2003 investigated the metabolism of K in humans and found that *p*-hydroxykavain is the major metabolite that was found in blood and urine in its free and conjugate forms (glucuronide and sulfate). *p*-hydroxy-7,8-dihydrokavain was detected only in the urine. O-desmethyl-hydroxy-5,6-dehydrokavain and 5,6-dehydrokavain were the other K metabolites. After a single oral administration of kavain (800 mg), within 1 and 4 h after uptake, the serum concentrations ranged between 40 and 10 ng/ml for kavain, 300 and 125 ng/ml for p-hydroxykavain, 90 and 40 ng/ml for o-desmethyl-hydroxy-5,6-dehydrokavain, and 50 and 30 ng/ml for 5,6-dehydrokavain.

Toxicological studies

Acute toxicity

In an 8-day study, male Sprague-Dawley (SD) rats (6/group) received two different commercial kava products (kava A containing 80% or more kavalactones and kava B-unfiltered juice of the lateral roots) or vehicle by gavage. The results of the treatment with these products containing high doses of kavalactones (equivalent to approximately 380 mg kavalactones/kg/d; 100 times the suggested dose for humans) significantly increased liver weights, markedly enhanced the hepatic CYP1A1 mRNA expression (75-220 fold) as well as ethoxyresorufin O-deethylase (EROD) activities and CYP1A1 immunoreactivities. CYP1A2 mRNA expression was also moderately increased (2.8-7.3 fold) by both the kava products but to a much lesser extent than CYP1A1. The authors considered the NOAEL to be <380 mg/kg/day. The authors suggest that commercial kava products might exert their potencies to induce CYP1A1 in humans and its consequence may possibly be related to hepatotoxicity especially in susceptible individuals (Yamazaki et al. 2008).

A 2-week study was undertaken to mimic a short-term interaction between heavy kavalactones (KL) dosage and incidental consumption of kava alkaloid, pipermethystine (PM) in humans. The toxic effects of PM, abundant in leaves and stem peelings and acetone-water extracts (75:25, v/v) of kava rhizome (KRE) of

Hawaiian cultivar Mahakea were compared in F344 rats. PM and KRE were mixed in corn oil and administered via intragastric gavage daily for 2 weeks. The total content of KL in the acetone-water extract was 62.67%. This study KL dosage (63 mg/kg/day) was 10 times higher than the daily recommended dosage for human consumption (6–7 mg/kg/day) and may be comparable to mimicking the ‘‘heavy kava drinkers.’’ The results indicate that the treatment of F344 rats with PM (10 mg/kg) and KRE (100 mg/kg) for 2 weeks failed to elicit any significant changes in liver function tests or cause severe hepatic toxicity as measured by lipid peroxidation (malondialdehyde formation) and apoptosis markers (Bax, and Bcl-2 mRNA expression). Rats in all experimental groups lost overall body weight; however, KRE caused the most significant weight loss (42 g) compared with the control group. PM-treated rats demonstrated a significant increase in hepatic glutathione, cytosolic superoxide dismutase (Cu/Zn SOD), tumor necrosis factor α mRNA expression, and CYP 1A2, 2E1 and 2D6. The authors suggest that these effects reflect an adaptation to ROS-induced oxidative stress and possible drug-drug interactions. The lack of severe PM toxicity in rats may reflect possible differences in absorption, metabolism, and/or the variety of kava used. (Lim et al. 2007).

Singh and Devkota (2003) demonstrated that SD rats treated with aqueous kava extracts containing 200 or 500 mg KL/kg/d for 2 or 4 weeks did not exhibit any significant adverse effects in the liver function tests. Serum levels of any of the marker enzymes of liver toxicity such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase or lactate dehydrogenase were not elevated. There were no overt signs of clinical toxicity. Similarly, malondialdehyde (indicative of lipid peroxidation) levels in the liver homogenates did not increase suggesting a lack of liver toxicity by aqueous kava extract. The authors note that these kava doses were up to three times higher than the maximum recommended levels in humans.

Hepatotoxicity

The National Toxicology Program (NTP) conducted a comprehensive toxicology rodent study comprising a 2-week, 14-week (3 month), and 2-year toxicity and carcinogenicity studies in F344/N rats and B6C3F1 mice to address kava associated liver toxicity and carcinogenicity concerns. The study revealed clear evidence of carcinogenic activity in male mice with some evidence of carcinogenic activity in female mice, and an equivocal evidence of carcinogenic activity among male rats. In addition, kava extract caused increased incidences of tumor-like lesions in eyes, kidneys, liver, pancreas and forestomach in male and female rats, in the liver of male and female mice, and in the forestomach of female mice.

In the two-week studies, rats and mice were administered orally 0, 0.125, 0.25, 0.5, 1 and 2 g/kg/d kava extract by gavage. Kava-induced toxicity was observed in the livers of both rats and mice. Dose dependent increases in the absolute and relative liver weights were observed in the 1.0 g/kg and 2.0 g/kg males and in $\geq$0.5 g/kg in female rats. This was accompanied by significant increased incidences of minimal

hepatocellular hypertrophy (HP) in the 2.0 g/kg male and in 0.25 g/kg or greater female rats. In mice, liver weights were significantly increased in 2.0 g/kg males and females with accompanying increases in the incidence of hepatocellular hypertrophy in the 2.0 g/kg female mice. No other significant treatment-related effects were noted (Behl et al. 2011).

Subchronic study (NTP study)

Rats and Mice

In the 14-week NTP study, F344 rats and B6C3F1 mice (10/sex/group) were administered kava extract (30% kavalactones) in corn oil by gavage at doses 0, 0.125, 0.25, 0.5, 1.0, and 2.0 g/kg/d, 5 days per week, for 14 weeks. Exposure to kava extract resulted in unscheduled deaths of one female in the 1.0 g/kg group and three male and four female rats in the 2.0 g/kg groups. The authors attribute the cause of death to kava-induced central nervous system (CNS) and/or respiratory depression. Kava induced decreases in the body weights in the high dose groups in both sexes. Clinical chemistry analyses indicated increases in the activities of γ-glutamyl-transpeptidase (GGT) in the 1.0 g/kg females and both sexes of 2.0 g/kg group. Increased serum cholesterol levels were found in 0.5 g/kg and higher dose groups of both sexes. Dose-related increases in the absolute and relative liver weights and the incidence and severity of HP observed in males at 1.0 g/kg and females at 0.5 g/kg and higher were considered to be adaptive in nature by the authors. Immunohistochemical analyses of the protein expression of CYP enzymes in livers of these same rats showed an increased expression of CYP 1A2, 2B1, and 3A1 in both sexes from the 1.0 and 2.0 g/kg dose groups and decreased expression of CYP 2D1 (human 2D6 homolog) in female rats in the 2.0 g/kg group. Based on the neurotoxic and hepatotoxic effects, the authors considered NOAEL to be 0.25 g/kg in both sexes (Clayton et al. 2007). In mice, deaths of four male and three female 2.0 g/kg mice died during week 1 were attributed to kava extract. The mean body weights of the kava-treated groups were not significantly different from the controls. Ataxia and lethargy occurred in males and females of highest dose groups during week 1. The liver weights of 2.0 g/kg males and 1.0 and 2.0 g/kg females were significantly increased compared to those of the control groups. The incidences of centrilobular hypertrophy in the liver of 0.5 g/kg or greater males and 1.0 and 2.0 g/kg females were significantly greater than those in the vehicle controls.

Guo et al. (2009, 2010) analyzed the whole gene expression changes in the livers of male F344 rats and male B6C3F1 mice administered five different doses (0, 0.125, 0.25, 0.5, 1.0, 2.0 g/kg/d) of kava extract (30% kavalactones) in corn oil by gavage, 5 days per week, for 14 weeks. Microarray analyses of the changes in gene expression were also validated by real-time PCR. In rats, in the high dose group (2.0 g/kg), 72 drug metabolizing enzyme associated genes were significantly altered including 19 Phase I metabolizing enzymes genes; 21 Phase II genes; and 32 transporters (Phase III). In all the three higher dose groups, 7 Cyp genes were altered in a dose-dependent manner. While gene expression of Cyp1a1, 1a2, 2c6,

3a1, and 3a3 increased; Cyp 2c23 and 2c40 decreased. The authors point out that Cyp1a1 is primarily expressed in extrahepatic tissues and there is a low amount in the liver. The Cyp1a1 isozyme can metabolize a number of xenobiotics, including those with flat and planar structures, which include the highly toxic and tumorigenic polycyclic aromatic hydrocarbons (PAH). Therefore, the authors suggest that kava induced Cyp 1a1 may enhance the metabolism of PAHs and adversely affect human health.

In mice, in the high dose treatment group, there were some early deaths in the first week of treatment. Mean body weights were about 6% lower and the absolute and relative liver weights were significantly increased when compared to the controls. Gene expression profiles from the livers revealed that there were 95 drug metabolizing enzyme associated genes significantly altered including 28 Phase I metabolizing enzymes genes; 29 Phase II genes; and 38 transporters (Phase III). The expression of 5 genes (Gsta1, Gsta2, Cyp2a5, Cyp2b20, and Cyp2c55) increased in a dose-dependent manner. Significant changes were observed in the gene expression of Cyp 1a1, Cyp1a2, and Cyp3a11. Further, the most prominent changes were observed in the highest dose group, in the genes involved in the detoxification process, with Gsta1, Gsta2 and Nqo1 genes increased by about 50-, 24- and 4-fold, respectively. The authors speculate the enhanced expression to Nrf2 activation, since these genes are target genes controlled by transcription factor, Nrf2. Histopathology results in the male mice administered 0.5 g/kg and higher dosages of kava extract showed minimal to moderate hepatocellular centrilobular hypertrophy (increased severity with increasing dose). Interestingly, no other severe liver toxicities were observed. Based on the gene expression changes in both rats and mice, the authors suggest that kava extract can significantly modulate drug metabolizing enzymes, potentially leading to herb-drug interactions and hepatotoxicity.

Interestingly, in a study investigating the toxicity of an ethanolic kava extract (7.3 or 73 mg/kg/day) in Wistar rats for 3 or 6 months, no signs of toxicity were found, based on changes in body weight, hematological and liver parameters, and macroscopic and microscopic histological changes in the major organs. Although, the authors concluded that their results do not support kava induced liver toxicity, it should be noted that the doses used are significantly lower than those used in NTP study (Sorrentino et al., 2006).

Dog studies

Mongrel dogs received oral exposure to kavain at doses 10-400 mg/kg daily for 3 months. The results revealed the presence of mild toxicity in high dose group dogs and proliferation of small cells of the thyroid epithelium and a multicentric liver necrosis in one dog in high dose group (Hapke et al., 1971).

Chronic toxicity study (NTP study)

In the 2-year toxicity and carcinogenicity studies (Behl et al., 2011), F344 rats and B6C3F1 mice (50/sex/group) were administered kava extract in corn oil by gavage, at concentrations of 0, 0.1, 0.3, 1.0 g/kg (rats) and 0, 0.25, 0.5, 1.0 g/kg (mice), respectively. Chronic administration of kava in rats did not significantly affect survival or body weight in either males or females. In mice, the survival was not affected in either of the sexes. However, there was a slight reduction in the body weight gain in the female mice in the highest dose group. In rats, GGT activity increased several-fold at 18 months in males and at 6, 12, and 18 months in females. Bile salt concentrations were increased in both sexes. Cystic degeneration was observed in all dose groups of male rats. There were dose-related increases in the incidences of hepatocellular hypertrophy in rats and mice administered kava for up to 1 g/kg body weight. This was accompanied by significant increases in incidences of centrilobular fatty change. There were increased incidences of non-neoplastic lesions in the liver, forestomach, kidney, eye, and pancreas of male and female rats. In addition, a unique lesion was noted in the pancreas in the 1.0 g/kg males and females which included incidences of metaplasia of pancreatic acinar cells to a hepatocytic morphology. Microscopically, this lesion was characterized by the presence of small clusters of apparently normal hepatocytes adjacent to islets of Langerhans. The authors state that the etiology of this lesion remains unknown. There was no treatment-related increase in carcinogenic activity in the livers of male or female rats.

Male mice showed significant dose-related increases in the incidences and multiplicities of hepatoblastomas and hepatocellular adenomas as well as an increase in the combined incidences of hepatocellular carcinomas or hepatoblastomas indicating a **clear evidence** of carcinogenic activity in male mice. In female mice, there was a significant increase in the incidence of hepatocellular carcinomas and in the combined incidence of hepatocellular adenomas or carcinomas in the low and mid dose groups but not in the high dose group indicating **some evidence** of carcinogenic activity in female mice, accompanied by non-neoplastic lesions in the liver and forestomach. Based on these findings, NTP included this kava preparation into **group 2B**, meaning sufficient evidence in experimental animals.

In rats, although liver toxicity was observed, kava extract did not induce liver neoplasms suggesting species differences in the sensitivity of induction of liver neoplasms.

Retinal degeneration

In the 2-year NTP bioassay in F344/N rats, the frequency of retinal degeneration was significantly increased in a dose-dependent manner in the 0.3-g/kg and 1.0-g/kg groups in males, and in the 1.0-g/kg group in female rats, compared to the control groups. The proportion of bilateral change was significantly increased in the 1.0-g/kg group compared to the control group in both males and females. In the evaluation of peripheral retinal degeneration, the average severity grade was significantly increased in a dose-dependent manner in the 0.3-g/kg and 1.0-g/kg

groups in males, and in the 1.0-g/kg group in females, compared to the control groups. The degeneration consisted of a thinning and loss of the external retinal layers, such as the photoreceptors and external nuclear layers, with a decreased cellularity and disorganization of the remaining retinal layers. Reduced photoreceptor outer segment disc shedding and subsequent lower number of phagosomes in the retinal pigment epithelium and alterations in the melatonin pathway may have contributed to the increased incidences of retinal degeneration (Yamashita et al. 2016; 2018).

Effect of kava on CYP 450 enzymes

***In vitro* studies**

Rats

Rat hepatocytes treated with the six kavalactones, showed that only DHM and DMY markedly induced CYP3A23 expression (~7-fold) accompanied by increased levels of CYP3A23 mRNA. Interestingly, six kavalactones, mixed at a non-inductive concentration (15 µM for each), caused induction similar to 90 µM DHM or DMY. However, selective removal of both DHM and DMY, completely abolished the inductive activity of the mixtures suggesting that the induction is additively/synergistically enhanced by other kavalactones. DHM and DMY only slightly activated rat and human pregnane X receptor (PXR). The authors suggest that the induction of CYP3A23 by these 2 kavalactones involves transcription activation through a PXR-independent or PXR-involved indirect mechanism (Ma 2004).

The *in vitro* studies suggest that kava supplementation may give rise to significant CYP-mediated herb-drug interactions.

Humans

Côté et al. (2004) compared the kavalactone composition of the traditional aqueous kava root extract (Moi variety), organic kava extracts (acetone, ethanol or methanol) and extracts from commercial caplets which revealed significant differences in the total amount of kavalactones (2-3 fold) and the ratio of the six major KL. The ratio of the 6 major KL was significantly different in aqueous extracts with very low concentration of yangonin whereas the organic extracts were almost identical to one another. The commercial caplets were high in kavain and dihydrokavain. The aqueous kava root extract contains the lowest proportion of KL of all the root extracts, as expected from the reported low water solubility of KL. All the extracts (aqueous, acetone extract and caplet extract) inhibited the activity of the human liver microsomal P450 enzymes, CYPs 1A2, 2C9, 2C19, and 3A4, with the aqueous extract being the least potent. The authors suggest that the variations in the health effects reported for the kava extracts may be due to the differences in the proportion of KL and use of different preparation protocols.

The effect of kava extract and its constituents on human P450 enzyme activity was investigated *in vitro* using human liver microsomes. When hepatic microsomes were incubated with whole kava organic extract (normalized to 100 µM kavalactones), the activities of CYP2C9, CYP2C19, and CYP3A4 were most markedly inhibited (78 to 92%) compared to the control. There were also significant decreases in the activities of CYP1A2 (56%), CYP2D6 (73%), and CYP4A9/11 (65%). In the case of individual kavalactones at a concentration of 10 µM, M, and DHM, were most potent inhibitors followed by DMY. K did not inhibit these enzymes. DHM strongly inhibited CYPs 2C9, 2C19 and 3A4 (54-76%), M inhibited 2C9, 2D6 and 3A4 (27-58%) and DMY inhibited 2C9 and 3A4 (40-42%) (Mathews et al. 2002). *K*i values for the inhibition of CYP2C9 and CYP2C19 activities by M, DHM, and DMY ranged from 5 to 9 µM. K and DMY (<9 µM) modestly stimulated human P-glycoprotein ATPase activities (Mathews 2005).

In another *in vitro* study (Zou et al. 2004) using both cDNA-expressed human enzymes and cryopreserved human hepatocytes, ethanolic extract of dried kava root and three purified kava lactones (M, DMY, and Y) were found to be potent inhibitors of CYPs 1A2, 2C9, 2C19, 2E1, and 3A4 with IC_{50} values <10 µM. The individual KL were also moderately cytotoxic to human hepatocytes (EC_{50} values of approximately 50 µM). Methysticin was the most potent CYP enzyme inhibitor and most cytotoxic affecting hepatocyte viability followed by kava root extract, DMY and Y. These results suggest that kava could potentially reduce the metabolic clearance of a number of co-administered drugs. Moreover, the CYP2C9 and 2C19 being polymorphic, the effects could vary among genetically different individuals.

In vitro studies in human hepatocytes (HepG2) examining the hepatotoxicity of kavain, methysticin and yangonin demonstrated that kavain had minimal cytotoxicity, methysticin showed moderate concentration-dependent toxicity and yangonin (25 µM) displayed marked toxicity with ~ 40% reduction in cell viability unlike it's least toxicity in cryopreserved hepatocytes (Zou et al. 2004). Apoptosis was induced by yangonin and methysticin indicating that the predominant mode of cell death was apoptosis rather than necrosis. No significant changes were observed in glutathione levels suggesting that glutathione depletion may not be involved in the kavalactone induced injury (Tang et al., 2011). The authors note that the discrepancy in yangonin toxicity may be due to the use of cultured hepatocytes versus cryopreserved hepatocytes.

The above *in vitro* studies using cDNA–expressed CYPs, human liver microsomes, or cryopreserved or cultured hepatocytes, kava extracts and specific kavalactones have been shown to inhibit a variety of human CYP isoforms in the low micromolar range.

***In vivo* studies**

Russmann et al. (2005) conducted a small study in 6 healthy volunteers from New Caledonia, who were regular consumers (>6 years) of the traditional aqueous kava

extract (7-27 g kavalactones/week) up to the beginning of the study who agreed to abstain from kava for 30 days. Determination of metabolic ratios after oral administration of 5 probe drugs reflecting CYP enzyme activity during kava drinking and after a 30-day kava abstinence demonstrated the inhibition of CYP 1A2. However, this practice had no effect on the phenotypic markers of CYP2C19, 2D6, 2E1, or 3A4 function.

In contrast, Gurley et al. (2005) observed that 30 days of kava supplementation in healthy volunteers had no effect on the phenotypic markers of CYP1A2, CYP2D6, or CYP3A4 activity; but CYP2E1 activity was significantly inhibited (~40%).

M, DHM, and DMY appear to be the most potent inhibitors of CYP3A4. Inhibition of 3A4 could lead to elevated plasma levels of simultaneously ingested drugs with potential liver toxicity.

Mechanisms of toxicity

Many mechanisms have been postulated to explain the unexpected toxicity, one being pharmacokinetic interactions between kavalactones and co-administered drugs involving cytochrome P450 enzyme system. Alcohol is often co-ingested in kava hepatotoxicity cases.

It has been reported that 7-9% of Caucasians (Poolsup et al., 2000) 5.5% of Western European, almost 1% of Asian are homozygous deficient in CYP2D6, while it is almost 0% in persons of pure Polynesian descent (Wanwimolruk et al., 1998). Similarly, CYP 2C19 (wild type) gene is absent in 2 to 6% of Caucasian populations and in up to 20% of Asian populations (Zou et al 2004). Thus, genetic polymorphism of CYP enzymes may be one of the factors contributing to the differences in the hepatotoxic response between Pacific islanders and Caucasians.

Overall, it can be concluded that these findings indicate that kava has a high potential for causing drug interactions through inhibition of P450 enzymes responsible for the majority of the metabolism of pharmaceutical agents.

Neurological effects:

The major physiological action in humans is consistently reported as a pleasant, mild, centrally acting relaxant property which induces a generalized muscle relaxation and, ultimately, a deep natural sleep. A minor property of kava is its local anesthetic properties which are experienced as numbing of the mucous membranes of the mouth and tongue when the beverage is consumed.

K and DHK are reported to exert the strongest anxiolytic activity. The psychotropic effects of kava are achieved by the modulation of gamma-amino-butyric acid (GABA) receptors. Although the exact mechanisms are not known, studies suggest that the effects are mediated via different mechanisms such as upregulation of GABA-A receptor function, blockade of voltage-gated sodium ion channels,

enhanced ligand binding across GABA-A receptor subtypes, and reduced excitatory neurotransmitter release.

Using an *in vitro* neonatal rat gastric-brainstem preparation, it was shown that kavalactones and DHK significantly inhibited the activity of the neurons in the nucleus tractus solitarius of the brain stem suggesting their role in the modulation of GABAergic neurotransmission (Yuan et al. 2002). Another *in vitro* study examining the functional effects of kavain at 9 different human GABA-A receptor subtypes expressed in xenopus oocytes found that kavain positively modulated all receptors regardless of the subunit composition, but the degree of enhancement varied at certain receptors. Thus, providing evidence for the direct interaction of K with GABA-A receptors. The modulatory effect of kavain was unaffected by flumazenil, indicating that kavain did not enhance GABA-A receptors via the classical benzodiazepine binding site. It is interesting that K and diazepam did not modulate GABA-A receptors in an additive manner (Chua et al. 2016).

Thus, N-methyl-D-aspartate (NMDA) receptors and/or voltage-dependent calcium channels may be also involved in the elementary mechanism of action. Their effect on the brain is different from that of benzodiazepines or tricyclic antidepressants. The anticonvulsive properties are similar to those of local anesthetics, especially procaine. Analgesia produced by kava occurs via non-opiate pathways.

In addition, a synergistic effect is possible for substances acting on the central nervous system, such as alcohol, barbiturates and psychopharmacological agents.

Effects of Alcohol

Kava is often consumed with alcohol, which may potentiate the hepatic injury. Jamieson and Duffield observed the positive interaction of intraperitoneally administered ethanol and orally administered kava resin in male Balb/c mice. The authors stated that kava resin significantly increased alcohol hypnosis and noted that 300 mg/kg kava resin proved to be lethal to 3 of 6 mice treated with 4 g/kg ethanol, indicating that toxicity and hypnosis were increased. (Jamieson and Duffield, 1990).

Genotoxicity test

The mutagenicity of 6 major kavalactones as well as different solvents kava extractions of roots, leaves, and stem peelings were evaluated using the *umu* test (a sensitive test for point mutations). The results indicated that the 6 KL (100-300uM) were not mutagenic. Two C-glycoside flavonoids (2''-O-rhamnosylvitexin and schaftoside) isolated from *n*-butanol fraction of kava leaves displayed mutagenic potential (Jhoo et al. 2007). Bacterial mutagenicity and *in vivo* micronucleus studies also indicate that kava extract is not mutagenic (Whittaker et al. 2008).

VI. Safety Concerns of the Use of kava in Food

Although small doses of kava induce muscle relaxation and/or drowsiness, long-term and excessive use of kava can lead to malnutrition, weight loss, and apathy**.**

Adverse effects of kava consumption

Hepatotoxicity

Case reports

Kava associated hepatotoxicity is the most concerning adverse effect and has led to bans in Germany, Switzerland, France and Canada. Several cases of liver damage have been associated with kava exposure in Europe including hepatitis (Humberston et al., 2003; Stickel et al., 2003), cirrhosis and liver failure (Escher et al., 2001; Kraft et al., 2001), and death (Gow et al., 2003, Russmann 2001).

World Health Organization (WHO) identified and reviewed 93 case reports with presumed kava related hepatotoxicity. 79% cases involved women with an average age of 45 years using kava for anxiety. In this case series, 7 patients died and 14 had liver transplants. 8 cases with probable associations (essential information for standard assessment available) and 53 cases with possible kava use and hepatotoxicity (insufficient data for a full assessment, or there were other potential causes of liver damage). 5 cases with a positive rechallenge. WHO conclusions after the review of these cases are 1. There is a significant concern of a cause and effect relationship between kava products and hepatotoxicity. 2. A nonrandom effect is indicated by a higher rate for the organic extracts than for synthetic products. 3. In organic extracts, components other than kavalactones might be responsible for hepatotoxicity. 4. Kava products have a strong propensity for kava-drug interactions. 5. Risk factors for hepatic reactions appear to be the use of organic extracts, excessive dose, heavy alcohol intake, pre-existing liver disease, and genetic polymorphisms of cytochrome P450 enzymes. Also, co-medication with other potentially hepatotoxic drugs and interacting drugs, particularly other anxiolytics, antipsychotics, and anti-thrombotics might lead to harm (Coulter et al., 2007).

26 cases of suspected kava hepatotoxicity reported from Germany (20) & Switzerland (6), of which 3 died, 6 survived after liver transplantation and the rest liver issues resolved after kava cessation & supportive care. Patients with hepatotoxicity all used ethanolic and acetonic extracts of kava. Teschke et al. (2008) re-analyzed and assessed the causality using the system of the Council for International Organizations of Medical Sciences, for probability scoring. The results of the analysis were as follows indicating that kava when taken as recommended carries a lower risk whereas overdose, prolonged treatment, and co-medication may carry an increased risk.

16-excluded due to lack of temporal association, independent of kava or co-medication
2-low score excluded
8-various degrees of causality

1- Toxic liver injury, probable causality for kava, the patient followed kava usage recommendations (≤120 mg/d kavalactones and ≤3 months)
1- Probable
1- Highly probable (rechallenge)
2- possible co-medicated drugs
3- possible overdose and/or longer duration

78 cases of hepatotoxicity have been reported following ingestion of commercial kava caplets. In several of these cases, hepatic failure required liver transplantation or has been fatal (Clouatre, 2004). Two cases have been attributed to depletion of human CYP2D6, the enzyme responsible for kavalactones metabolism (Anke, J., Ramzan, I. 2004). Most other cases involved concomitant ingestion of drugs known for their potential hepatotoxicity or of other pharmaceuticals, which suggests that herb–drug interactions may be implicated.

Becker et al. 2019 report first detailed case report of liver transplantation in a 45-year old female associated with kava use (100 mg daily) for 52 days in Brazil. The authors thoroughly investigated the case, analyzed the sample used by the patient to exclude contaminants and intrinsic toxicity of the substance. The chemical analysis demonstrated methanolic extraction and all the kavalactones were present with no contaminants or adulterants. Causality was inferred between liver damage & kava usage through the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm.

Several studies show a clear association of increased level of liver enzymes GGT, ALP, and moderate to heavy kava beverage consumption as shown in Table 2.

Table 2

% population w/ Abnormal Liver function test results					
Study	Subjects	GGT	ALP	AST	ALT
Brown et al. 2007	Healthy Tongan (31+31)	65 vs. 26 control	23	Normal	Normal
Cairney et al. 2003	Australian Arboriginal (11)	73	65	NA	Normal
Clough et al. 2003	North Arnhem Aboriginal (98)	48	37	NA	24-29
Clough et al. 2003	East Arnhem Aboriginal (101)	61	50	NA	21-24
Russmann et al. 2003	New Caledonia (27)	85	NA	26-29	19-35
Mathews et al. 1988	Arboriginal	NA	NA	NA	NA

Hepatic injury due to traditional aqueous extracts of kava root was reported in a study of 27 heavy kava drinkers in New Caledonia (Russmann et al. 2003). Kava-induced toxic hepatitis was reported in a tourist after consumption of kava beverages (cumulative volume of 2-3L) in traditional Samoan Kava ceremonies (Christl SU et al. 2009). An outbreak of hepatitis A was associated with kava drinking in Western Australian Goldfields when a hepatitis A infected individual, a day after discharge from the hospital participated in kava drinking. The authors suggest that the source of hepatitis A infection was most likely during preparation of kava and/or via the shared drinking vessel (Parker et al. 2014).

In 2002, the US Centers for Disease Control and Prevention (CDC) issued a report on hepatotoxicity associated with kava-containing products. On March 25, 2002, the FDA warned that kava may be linked to serious liver damage, including hepatitis, cirrhosis, and at least four urgent liver transplants. FDA has issued warnings to consumers and physicians.

Phototoxicity

UVA irradiation of kava extract in the presence of a lipid, methyl linoleate, induced singlet oxygen and carbon-centered free radicals, which mediated lipid peroxidation, caused DNA strand cleavage, and generated 8-hydroxy-2′-deoxyguanosine (8-OHdG) adduct in human HaCaT skin keratinocytes. The results revealed that kava extract, 5,6-dehydrokawain, and yangonin are cytotoxic. The

authors of the study suggest that kava is photocytotoxic, photogenotoxic and human exposure to products that contain kava extract may enhance their sensitivity to skin dermopathy and skin cancer caused by ultraviolet A light or sunlight (Xia et al. 2012).

Dermopathy

Kava dermopathy is the most common side effect of excessive and chronic use of kava >310 g/week) and widely recognized in Fijians (Hannam et al. 2014). Kava dermopathy, a type of reversible icthyosiform dermatitis is presented as scaly skin rashes, urticaria, sebotropic eruption. It has been reported in approximately 45% of "regular" consumers, and up to 78% of heavy kava consumers (Rychetnic et al. 2011). Current and ex-kava users among Aboriginal population in northern Australia, showed a higher rate of kava dermopathy, lower body mass index, lowered blood lymphocytes and, in addition, current kava users showed elevated liver enzymes (Cairney et al. 2003). There are case reports of inflammatory sebotropic eruption with erythematous papules, pruritic eruptions on face and torso (Huynh et al 2014, Guro-Razuman et al. 1999). Recently, in the USA, inflammatory sebotropic eruption was reported in a female in her 30s who drank kava tea presented with notable facial swelling, postauricular lymphadenopathy and erythematous papules coalescing into plaques on the face, arms, thighs, chest, abdomen, and back. Her lab results showed significant elevation of white blood cell, eosinophil and neutrophil counts and liver enzymes (Brown-Joel et al. 2018). In UK, the first report of acute cutaneous toxicity in a 23-year old white woman to kava consumption showed inflammatory sebotropic eruption and urticaria with consistent clinical (pruritic, erythematous plaques with some facial swelling, fever and lymphadenopathy), histological (folliculocentric inflammation, rich in neutrophils lymphocytic) and biochemical (neutrophilia and transaminitis) features. (Steele et al. 2020). The sebotropic eruption is thought to be caused by the lipophilic nature of the kavalactones that accumulate in the lipids of the sebaceous glands which then leads to folliculocentric inflammation.

Allergy

Delayed hypersensitivity allergic skin reactions have been reported, including systemic/contact-type dermatitis, sebotropic reactions, and generalized erythema with papules following 2 – 3 weeks of use (Schmidt and Boehncke, 2000). Mast cells are key players in delayed hypersensitivity reactions. It is reported that when mast cells are exposed *in vitro* to aqueous extracts of kava prepared by traditional methods of Pacific islanders, highly active, unidentified components of the aqueous extract promoted calcium release, influx and the secretion of pro-inflammatory mediators which may be the causative components of kava-induced skin inflammation. Kavalactones (M, DHM and K) either alone or in combination did not elicit such response in mast cells (Shimoda et al. 2012).

Effect on Motor skills

In a population-based case-control study, the association between driving after consuming kava and serious injury-involved four-wheel motor vehicle crashes was conducted in Fiji. The results of the study showed that driving within 12 hr of consuming kava in recreational settings was associated with a four-fold increase in the odds of crash involvement, after controlling for confounding factors. Frequent use of kava over the previous 12 months (once a month to once a week and several times a week to daily) was also associated with increased odds of injury-involved crashes (Wainiqolo *et al*. 2016). Four experimental studies examining the effect of pharmacological doses of kavalactones (≤300 mg/d) using computer-based driving simulation have shown slowed reaction time, and the visuo-motor performance on driving simulation was significantly impaired when kava was consumed with alcohol (Wainiqolo *et al*. 2015).

If higher doses of kava are used when driving and operating heavy machinery, caution is advised, as visual attention may be possibly impaired under cognitive demand. In addition, caution is also advised when ingesting kava with alcohol or other substances, as deficits in attention, accuracy and concentration may occur (Foo and Lemon, 1997).

In Utah, a 44 yr old was convicted of 'driving under the influence' after ingesting 16 cups of kava beverage as his driving was impaired and was stopped for swerving in and out of traffic lanes (Deseret news, Aug.5, 1996). Similarly, in California, there were two cases of drivers arrested for 'driving under the influence' after ingesting kava tea. Neither of them was prosecuted.

Cardiovascular effect

A cross-sectional study in the Arnhem Land Aboriginal community revealed that kava's health effects include seizures and extreme weight loss in heavy users (up to 20% of body mass), Raised total and low-density lipoprotein (LDL) cholesterol levels may be a risk factor for cardiovascular disease and sudden cardiac deaths. Potential immunosuppressive effects are suggested by relative lymphocytopenia in heavy kava users. It has been associated with increased red blood cell volume, reduced platelet volume, and reduced serum albumin (Clough et al. 2003). In heavy kava users, tachycardia, electrocardiogram abnormalities (tall P waves-sign of right atrial enlargement) and shortness of breath have been reported (Mathews et al. 1988). P wave abnormalities reflect pulmonary hypertension.

Systemic effects associated with excessive kava use are hepatotoxicity, malnutrition, weight loss, renal dysfunction, and depression of plasma proteins, platelet and lymphocyte levels.

Neurological

Intoxicated kava drinkers (who consumed 205g of kava powder (approximately 150-times clinical doses) showed ataxia, tremors, sedation, blepharospasm and elevated liver enzymes (GGT, and alkaline phosphatase), together with saccadic dysmetria, saccadic slowing, and reduced accuracy performing a visual search task. Kava elicits a dose-dependent psychotropic effect. Kava intoxication is characterized by specific abnormalities of movement/motor coordination and visual attention but normal performance of complex cognitive functions. Saccade abnormalities suggest disruption of cerebellar and GABAergic functions (Cairney et al. 2003a).

A double-blind, randomized, placebo-controlled study in participants with generalized anxiety disorder (GAD) (n = 75) treated with either an aqueous extract of kava (120/240 mg kavalactones), for 6 weeks observed moderate effects on reducing anxiety in the kava group (Hamilton Anxiety Rating scale, HAMA) compared to placebo. However, more headaches were reported within the kava group, GABA transporter polymorphisms were associated with HAMA reduction. The authors conclude that standardized kava may be a moderately effective short-term treatment option for GAD (Sarris et al., 2013c).

Kava may also cause adverse neurological effects and cause excessive perioperative sedation. Such a reaction may be due to benzodiazepine and antidepressant activities on noradrenergic and/or serotoninergic pathways that may potentiate benzodiazepine and induction anesthetic potency (Raduege et al. 2004). A review implicates kava use to effect electroconvulsive therapy outcome in patients due to its neurological actions (Patra and Coffey, 2004). Several cases of central dopamine antagonism have been reported after short-term use (1 –4 days), including torticollis, oculogyric crisis and oral dyskinesias in young to middle-aged people, serious exacerbations of Parkinsonian symptoms (Schelosky et al. 1995; Meseguer et al. 2002)

Musculoskeletal effect

A case of rhabdomyolysis was reported in a 29-year old man after ingestion of an herbal product containing guarana (500 mg), ginkgo biloba (200 mg) and kava (100 mg) (Donadio et al. 2000). Another case of rhabdomyolysis associated with ingestion of large amounts of kava was reported where the 34-year old patient developed peak creatine phosphokinase levels in excess of 30,000 U/L but had no significant renal damage. The patient denied any other ingestions, medications, and excessive exertion (Bodkin et al. 2012).

VII. Drug, herb, and dietary supplement interactions

Kava displays a propensity for both pharmacokinetic and/or pharmacodynamic interactions with other drugs and herbs. This is of concern especially with drugs

that are metabolized by CYP1A2, CYP2C19, and CYP3A or those eliminated by P-glycoprotein, or that have sedative or hepatotoxic effects. Use of different kava cultivar varieties, plant parts other than the roots or contamination with mold hepatotoxins may increase toxicity. Co-administration of kava with acetaminophen (APAP) in mice indicated the possibility of kava potentiating APAP-induced hepatotoxicity. Further, the authors identified synergistic action of flavokavains A and B with APAP hepatotoxicity (Narayanapillai et al., 2014)

VIII. Overall Conclusion

After reviewing the available data and information, toxicology concludes that there is enough toxicological data that demonstrates that indiscriminate use of kava either as a "recreational" or "relaxation" beverage is not safe for human consumption. Moreover, there is no food additive regulation in effect that provides for the safe use of kava as an ingredient in conventional foods, and we are not aware of a basis for such use to be considered as generally recognized as safe (GRAS).

A safety determination for a substance that will be used as an ingredient in conventional food must be based on scientific studies appropriate to establish the safety of the substance under the conditions of its intended use. Further, the GRAS exemption requires not only the safety of the intended use of that substance but also that such safety is generally recognized by experts qualified by scientific training and experience to evaluate the safety of substances added to food. As discussed above in the overview of studies regarding the safe use of kava in foods, since the published literature and numerous case reports raise not only the known risk of hepatotoxicity but also several other adverse effects, we believe that the experts cannot come to a consensus regarding the safety of kava. There is sufficient evidence in rodents (NTP studies) for the carcinogenicity of kava extract. The relevance of such findings for humans cannot be ignored, especially when such neoplastic mechanisms were observed in the target organ, liver. The lack of adequate studies on kava preparations to assess any reproductive and developmental toxicities is also a concern. Additionally, kava has been shown to interact with a number of other drugs, herbs, and dietary supplements and co-administration of these substances with kava may lead to serious negative consequences.

In light of the safety concerns as discussed above, there is no basis to conclude that the use of kava as an ingredient in conventional foods is GRAS. Therefore, DFI/OFAS/FDA considers kava an unapproved food additive when used as an ingredient in conventional foods.

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