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Supporting document 1

Risk and technical assessment – Urgent Proposal P1057

Kava (*Piper methysticum*) beverage for traditional and recreational use

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Executive summary

The proposal was prepared following a request from the Chair of the Food Ministers' Meeting, Senator the Hon Richard Colbeck, to the Chair of the FSANZ Board. The request was for FSANZ to consider preparing and then declaring urgent a proposal to review the provisions of the Australia New Zealand Food Standards Code (the Code) relating to kava.

This assessment examines the public health and safety risks associated with the consumption of kava beverage in a manner consistent with traditional cultural practice and current regulatory policies in Australia and New Zealand. This risk assessment work was prompted in response to the commercial importation of kava into Australia becoming unlimited from December 2021, as part of the Australian Government's commitment to the Pacific.

Standard 2.6.3 of the Code permits the sale in Australia and New Zealand of kava root or kava beverage obtained by aqueous suspension of kava root.

Traditional and recreational use of kava

Kava beverage has significant traditional and cultural importance for tropical communities throughout Micronesia, Melanesia and Polynesia. Believed to originate in Northern Vanuatu, kava was likely carried across Oceania by early maritime explorers and traders, and has been consumed for more than 1000 years. Its place in traditional Pacific cultures is central to social ceremonies and gatherings.

Kava beverage is not a widely consumed food in Australia or New Zealand, except in some Pacific communities, or select First Nation communities in Australia. Kava was introduced into Arnhem land in the 1980s.

Method of preparation for traditional and recreational use

Traditional kava beverage is prepared by aqueous extraction using fresh or dried roots of the kava plant to produce a brew in a communal bowl. Fresh material is peeled before being chewed or ground until it is fine and fibrous, and infused with water. Dried material is ground

finely, wrapped in cloth and infused in water. The beverage is then typically consumed immediately.

Complementary medicines are manufactured differently and often involve extraction with organic solvents resulting in different chemical profiles to that of aqueous beverages. A consideration of the safety of kava in complementary medicines is outside the scope of this proposal.

Identity and composition of kava plants

There are more than 200 varieties of kava plant. 'Noble' kava varieties have been safely used by Pacific cultures for kava beverage production. Noble varieties are distinguished by their geographical distribution, physical plant characteristics and the properties of the kava beverage they produce. Other kava varieties are not suitable for making kava beverage.

The pharmacologically active compounds in kava are kavalactones - 4-methoxy-2-pyrones with phenyl or styryl substitutes at the 6th position. There are six major kavalactones and up to thirteen minor kavalactones that are extracted from the root of the kava plant during the preparation of kava beverage. The total kavalactone content of kava plants varies from 3% to 20% of dry weight, depending on variety, growth conditions and part of the plant.

Flavokawains and piperidine alkaloids, also found in kava plants, generally make up less than 1% of dry weight. It has been suggested that these compounds may be more toxic than kavalactones, however little toxicological data is available for either flavokawains or piperidine alkaloids.

Pharmacology

Kavalactones have been reported to have psychopharmacological effects as well as muscle relaxant, local anaesthetic, anxiolytic and anticonvulsive properties. Moderate to high doses of kavalactones can lead to drowsiness and sedation. The mechanism of action of kavalactones has not been well established, but may involve direct interactions with voltage-operated ion channels or activities through the cognate receptors for γ-aminobutyric acid, serotonin, endocannabinoids and glycine.

Pharmacokinetics

Limited information is available on the pharmacokinetics of kavalactones. In a rat study, kavain, the major kavalactone in kava beverage, was well absorbed and approximately 50% bioavailable. In humans, kavain is extensively metabolised in the liver by CYP-mediated biotransformation, before sulfonation, glucuronidation or glutathione (GSH) conjugation. More than 90% of a 100 mg/kg bodyweight (bw) dose of kavain was excreted within 72 hours as either unchanged kavain or kavain metabolites in the urine and faeces of rats. There is no evidence of bioaccumulation in humans, rats or mice.

Potential for drug interactions

Limited information is available on potential for drug interactions. However substances in kava have been shown to inhibit CYP isoforms 1A2, 2C9, 2C19, 2D6, 3A4 and 4A9/11 *in vitro* demonstrating the potential for drug interactions. Caution is recommended when consuming kava beverage in combination with alcohol, medicines (particularly benzodiazepines, opioids, barbiturates and paracetamol) or other herbal preparations.

Toxicological studies in laboratory animals

A non-guideline, four week oral administration study in rats using an aqueous extract of kava intended to be representative of kava beverage, did not report any adverse effects at doses of up to 500 mg/kg bw/day kavalactones.

An U.S. National Toxicology Program (NTP) report assessed the chronic toxicity and carcinogenic potential of an orally administered pharmaceutical kava extract in mice and rats. Increased liver weights and hepatocellular hypertrophy were observed in both species. In male mice, there was a dose-related increase in the incidence of hepatoblastoma at doses above 500 mg/kg bw/day. In female rats, hepatocellular adenoma or carcinoma were observed in all treatment groups. A small but statistically significant dose-related increase in testicular interstitial (Leydig) cell adenoma was seen in all male treatment groups. The findings demonstrate a potential for kava extracts to elicit hepatotoxicity but the relevance of the test article to an aqueous extract is unknown.

No genotoxicity studies were available for aqueous kava extracts. The kava extract assessed by the U.S. NTP was not genotoxic in bacterial mutagenicity or *in vivo* micronucleus studies.

No reproductive or developmental studies are available in laboratory animals.

Studies in humans

There were no high quality clinical trials that used kava beverage as the test item. Three clinical trials were available using a capsule prepared from hot-water kava extract, which provided the best comparator for understanding kava beverage safety.

A 16-week randomised, double-blind, placebo-controlled clinical trial investigated the effects of hot water kava extract tablets (240 mg/day kavalactones) in participants with diagnosed generalised anxiety disorder. The kava group self-reported more frequent occurrences of poorer memory and tremor/shakiness. Statistically significant increases in the proportion of liver function tests reporting above baseline abnormalities were observed in the kava group, measured by increases in γ-glutamyl transferase (GGT), aspartate transaminase (AST) and alanine aminotransferase (ALT).

In two separate three- and six-week clinical trials using a similar aqueous extract (250 mg/day kavalactones), no treatment-related changes in liver abnormalities or adverse events were observed.

A number of cases of liver toxicity have been reported in association with kava extracts used for medicinal purposes in Germany and Switzerland. These cases varied in severity from abnormal liver function (high levels of GGT and alkaline phosphatase (AP), with associated increases of ALT) to liver failure, including fatality and liver transplants. The causative factor of these observed hepatotoxicity events remains unknown. In all of these reported cases, kava had been consumed as complementary medicines, supplements or herbal medicines.

Health effects associated with traditional or recreational use of kava beverage

Kava beverage is culturally significant to communities in the South Pacific, where it has a long history of consumption. Kava beverage is not a widely consumed food in Australia or New Zealand, except in some Pacific communities, or select First Nation communities in Australia. Acceptance of kava beverage as a safe recreational beverage has increased kava consumption in traditional and non-traditional communities. The long tradition of use with minimal evidence of adverse health events from kava beverage consumption in moderation demonstrates that it is possible to allow kava beverage consumption into communities safely.

However, the consumption of kava beverage results in kavalactone intakes greater than the recommended daily intake for therapeutic goods, and kava beverage has the potential to become a substance of abuse. Evidence of negative health outcomes have been observed in communities with established patterns of ongoing high-level consumption of kava beverage. Such ongoing high-level consumption has been associated with a scaly skin rash, altered liver function and other general reductions in overall health. Altered liver function is observed as an increase in the liver enzymes GGT and AP. These changes are reversible, and occur without an observed increase of ALT or other signs of liver toxicity. Changes in liver function associated with kava beverage consumption are not consistent with the severe hepatotoxicity events observed in consumers of herbal medicines.

It has been suggested that the negative health effects associated with kava beverage become pronounced with consumption in excess of 400 g/week of dried kava powder.

No information was available to allow an assessment of the use of kava beverage in pregnant or lactating females, adolescents or children.

Kava beverage is not consumed for nutritional benefit, rather as part of cultural practices and for its intoxicating properties. There are no known nutritional problems associated with the moderate use of kava.

Microbiological assessment

The microbiological risk from the consumption of kava beverages obtained by aqueous suspension of dried or raw kava root is low when kava is produced and prepared in line with current risk management measures, including the application of Good Agricultural Practices and Good Handling Practices.

Limitations in the available data

Data gaps exist in the available scientific literature to understand the toxicity, potential dosage and pharmacokinetics of each biologically-active chemical constituent in kava beverage. The majority of available data relate to herbal extracts of kava, which are chemically distinct from the kava beverage.

There is insufficient information on the prevalence of pathogenic microorganisms on fresh or dried/powdered kava root or in kava beverages; and on the potential for persistence or growth of any such pathogens on the product.

However, in the absence of this information, there remains significant population-based evidence demonstrating that traditional and recreational consumption of kava beverage in moderation is safe.

Conclusion

Kava beverage has a long history of consumption in the South Pacific and has an important role in traditional community ceremonies. In recent times, it has become more widely consumed as a recreational beverage in both the Pacific community as well as in the wider international community. This significant history of use demonstrates that it is possible to safely consume kava beverage in moderation for traditional and recreational purposes.

No information was available to allow an assessment of the safety of kava beverage consumption in pregnant or lactating females, adolescents or children. Therefore it is not

possible to draw a conclusion on the safety of kava beverage consumption by these population subgroups.

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Glossary

AP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
CYP	Cytochrome P450 enzymes
FAO	Food and Agriculture Organisation of the United Nations
GAP	Good agricultural practices
GGT	γ-glutamyl transferase
GHP	Good hygienic practices
GSH	Glutathione
Kava	Also known as: *kawa, kava kava, awa, ava, yati, wati, jagona and yangona*
Kava beverage	Traditional cold water extraction from kava plant
Kava extract	Herbal extracts from kava plant that are not traditional kava beverage
Kava plant	*Piper methysticum* G. Forst
LC50	50% lethal concentration
LD50	50% lethal dose
NTP	U.S. National Toxicology Program
WHO	World health Organisation of the United Nations

1 Introduction

This assessment examines the public health and safety risks associated with the consumption of kava beverage in a manner consistent with traditional cultural practice and current regulatory policies in Australia and New Zealand. This risk assessment work was prompted in response to the commercial importation of kava into Australia becoming unlimited from December 2021, as part of the Australian Government's commitment to the Pacific.

The term kava is used interchangeably for the kava plant or various extracts of the kava plant. The kava plant (*Piper methysticum* G. Forst) is a robust perennial shrub belonging to the black pepper family *Piperaceae*. Kava beverage is a cold water extraction from the roots, rhizomes or basal stems of select kava plant varieties.

The term kava is also used to refer to herbal preparations of kava in medicinal products that are formulated using the kava plant, or processed extracts of the kava plant. Other common names for kava are: *kawa, kava kava, awa, ava, yati, wati, jagona* and *yangona* (Singh, 1992; FAO/WHO, 2016).

Drinkers of the traditionally prepared kava beverage report a sense of relaxation and tranquillity, and the drink is taken to promote a sociable attitude. Standard 2.6.3 of the Australia New Zealand Food Standards Code permits the sale of kava root, or kava beverage obtained by aqueous suspension of kava root, in Australia and New Zealand.

1.1 Traditional use of kava

Kava beverage has significant traditional and cultural significance to select tropical communities throughout Micronesia, Melanesia and Polynesia. Believed to originate in Northern Vanuatu, kava was likely carried across Oceania by early maritime explorers and traders, and has been consumed for more than 1000 years (Lebot et al., 1992). Its place in traditional pacific cultures is central to social ceremonies and gatherings (Lebot et al., 1992; Aporosa, 2019).

Traditional kava beverage is prepared by aqueous extraction using fresh or dried roots to produce a brew in a communal bowl. Fresh material is peeled before being chewed or ground until it is fine and fibrous, and then infused with water. Dried material is ground finely, wrapped in cloth and infused in water. The kava is then drunk from a cup or sometimes a coconut shell (Cairney et al., 2002; Aporosa, 2019).

Kava beverage is consumed in Pacific communities living in both Australia and New Zealand and by select First Nation communities in Australia.

1.2 Botanical characteristics

Kava plant is native to the tropical Pacific Island regions, with the exception of New Zealand, New Caledonia and most of the Solomon Islands (Singh, 1992). It thrives at altitudes of between 150m and 300m above sea level and grows well in stony ground. The generic name Piper comes from the Latin for "pepper", and the species name methysticum from the Greek meaning "intoxicant", thus *Piper methysticum* when translated into English means "intoxicating pepper" (Singh, 1992). Kava plant does not grow readily in New Zealand.

The plant is usually about 2 to 2.5m tall when it is harvested (Singh, 1992). Leaves are heart shaped, pointed, smooth and green on both sides, being about 15 cm in length. Although kava is a dioecious species, viable kava seeds have not been reported and the plant is cultivated through vegetative propagation (Singh, 1992).

The kava plant reaches maturity about 3-5 years after planting and the plant is usually harvested around this age. The Vanuatu government requires that kava for export must have been planted at least 5 years before it is harvested and kava for domestic use must have been planted at least 3 years before it is harvested (The Kava Act, 2002).

1.3 Varieties of kava plant

There are more than 200 varieties of kava plant (Singh, 1992). Not all kava varieties are suitable for making kava beverage. Each Pacific culture with a history of traditional kava consumption has known varieties for making kava beverage. Kava plant varieties can be divided into four categories:

1. **Traditional kava beverage varieties.** Also known as noble kavas: These varieties have been safely used by Pacific cultures for kava beverage production. They are distinguished by their geographical distribution, physical plant characteristics and the quality of the kava beverage they produce (FAO/WHO, 2016). Appendix 1 lists known noble kava varieties.
2. **Tu-dei (two day) kava varieties.** Tu-dei kavas are used to make kava beverage, but are not traditional varieties and are known to produce longer psychotropic experiences, as well as nausea and other hangover effects (e.g. headache, dizziness, lethargy) (Lebot & Lèvesque, 1989; FAO/WHO, 2016).
3. **Medicinal kava varieties.** Medicinal kava are used by Pacific herbalists in traditional medicines (FAO/WHO, 2016).
4. **Wild kava.** Wild kava (*Piper wichmanni*) is closely related to *P. methysticum*. Wild kavas are not used to make kava beverage or used in traditional medicines (FAO/WHO, 2016).

There is international acceptance of the importance for using noble kava plant varieties to make kava beverage, outlined in the Codex Alimentarius regional standard for kava products, Vanuatu's Kava Act (2002) and national kava standards of Vanuatu, Fiji, Samoa and Tonga (Appendix 1).

Standard 2.6.3 of the Australia New Zealand Food Standards Code (the Code) does not specify varieties of kava (*P. methysticum*) that are to be used to make kava beverage.

1.4 Other uses of kava

Only kava root, or kava beverage obtained by aqueous suspension of kava root, is currently permitted for sale by the Code.

Commercial herbal extracts of kava herbal extracts of kava are used in dietary supplements in New Zealand and in complementary medicines listed on the Australian Register of Therapeutic Goods. Kava extracts are water or organic solvent extracts from kava plant, standardised to contain the maximum yield of kavalactones, the pharmacologically active compounds present in kava beverage (WHO, 2008; White, 2018). Kava extracts are prohibited as an ingredient in food (Standard 1.1.1)

Kava extracts are used for the treatment of anxiety, insomnia, premenstrual syndrome and stress (White, 2018).

Kava (including kavalactone extract) is currently listed as a Schedule 4 medicine in the Poisons Standard[1], except when included in approved products on the Australian Register of Therapeutic Goods.

2 Composition and properties

2.1 Traditional kava beverage

Fresh kava rootstock contains 80% water, while dried rootstock consists of approximately 43% starch, 20% fibre, 12% water, 3.2% sugars, 3.6% proteins, 3.2% minerals and 15% (3-20%) kavalactones (Lebot et al., 1992). Minor chemical components (less than 1%) include flavokawains and piperidine alkaloids (Dragull et al., 2003; Lebot et al., 2014).

Kavalactones

Kavalactones (also referred to as kavapyrones) are 4-methoxy-2-pyrones with phenyl or styryl substitutes at the 6th position (Appendix 1; Lebot et al., 1997). They are lipophilic compounds that are sparingly soluble in water and ethanol (Appendix 2; Lebot et al., 1992).

The total kavalactone content in kava varies from 3% to 20% of dry weight, depending on subspecies, growth conditions and plant component. Concentrations of kavalactones are highest in the lateral roots and decrease progressively towards the aerial parts of the plant (Lebot and Lèvesque, 1996). Some tu-dei varieties are known to have higher kavalactone concentrations than the noble kava plant varieties (Lebot and Lèvesque, 1996; Bian et al., 2020).

There are six major kavalactones and up to thirteen minor kavalactones extracted from the root extracts of the kava plant (Appendix 2). Kavalactones are subject to degradation when stored at room temperature, such that the pharmacological effects of stored kava plant material becomes diminished over time (Duve & Prasad, 1983)

Minor kava components

In addition to the kavalactones, chalcones and alkaloids are other biologically relevant compounds found in kava plant.

Flavokawain A, B and C are dihydrochalcones that can be extracted into kava beverage (Appendix 2; Lebot et al., 2014). Analytical testing has shown these flavokawains constitute less than 1% dry weight of the chemical component of kava plant. Tu-dei kava plant varieties were found to be higher in flavokawains when compared with noble kava varieties, but still at concentrations < 1% (Lebot et al., 2014).

Five distinct alkaloids have been extracted from kava plant and are collectively called piperidine alkaloids (Appendix 2; Achenbach & Karl, 1970; Dragull et al., 2003; Lechtenberg et al., 2008). Piperidine alkaloids, such as pipermethystine, are found at the highest levels in the aerial parts of the plant (Dragull et al., 2003).

2.2 Kava Beverage Quality

Kava beverage prepared from kava plant material that is contaminated with leaves, stems or bark, or that is not of a noble kava plant variety, can contain higher concentrations of

[1] The Poisons Standard is available at https://www.legislation.gov.au/Details/F2021L01345

flavokawains and piperidine alkaloids, and is considered to be toxic (Dragull et al., 2003; Lebot et al., 2014; Martin et al., 2014).

Additionally, the tropical climate in kava-production regions places kava product at greater risk of contamination and spoilage from aflatoxin-producing *Aspergillus* species and low levels of aflatoxins have been detected in kava root (Weaver & Trucksess, 2010). Kava material becoming contaminated with aflatoxins has been proposed as a key risk factor in historical hepatotoxicity arising from consuming kava extracts (Teschke et al., 2012). However, aflatoxin concentrations have not been reported at levels that would pose a risk to human health, nor have any adverse events linked to the presence of aflatoxins in kava beverage been demonstrated (Rowe & Ramzan, 2012).

Kava quality testing

Analytical quantification of relative kavalactone, flavokawains and piperidine alkaloid abundance in kava plant material can be an effective method for determining kava quality (Teschke & Lebot, 2011; Tang et al., 2019). With established reference samples, kava quality parameters such as plant variety, kavalactone strength and likely contamination with bark, leaves or other aerial parts, could all be verified by enforcement agencies.

Laboratory testing of kava plant material occurs in the United States, supported by the American Kava Association (White, 2018). Private laboratory testing providers claim that testing methodology can identify kava cultivar, plant material adulteration and kavalactone concentration, as well as microbiological, pesticide and heavy metal contamination.

2.3 Medicinal products

Kava extracts for medicinal purposes are sold as concentrated powders, capsules or liquid extracts, and are manufactured to maximise the extraction of kavalactones from plant material.

Organic solvents (60% and above of ethanol or acetone) are used to increase the total amount of kavalactones extracted from kava plant. These commercial kava extracts are generally standardised to contain approximately 30% kavalactones (Whitton et al., 2003; Brown et al., 2007).

The kavalactone and flavokawain profile in commercial extracts differs from that of aqueous preparations. Kava extract prepared using ethanol has been reported to contain up to fifty times higher concentrations of flavokawains when compared to water extracts prepared using the same kava plant variety (Côté et al., 2004; Martin et al., 2014). Commercial extracts do not generally contain proteins, amino acids or sugars (Xuan et al., 2008).

2.4 Pharmacological properties and pharmacokinetics

Pharmacology

Kavalactones have been reported to have psychopharmacological effects as well as muscle relaxant, local anaesthetic, anxiolytic and anticonvulsive properties. Moderate to high doses of kavalactones leads to drowsiness and sedation, without reducing cognitive performance (Cairney et al., 2002; LaPorte et al., 2011).

A systematic review of clinical trials investigating the efficacy of kava extracts supported a small but statistically significant therapeutic effect on anxiety (Pittler & Ernst, 2003; Smith & Leiras, 2018). However, apparent differences were observed between kava extracts, and

there were some concerns about reporting bias in the body of evidence (Pittler & Ernst, 2003).

The mechanism of action of kavalactones has not been well established, but may involve direct interactions with voltage-operated ion channels or activities through the cognate receptors for γ-aminobutyric acid, serotonin, endocannabinoids and glycine (Bian et al., 2020).

Pharmacokinetics

Kavalactones

Based on available data from human faeces and urine, kavalactone metabolism is complex and involves hydroxylation or demethylation by cytochrome P450 (CYP) monooxygenase enzymes in the liver, before undergoing sulfonation, glucuronidation or glutathione (GSH) conjugation (Tarbah et al., 2003; Wang et al., 2019).

Kavalactone metabolites or unchanged pyrones are excreted in the urine or faeces (Duffield et al., 1989; Tarbah et al., 2003; Mathews et al., 2005).

The major kavalactone kavain, which is abundant in kava extracts and noble kava varieties, is readily absorbed after oral ingestion and approximately 50% bioavailable (Mathews et al., 2005).

In a single non-guideline study in humans, orally administered kavain reached peak serum concentration after 30 mins, and was rapidly metabolised. However, the short four hour study window used in this study was insufficient to determine a complete kinetic time course (Tarbah et al., 2003).

Kavain is extensively metabolised in the liver though CYP-mediated biotransformation with, 28 individual metabolites and conjugates detected (Wang et al., 2019). Both kavain and kavain metabolites have been detected in brain tissue, demonstrating an ability to cross the blood-brain barrier (Keledjian et al., 1998; Mathews et al., 2005).

Within 72 hours of an orally administered dose of 100 mg/kg bw in rats, more than 90% of kavain was excreted as either unchanged kavain or kavain metabolites in the urine and faeces. Excretion of kavain following intravenous injection is similar to that of orally administered kavain, demonstrating that the detection of unchanged pyrones excreted in rat faeces after oral ingestion does not preclude the absorption of kavalactones having occurred (Mathews et al., 2005).

Flavokawains and piperidine alkaloids

In a single study in rats, maximum plasma concentration was achieved approximately one hour after oral administration of 10 mg/kg bw synthetic flavokawain B (Yang et al., 2019).

In vitro studies show flavokawains can undergo CYP-mediated biotransformation and that GSH is depleted in HepG2 cells treated with flavokawains B (Zhou et al., 2010; Zenger et al., 2015).

No data was available for piperidine alkaloids.

2.5 Toxicological Studies

In vitro studies

Weak cytotoxic potential was observed in HepG2 cells for the major kavalactone yangonin (LC50 = 100 µM) (Zhou et al., 2010).

The LC50 values for flavokawains A and C were between 10 - 50 µM and for flavokawain B the LC50 was 15 µM. A cytotoxic potency value was not determined for pipermethystine, but treatment with 50 µM caused 65% cell death (Nerurkar et al., 2004; Zhou et al., 2010)..

Flavokawains A and B have been identified through *in vitro* screening as potential precursors for future selective inhibitors of malignant cell growth, with higher cytotoxic activities recorded for cancer cell lines when compared to controls (Zhou et al., 2010; Martin et al., 2014; Wang et al., 2021).

Animal toxicity data

Kavalactones

A non-guideline, four week study in rats using orally administered aqueous extract of kava that was intended to be representative of kava beverage, did not report any adverse effects at doses of up to 500 mg/kg bw/day kavalactones (Singh & Devkota, 2003).

Short-term and long-term toxicity studies were carried out on kava extract in mice and rats by the U.S. National Toxicology Program (NTP, 2012). The test item was characterised as containing yangonin (42.76%), 7,8-dihydrokawain (34.69%), kavain (8.87%), 7,8-dihydromethysticin (4.03%), methysticin (3.23%), and 5,6-dehydrokawain (2.42%) (Clayton et al., 2007). Mice and rats were administered the test substance by oral gavage up to a maximum dose of 2000 mg/kg bw/day for 90 days, or 1000 mg/kg bw/day for two years.

In the two-year study in rats, statistically significant reductions in body weight occurred in the high-dose group (1000 mg/kg bw/day) for both male and females. Dose related increases were seen in liver weights (all treatment groups) and were associated with hepatocellular hypertrophy in the high dose groups (1000 mg/kg bw/day). Twitching/seizures were observed in all treatment groups after 1 year, with higher incidences in the high dose groups (1000mg/kg bw/day). In male rats, there was small but statistically significant dose-related increase in the occurrence of testicular interstitial (Leydig) cell adenomas in all treatment groups (NTP, 2012).

In the two-year study in mice, statistically significant reductions in body weight occurred in the high-dose groups (1000 mg/kg bw/day) for both male and females. Dose related increases were seen in liver weights (all treatment groups) and the occurrence of centrilobular hypertrophy (all treatment groups). In male mice, there was a dose-related increase in the incidence of hepatoblastoma between the 500 mg/kg bw/day and 1000 mg/kg bw/day test groups. In female rats, hepatocellular adenoma or carcinoma were observed in all treatment groups (NTP, 2012).

Concurrent bacterial mutagenicity and *in vivo* micronucleus studies were undertaken by the NTP that indicated kava extract was not genotoxic, consistent with previously published results (Jhoo et al., 2007; Whittaker et al., 2008). Therefore, it was suggested that the observed carcinogenic activity in mice was mediated independently of genotoxicity, most likely through the upregulation of liver enzymes or generation of free radicals and subsequent oxidative stress.

A no-observed adverse effect level could not be determined from the results of the NTP study. These results are of questionable significance to the consumption of aqueous kava beverages as the test substance is not representative of aqueous kava beverage.

Flavokawains and piperidine alkaloids

In a non-guideline study, mice were administered of flavokawain A at dietary concentrations of 6 g/kg over 3 weeks. No signs of toxicity were observed (Li et al., 2014).

The liver was the target organ in a non-guideline, seven day study in mice using orally administered flavokawain B at a single concentration of 25 mg/kg bw/day (Zhou et al., 2010). Hepatocellular swelling and macrophage infiltration, with increases in serum aspartate transaminase (AST) and alkaline phosphatase (AP) levels, was described in treated animals (Zhou et al., 2010).

A non-guideline study in mice examined orally administered the piperidine alkaloid, pipermethystine, at a single concentration of 10 mg/kg bw/day for two weeks (Lim et al., 2007). No signs of toxicity were observed. Levels of alanine aminotransferase (ALT) and AST were unchanged after treatment. Reactive oxygen species production and oxidative stress were reported in the livers of treated animals (Lim et al., 2007).

Human Clinical Trials

Multiple clinical trials were available using kava extracts as the test subject (see the references reviewed in: Pittler & Ernst, 2003; Smith & Leiras, 2018). However, as these did not reflect kava beverage, they were unsuitable for risk assessment.

A 16-week phase III randomised, double-blind, placebo-controlled clinical trial investigated the effects of kava extract tablets (240 mg/day kavalactones) using non-medicated participants with diagnosed generalised anxiety disorder (Sarris et al., 2020). The kava extract was prepared by hot water extraction from a noble variety of kava plant, and the dose of kavalactones (70.2 mg/day kavain; 58.6 mg/day dihydrokavain; 33.3 mg/day trans-yangonin; 1.6 mg/day cis-yangonin; 24.5 mg/day des-methoxy yangonin; 24.7 mg/day dihydromethysticin; 27.1 mg/day methysticin) and flavokawains (4.92 mg/day flavokawain A; 5.56 mg/day flavokawain B) was determined by high-performance liquid chromatography (Sarris et al., 2020). Flavokawain B concentrations in these herbal extracts are higher than those reported for kava beverage prepared from noble kava varieties (Lebot et al., 2014).

Participants in the Kava treatment group self-reported more frequent occurrences of poorer memory and tremor/shakiness (Sarris et al., 2020). A statistically significant increase in the proportion of liver function tests reporting above baseline abnormalities were observed in the Kava group, measured by increases in γ-glutamyl transferase (GGT) and AST, with concomitant increases in ALT. These readings were not sufficiently elevated to indicate liver injury.

Although not statistically significant, an additional 8% of participants in the kava treatment group were withdrawn over the study period due to abnormalities in liver function tests, compared to 2% of the control group (Sarris et al., 2020).

No change in liver abnormalities or adverse events were observed in clinical trials with lower participant numbers, occurring over three (Sarris et al., 2009) and six weeks (Sarris et al., 2013). Both clinical trials used comparable aqueous kava extract preparations, which was also generally comparable to the 16-week trial of aqueous kava extract (Sarris et al., 2020). An increased incidence of headaches in the kava group was observed in the six week study (Sarris et al., 2013), while some participants in the kava group reported nausea and/or gastrointestinal side-effects in the three weeks study (Sarris et al., 2009).

While kava beverage was not used as the test substance in these clinical trials, the quantities of kavalactones in the aqueous kava extract better reflects kava beverage than organic kava extracts (Lebot and Lèvesque, 1996; NTP, 2006; Sarris et al., 2020).

3 Human health risks

3.1 Traditional kava beverage consumption

There is little evidence of significant adverse health effects in Pacific Island communities with high levels of traditional kava beverage consumption. The lack of reports available may indicate a low incidence of adverse events associated with kava beverage, or reflect the limited mechanisms for collecting and reporting the incidences of adverse events that arise within these communities (FAO/WHO, 2016).

However available studies conducted in communities with established patterns of kava beverage consumption in Australia and the South Pacific indicates that ongoing consumption of high levels of kava beverage is associated with a scaly skin rash, altered liver function and other general physical health effects (Rychetnik & Madronio, 2011). Based on observations of Australian consumers in Arnhem land, 400 g/week of dried kava powder has been proposed as the level where negative effects from kava beverage consumption readily occur (Clough et al., 2004).

Scaly skin rash

The most commonly observed side effect of ongoing consumption of high-quantities of kava beverage is a form of ichthyosiform skin rash or kava dermopathy. Kava dermopathy is characterised by dry, flaky skin and yellow discolouration of skin and nails (Hannam et al., 2014).

Onset typically begins in the face and descends towards the feet, with subsequent desquamation and cracking in a scaly pattern. In addition to the desquamating keratosis, palmar and plantar keratoderma and ocular photosensitivity can also develop (Singh, 1992). These effects are reversible once kava consumption has been discontinued (Hannam et al., 2014).

Altered Liver Function

Changes in liver function parameters, including liver enzyme levels have been reported with kava beverage consumption. Studies of the health effects of kava beverage use in Arnhem land communities documented changes in liver function tests in kava drinkers, with increased serum GGT and AP activity in 61% and 50% of kava users respectively (Mathews et al., 1988; Clough et al., 2003). Serum levels of ALT were not raised in any kava drinkers in the study, which included very heavy users. Hence, these changes in liver function did not appear to be indicative of acute liver inflammation and generally returned to normal within 1-2 months of stopping kava use (Mathews et al., 1988; Clough et al., 2003; Brown et al., 2007).

Three potential hepatotoxicity events have been reported associated with kava beverage consumption (Russmann et al., 2003; Christl et al., 2009). These rare events were characterised as increased GGT and AP activity, accompanied by concomitant increases in ALT and AST. Hepatotoxicity has not been widely reported in Pacific cultures that regularly consume kava beverage.

General physical health effects

Ongoing excessive consumption of kava beverage has been associated with a decrease in body weights (Rychetnik & Madronio, 2011). More work is needed to determine the direct cause of this observation. However, a regular reduction in dietary intakes due to acute kava beverage side effects such as nausea, indigestion and loss of appetite, is a likely factor in consumers of high amounts of kava beverage (Rychetnik & Madronio, 2011).

Other reported general health effects with a clear association with ongoing high levels of kava consumption include conjunctivitis, loss of sexual drive and raised cholesterol (Rychetnik & Madronio, 2011).

Allergenicity

Acute formation of urticarial rash arising from contact with kava plant or consumption of kava beverage has been reported (Süss & Lehmann, 1996; Grace, 2005; Steele et al., 2019).

3.2 Kava beverage as a substance of abuse

Kava does not demonstrate the same addictive properties as other substances of abuse, and infrequent consumption of kava beverage does not pose significant risk to public health (FAO/WHO, 2016). However, excessive and recurrent consumption of kava (greater than 400 g/week dried kava powder) is associated with adverse health outcomes for individuals and communities (Clough et al., 2004).

Increasing the availability of kava introduces the potential for misuse in the wider population, outside communities with established kava consumption patterns. Kava was introduced to Arnhem Land in the 1980s, where it was thought that kava beverage may provide a safer alternative to alcohol. Over the subsequent years, kava became a substance of abuse in these communities, steadily increased in prevalence and quantity during periods where regulatory settings permitted commercial importation (Clough et al., 2000; Butt, 2019). In 2007, the Australian Government imposed import restrictions in a policy effort to reduce the kava abuse in Arnhem Land communities. Kava consumption still persists in some communities in East and West Arnhem land, despite import restrictions being enforced since 2007 (Butt, 2019).

The rise in kava abuse in communities without a cultural connection to kava beverage is not unique to Australia. In Fiji, Indo-Fijian communities have acquired high-levels of kava beverage consumption, often exceeding typical consumption of native-Fijian communities (Aporosa, 2012).

3.3 Sensitive sub-populations

No information was available to allow an assessment of the safety of kava beverage consumption in pregnant or lactating females, adolescents or children. Therefore it is not possible to draw a conclusion on the safety of kava beverage consumption by these population subgroups.

3.4 Kava extracts used for medicinal purposes

Liver toxicity is the main adverse effect that has been associated with kava extracts used for medicinal purposes. Reports of hepatotoxicity emerged in Europe in 1998 and cases were later reported in non-European countries, including Australia (WHO, 2008; Teschke, 2010).

These reports contrast significantly to the effects of consuming kava beverage that are discussed above. Reported dosages ranged from 45 mg to 1200 mg kavalactones per day, taken for one week to twelve months.

In November 2001 the German Federal Institute for Drugs and Medicinal Products (BfArM) published evidence that suggested an association of kava consumption with liver damage in 26 cases reported from Germany and Switzerland (Teschke et al., 2008). These cases varied in severity from abnormal liver function (high levels of GGT and AP, with associated increases of ALT) to liver failure, including fatality and liver transplants. The causative factor of these observed hepatotoxicity events remains unknown. The evidence in some cases is compounded by other factors including previous history of compromised liver function, missing information in relation to patient history, co-medication and the consumption of alcohol. In all of these reported cases, kava had been consumed as complementary medicines, supplements or herbal medicines (WHO, 2008).

A review by the World Health Organization (WHO) found that, out of 93 cases, eight had probable association with kava use (WHO, 2008). Subsequent analysis supported that there is a likely association with kava use for medicinal purposes and hepatotoxicity (Teschke et al., 2008; Teschke, 2010).

The following have been proposed as explanations for the difference in liver effects seen between traditional uses of aqueous kava beverages and kava extracts used for medicinal purposes:

- Different chemical composition of extracts produced using organic solvents (Teschke et al., 2012).
- Potentially sourced from non-noble kava varieties, different parts of the plant or aflatoxin contamination (Teschke et al., 2011; Teschke 2012).
- Potential interactions with other medicines or herbal medicines (WHO, 2008; Teschke, 2008; Teschke, 2010).
- Possible genetic differences between Polynesian populations and Western populations with respect to CYP 2D6 (Wanwimolruk et al., 1998; Poolsup et al., 2000).

This highlights the difficulty of comparing the effects of traditional kava beverage to standardised kava extracts, which can contain up to 30 times the kavalactone concentration. The relevance of safety and efficacy studies on traditional extracts for assessing the safety of standardised extracts has been questioned.

3.5 Drug interactions

Alcohol

Alcohol consumption did not feature in Pacific cultures with traditional kava consumption practices until the arrival of European traders. Heavy alcohol consumption has been identified as a risk factor associated with hepatotoxicity events (Li & Ramzan, 2010; FAO/WHO, 2016). However, no direct mechanism for kava beverage potentiating the incidence of alcohol related hepatotoxicity events has been demonstrated (Li & Ramzan, 2010; Teschke, 2010).

The co-consumption of kava and alcohol intensifies the effects of alcohol on cognition, and alcohol and kava co-consumption has been identified as a risk factor in motor vehicle accidents on Fijian roads (Foo & Lemon, 1997; Wainiqolo et al., 2016).

Drugs and other herbal preparations

The xenobiotic metabolism pathway for kavalactones and flavokawains is shared with other active drugs and herbal products. Substances in kava have been shown to inhibit CYP isoforms 1A2, 2C9, 2C19, 2D6, 3A4 and 4A9/11 *in vitro* (Anke & Razman, 2004; Mathews et al., 2005; Li et al., 2016). Consequently, kava beverage consumption may increase the likelihood of adverse events by changing the pharmacokinetics of co-administered drugs or herbal extracts (Rowe et al., 2011). To demonstrate this potential, a single study in mice has revealed that flavokawains may increase paracetamol-induced hepatotoxicity (Narayanapillai et al., 2014)

There is insufficient *in vivo* information available to definitively outline substances that must be avoided when consuming kava. However, given the anxiolytic activity of kavalactones (Pittler & Ernst., 2003), and the potential of kavalactones and flavokawains to inhibit CYP-mediated drug metabolism pathways, care should be taken when consuming kava beverage in combination with medicinal drugs (particularly benzodiazapines, opiods, barbiturates and paracetamol) or other herbal preparations.

4 Microbiological Risks

A qualitative analysis was undertaken of microbiological risks pertinent to the consumption of kava beverages obtained by aqueous suspension of dried/powdered or raw kava root by Australian and New Zealand consumers. The assessment includes an analysis of risk factors in the growing and primary processing of kava root, and in the storage distribution and consumption of kava beverages prepared from kava root. The likely effect of risk mitigation measures, including application of Good Agricultural Practices (GAP) on-farm, Good Hygienic Practices (GHP) in handling and processing of kava, and other potential food safety / quality assurance measures is analysed.

4.1 Primary production of kava

Kava is a root crop—roots, rhizomes and basal stems are harvested from plants typically after 3–5 years of cultivation. There is very limited information available on risk factors and hazards specifically associated with the primary production of kava. As a result, the following analysis draws on information on other similarly cultivated fresh produce—particularly root/rhizome crops, such as carrots and sweet potato—and the known properties of potential associated pathogens. It is noted that the FAO/WHO expert meeting on microbiological hazards associated with fresh produce (FAO/WHO 2008) considered carrots to be a level 3 priority product. This priority group of products (i.e. level 3), although linked to foodborne illness, had limited public health impact, and there was little information available on associated hazards and potential control measures. The expert meeting did not provide a priority ranking for any other root/rhizome crop, reflecting the lack of concern about such products expressed by countries that provided data for the meeting.

It is generally recognised that contamination of fresh produce during primary production is mainly due to contact of edible parts of the plant with untreated or insufficiently treated manure/compost soil amendments and contaminated pre-harvest water (for irrigation or application of agricultural chemicals) (EFSA, 2014).

In its microbiological assessment for Proposal P1052 – Primary production and processing requirements for horticulture (berries, leafy vegetables and melons) – FSANZ identified that the risk of agricultural water being contaminated with pathogenic microorganisms is dependent on its source (e.g. surface, underground, reticulated); the location of growing areas near or on land used for livestock production, as a wildlife habitat, or for dumping of urban or industrial waste; and the occurrence of extreme weather events, such as flooding or

heavy rain (FSANZ, 2021). Other risk factors during primary production include wildlife incursion into growing areas, inadequate worker health and hygiene; and contaminated harvesting and field storage equipment. Hand harvesting can also increase the risk of contamination of the crop (FSANZ, 2021).

Kava is considered to be a heavy feeder, and producers are advised to use composts and animal manures to meet the crop's nutritional needs (Secretariat of the Pacific Community 2001). Hence, *Salmonella* spp. and pathogenic strains of *E. coli* are the microbiological hazards most likely to be associated with kava during primary production. Data on the prevalence of these pathogens in dried/powdered kava root products are lacking.

4.2 Primary processing

The lateral roots, rootstock and part of the basal stems of kava plants are harvested. Other parts of the plant are considered toxic. The product is washed to remove soil, then sorted, peeled, cut into pieces and dried. The dried roots may then be further processed into powdered kava by maceration in a mortar and pestle or by use of a mechanical grinder. Risk factors for microbiological contamination in primary processing include:

- the quality of water used for washing, including the frequency of changing the wash water. Poor practices in washing can cause cross-contamination, increasing the risk of pathogens being present in the product at this stage.
- worker and equipment hygiene and sanitation during sorting, peeling, cutting, drying and grinding. Extensive handling of the product is another cross-contamination risk.
- contamination by animals, birds, insects or dust during drying. Traditionally, drying is carried out in the open air, in the sun, on racks or screens off the ground. Increasingly, as the scale of kava production increases, drying is carried out under plastic covers or in dedicated drying sheds, which reduces the risk somewhat.

The risk arising from cross-contamination during washing is largely ameliorated by subsequent peeling of the product. The main risk factors in primary processing are, therefore, those arising during peeling, cutting, drying and grinding. The extensive amount of product handling risks introduction of norovirus and hepatitis A virus from infected food handlers, while inadequate protection of the product during drying could lead to re-introduction of *Salmonella* spp. and pathogenic *E. coli*. Data on the prevalence of these pathogens in dried/powdered kava root products are lacking.

4.3 Handling, storage, distribution and retail of dried/powdered kava products

Further product handling of kava after drying/grinding adds further opportunity for contamination of the product with norovirus and hepatitis A virus from infected food handlers. GHP throughout the post-harvest processing/supply chain can help to reduce that risk.

A further risk arises from the potential for growth of mycotoxigenic fungi, such as *Aspergillus* spp., on dried kava root and root products (e.g. powdered kava). Fresh kava root has a water content of around 80%, and the recovery of dried kava from fresh kava is about 20–25%, depending on drying time, temperature and humidity. For quality and safety reasons, producers are advised that the dried product should not contain more than 12% moisture, and typically aim for around 6%. The dried product is usually packed and stored in woven polypropylene bags so it can continue to dry/equilibrate during storage (Secretariat of the Pacific Community, 2001). Inadequate drying and improper storage conditions (e.g. high humidity), leading to water content above 12%, are the key risk factors that could lead to growth and production of aflatoxin spoilage by *Aspergillus* spp. Data on the prevalence of aspergilli in dried and/or powdered kava root products are lacking.

4.4 Preparation and consumption of kava beverage

Kava beverage is prepared from root pieces by soaking macerated roots in water, then filtering to remove the extracted solids. While the tradition of pulverising the root by mastication holds in some regions of the Pacific, it is more generally prepared by pounding the root in a mortar and pestle or using a mechanical grinder before soaking in water (FSANZ, 2004). When kava beverage is prepared from powdered kava root, the powder is mixed with water, strained and consumed. Extensive handling of the product during preparation, including the practice of mixing the suspension by hand, again raises the risk of contamination with norovirus or hepatitis A from infected food handlers. Hepatitis A is considered to be endemic in the Asia-Pacific region, as evidence by high rates of seropositivity in young children (Brown, 1987; Getahun et al., 2015). It has also been hypothesised that high rates of transmission of *Salmonella* Typhi in Fiji is related to preparation and consumption of kava, but direct evidence is lacking (Thompson et al., 2014).

Data on illness caused by consuming kava beverages contaminated with pathogenic microorganism is extremely limited. There is a single report of 2 cases of illness due to hepatitis A linked to kava consumption in Australia (Parker et al., 2014). Cases were linked to preparation of kava beverage by someone who had been recently-diagnosed as having contracted hepatitis A during recent overseas travel. No other reports of illness due to pathogens in kava beverages were identified.

There is some evidence that kava beverage is highly susceptible to microbial growth and is unsuitable for storage, even under refrigeration. Kandukuru et al. (2009) identified 16 genera of bacteria—including *Bacillus*, *Klebsiella*, and *Staphylococcus*—in extracts of kava root by PCR and DNA sequencing. Identification of *Pseudomonas* spp. implied that the extract was prone to spoilage, even at refrigeration temperatures. In further studies, Dong et al. (2011) analysed the dynamics of the microbiota of freshly made kava beverages obtained from ‘kava bars’ and stored at 4°C for up to 6 days. Increases in populations of lactic acid bacteria and *Pseudomanas* species correlated with acidification and spoilage of the product during refrigerated storage. The combination of the rapid drop in *p*H and short shelf life reduce the food safety risk from the storage of kava beverage, in spite of its high starch content and near neutral *p*H initially providing a suitable environment for growth of bacterial pathogens.

Kava beverage is not widely consumed in Australia or New Zealand, except in some Pacific communities, and some First communities in Australia. Kava plant or beverage is not currently commercially available as a food in Australia. There is little data on actual levels and frequency of consumption, or on potential levels of consumption if kava were more readily available in Australia (see Section 5 – Dietary intake).

4.5 Risk characterisation and mitigation

The extremely limited available data and evidence on the presence of microbial pathogens on kava products or in kava beverages presents challenges to assessing the risk posed to consumers in Australia and New Zealand. The one identified outbreak report demonstrates the potential for illness arising from unhygienic preparation of kava beverage by a food handler shedding hepatitis A. This can readily be extrapolated to risk arising from pathogens similarly capable of being transmitted by the faecal-oral route, such as norovirus, *Salmonella* spp, *Shigella* spp. and so on. However, the literature does not support any hypothesis that this occurs commonly. The communal nature of kava consumption would tend to this being evident as outbreaks, as opposed to isolated sporadic cases of illness.

Available production and risk management guidelines for kava include the Codex draft regional standard for kava products for use as a beverage when mixed with water (Codex, 2020); the Pacific kava producer's guide (Secretariat of the Pacific Community, 2001); and some national standards (Appendix 1). These outline the risk mitigation measures necessary for the production of kava and preparation of kava beverages. They emphasise the application of Good Agricultural Practices (GAP) in the production, harvesting and post-harvest preparation of kava root; and Good Hygienic Practices (GHP) in processing and handling of the product. The standards specify a maximum moisture content of 10% or 12% for dried, powdered kava products, to reduce the risk of fungal growth and the production of mycotoxins. The use of potable water for cleaning of kava root and in the preparation of kava beverages is also specified.

Evidence for the potential growth of bacteria in prepared kava beverages indicates that they should be consumed soon after preparation, and not stored or transported, in line with requirements for potentially hazardous foods in Standard 3.2.2 – Food safety practices and general requirements – of the Australia New Zealand Food Standards Code.

In the absence of data to the contrary, it is concluded that the microbiological risk from the consumption of kava beverages obtained by aqueous suspension of dried or raw kava root is low when kava is produced and prepared in line with current risk management measures, including the application of GAP and GHP.

5 Dietary intake

5.1 Consumption of kava

Kava beverage is not a widely consumed food in Australia or New Zealand, except in some Pacific communities, or select First Nations communities in Australia. Kava plant or beverage is not currently available in Australia as a commercial food commodity.

Kava consumption was not a feature in the traditions of Aboriginal and Torres Strait Islander peoples until it was introduced into Arnhem land in the 1980s as an alternative to alcohol. (Cawte, 1985; Mathews et al., 1988). Kava beverage does not feature in Māori tradition. However, *kawakawa* or *kava* refers to the closely related *Piper excelsum* is used as an ingredient in traditional medicine and features in traditional Māroi culture. *P. excelsum* does not possess psychotropic properties (Singh, 1992; Butts et al., 2019).

Kava extracts are used in dietary supplements in New Zealand and in complementary medicines listed on the Australian Register of Therapeutic Goods. The principal means of exposure of the broader Australian and New Zealand community to kava products would be through kava extracts in complementary medicines.

No information on kava consumption is captured by the 2011-2012 Australian National Nutrition and Physical Activity Survey (ABS, 2014) or the 2012-2013 Australian National Aboriginal and Torres Strait Islander Nutrition and Physical Activity Survey (ABS, 2015). In the 2007 National Drug Strategy Household Survey, 1.8 % of Australians 14 years and older reported being offered or having the opportunity to use kava within the last 12 months (AIHW, 2008). This was highest for males in the 20-29 year old age group at 3.4% (AIHW, 2008).

A 1988 assessment of the health status of Australian kava beverage consumers in a community in Arnhem land categorised kava users into occasional consumers (average 100 g/week dried kava root powder), heavy consumers (average 310 g/week) and very heavy consumers (average 440 g/week) (Mathews et al., 1988). This is consistent with a 1991

assessment in a nearby Arnhem land community, where the average kava drinker consumed an estimated average of 368 g/week of dried kava powder (Clough et al., 2000; Clough, 2003b). Based on these observations, 400 g/week of dried kava powder has been proposed as the level where negative effects from kava beverage consumption may occur (Clough et al., 2004).

Subsequent observational studies in Australian and Pacific communities show that, while some variances exist, these Australian estimates of high kava consumption largely reflect wider kava beverage consumption patterns (Jowitt & Binihi, 2001; Grace, 2003; Shimoda et al., 2015; Aporosa et al., 2020).

5.2 Kavalactone intake from traditionally prepared beverage

Total kavalactone content of kava plant varies from 1%-20% of dry weight, depending on plant variety, the age of kava plant when harvested, product storage conditions and post-harvest processing (i.e. fresh or dry) (Duve & Prasad, 1983; Lebot & Lèvesque, 1996; Lebot et al., 1997). Kavalactone concentration in beverages is impacted by the method used for preparation, often heavily influenced by social context and practices (Aporosa, 2019).

Clough et al. (2000) estimated the quantity of kavalactones consumed by kava drinkers in an Arnhem land community with a high level of kava consumption. Assuming a total kavalactone content in kava powder of 12.5% of dry weight, a kavalactone extraction efficiency of 83%, and ingestion of 670 mL of liquid containing 37 g of kava powder per hour, the estimated intake of kavalactones would be 3800 mg per hour by high consumers (Clough et al., 2000).

Aporosa et al. (2020) examined the effects of a six hour kava session on cognitive function of regular kava in New Zealand consumers. The kavalactone content of a single batch of commercially available kava powder, obtained in Hamilton, New Zealand, was determined to be 9.26% w/w kavalactones. When used to prepare kava beverage reflective of an average ‘strength’, a kava consumer would consume 145 mg kavalactones in a 100 mL serving. Assuming an average consumption rate of 500 mL per hour, the authors concluded that kavalactone intake would equal 725 mg per hour.

The duration of a single kava drinking session can vary widely based on cultural norms, occasions and user preferences, where individuals have self-reported drinking kava for up to 22 hours in a single session (Jowitt & Binihi, 2001; Cairney et al., 2003).

The traditional use of kava therefore results in intakes of kavalactones which are far in excess of the recommended maximum daily dose of 250 mg kavalactones for preparations included on the Australian Register of Therapeutic Goods.

6 Nutritional Impact

Kava beverage is not consumed for nutritional benefit, rather as part of cultural practices and for its intoxicating properties.

There are no known nutritional problems associated with the moderate use of kava. Kava root consists of 43% starch, 3.2% sugars and 3.6% protein (Lebot et al., 1992). It is unclear what nutritional impacts these constituents may have in high consumers of kava beverage.

Malnutrition can be higher amongst kava users than non-users in communities with high rates of kava abuse. A 2000 study of kava use in some First Nations communities in Arnhem land found that kava users was associated with markers of malnutrition; however, these

results were confounded by the general malnutrition rate that occurred in these communities (Clough et al., 2004).

7 Data limitations

In preparing this rapid risk assessment FSANZ has identified a number of limitations in the evidence base. These include:

- Comprehensive information was not available with regard to the source of kava plant, kava plant varieties or parts (root, rhizome or lateral roots) to ensure that supplied kava plant and powder is of a consistent quality.

- Validated analytical methodology for regulatory compliance has not been established for monitoring kava chemical components such as kavalactones, alkaloids and flavokawains, and other potential contaminants.

- Reliable and reproducible information on the concentration ranges of kavalactones, alkaloids and flavokawains, and other potential contaminants from different parts of the plant was not available

- Independently verified analytical methodology has not been established for identifying imported kava plant material that is sourced from unsafe kava plant varieties or unsafe kava plant parts.

- The toxicological database for aqueous and solvent extracts of kava is very limited. No data are available to support the use of kava in pregnant or lactating women or in children or infants.

- The risks of adverse events posed by kava consumption and co-medications are poorly described. This is especially pertinent given kava substances have anxiolytic activity and the potential to inhibit CYP-mediated drug metabolism pathways.

- There is insufficient information on the *in vivo* toxicity of kavalactones, flavokawains, piperidine alkaloids, and their metabolites, to establish health-based guidance values for these substances in kava beverage.

- There is insufficient data available to understand individual exposure levels to kavalactones from kava beverage consumption.

- There is insufficient information on the prevalence of pathogenic microorganisms on fresh or dried/powdered kava root or in kava beverages; and on the potential for persistence or growth of any such pathogens on the product, aside from mycotoxigenic fungi.

8 Risk characterisation

Based on the available evidence assessed by FSANZ, the following risks associated with kava beverage have been identified as important considerations regarding public health and safety.

- Ongoing consumption of high quantities of kava beverage (more than 400 g/week dried kava powder) is associated with ichthyosiform skin rash, altered liver function and a decline in general health.

- Moderate consumption of kava beverage can develop into substance abuse over time. This can occur in communities with and without previously established kava consumption.

- Kava beverage prepared using kava plant varieties without a history of safe use, or using aerial parts of the kava plant, are considered to be potentially toxic and not safe for human consumption.

- No information was available to allow an assessment of the safety of kava beverage consumption in pregnant or lactating females, adolescents or children.

- In rare cases, hepatotoxicity has been reported following consumption of kava beverage and complementary medicines containing kava. The aetiology of these cases is not well understood but may relate to factors including non-traditional varieties of kava plants, methods of extraction, drug interactions, or aflatoxin contaminated kava.

- Given the anxiolytic activity of kavalactones and the potential to inhibit CYP-mediated drug metabolism pathways, care should be taken when consuming kava beverage in combination with medicinal drugs (particularly benzodiazapines, opiods, barbiturates and paracetamol) or other herbal preparations.

- Kava beverage causes drowsiness, potentiates the effects of alcohol and has been linked with increased motor vehicle accidents. Individuals should not drive motor vehicles or operate heavy machinery after consuming kava beverage.

- The microbiological risk from the consumption of kava beverages obtained by aqueous suspension of dried or raw kava root is low when kava is produced and prepared in line with current risk management measures, including the application of GAP and GHP.

9 Conclusions

Kava beverage has a long history of consumption in the South Pacific and has an important role in traditional community ceremonies. In recent times, it has become more widely consumed as a recreational beverage in both the Pacific community as well as in the wider international community. This significant history of use demonstrates that it is possible to safely consume kava beverage in moderation for traditional and recreational purposes.

No information was available to allow an assessment of the safety of kava beverage consumption in pregnant or lactating females, adolescents or children. Therefore it is not possible to draw a conclusion on the safety of kava beverage consumption by these population subgroups.

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Appendix 1: Kava varieties with a history of safe use

Samoa[1,2]

Ava La'au
Ava Le'a
Ava Loa
Ava Mumu
Ava Talo

Fiji[2,3]

Damu
Dokobana loa
Dokobana vula
Loa kasa balavu
Loa kasa leka
Matakaro balavu
Matakaro leka
Qila balavu
Qila leka
Vula kasa balavu
Vula kasa leka
Yalu
Yonolulu

Tonga[2,4]

Kava 'Akauhina
Kava 'Akaukula
Kava Fulufulu
Kava Kofe
Kava Lekahina
Kava Lekakula
Kava Valu

Vanuatu[2,4,5]

Ahouia
Amon
Asiyai
Bir Kar
Bir Sul
Biyaj
Borogoru
Borogu
Ge gusug
Ge vemea
Ge wiswisket
Gorgor
Kelai (or Miaome)
Leay
Melmel (or Sese)
Melomelo
Miela
Naga miwok
Olitao
Palarasul
Palasa
Palimet
Pia
Poivota
Pualiu
Puariki
Silese
Urukara

‡Hawaii[2]

Hanakapi'ai
Hiwa
Honokane Iki
Kumakua
Mahakea
Mapulehu
Moi
Nene
Opihikao
Pana'ewa
Papa 'Ele'ele
Papa 'Ele'ele Pu 'upu'u
Papa kea

‡Papua New Guinea[2]

Kau kupwe

‡Federated States of Micronesia[2]

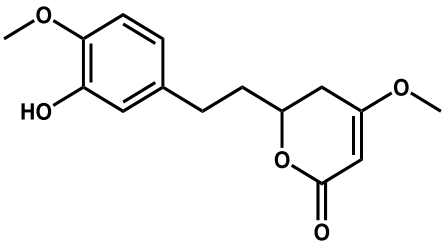
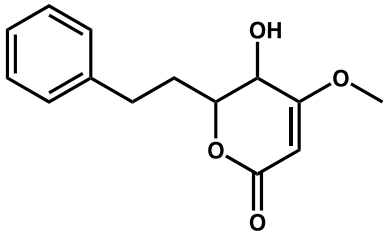
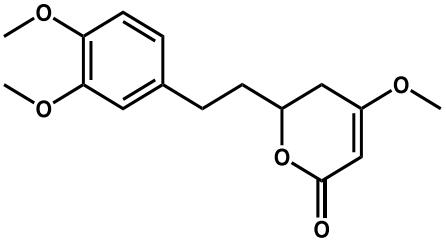
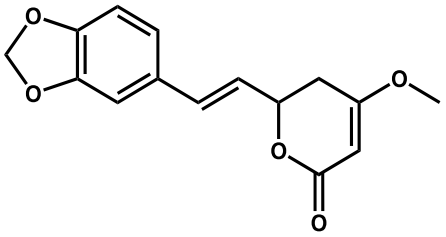
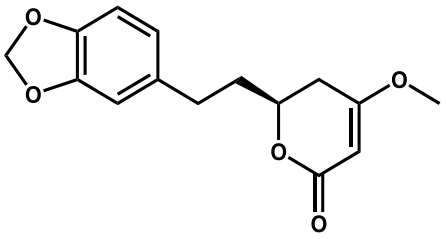
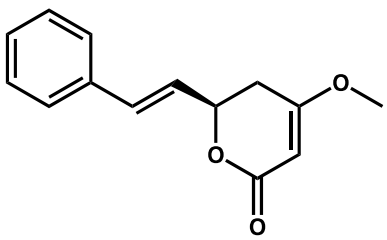
Rahmwahnger

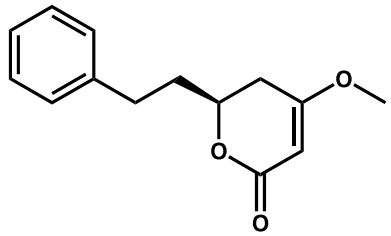
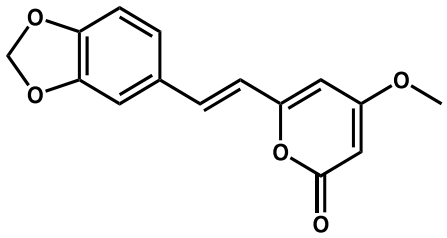
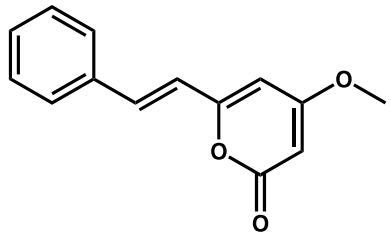
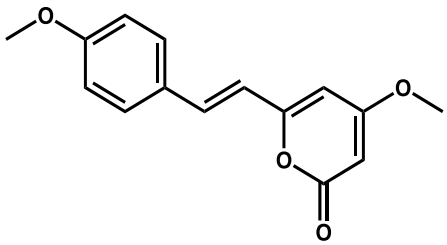
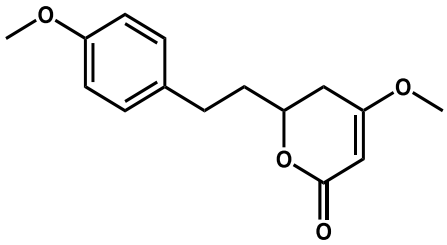
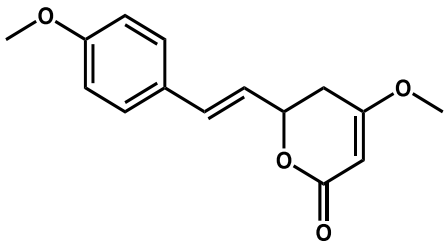
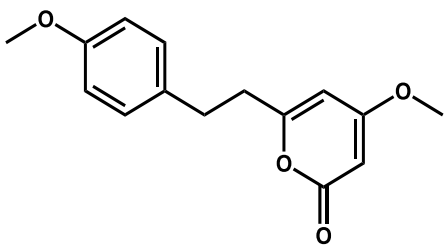
‡Solomon Islands[2]

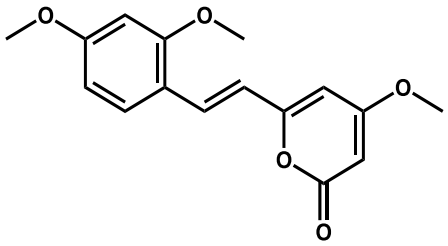
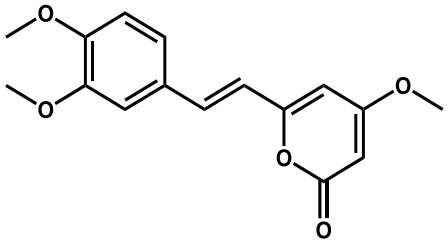
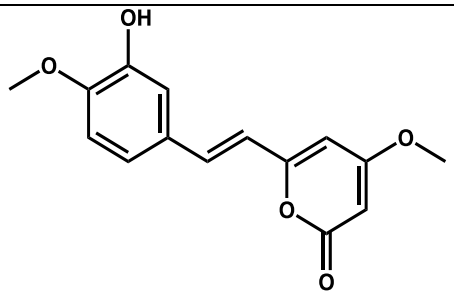
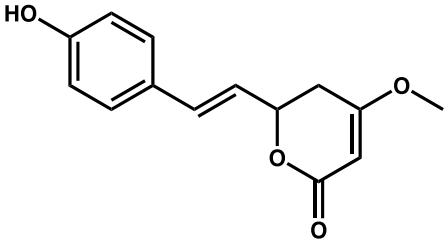
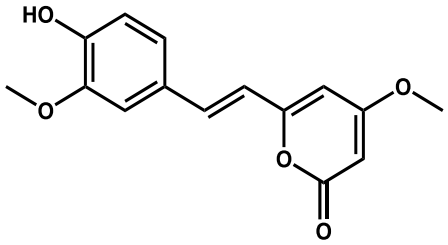
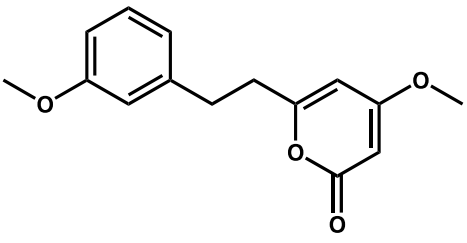
Feo
Tahu
Temo

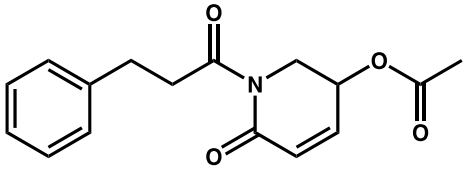
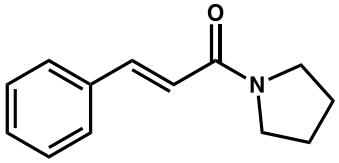
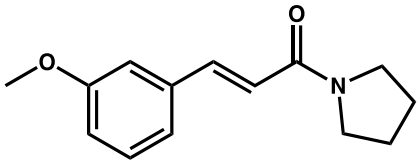
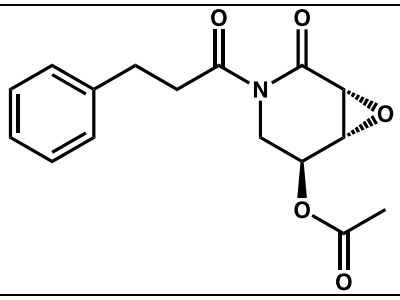
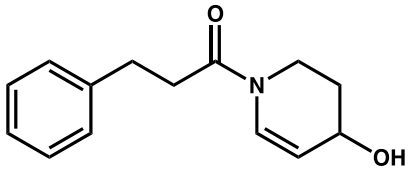
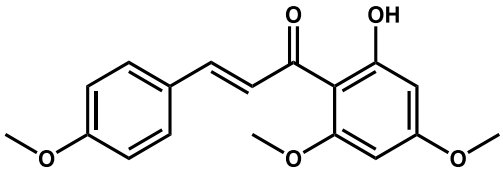
[1] Samoa 'Ava Standard (2018)
[2] Codex Alimentarius Commission (2020)
[3] Fiji Ministry of Agriculture (2017)
[4] Government of Tonga (2020)
[5] The Kava Act 2002. Republic of Vanuatu (2008)
[6] The National Quality Standard for Kava Export – Vanuatu (2017)
‡ FSANZ is unaware of any local kava quality and safety standards that are specific to kava produced in this region.

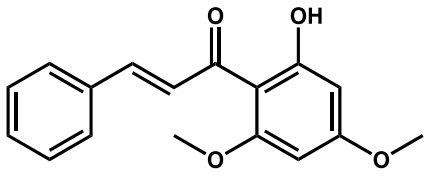
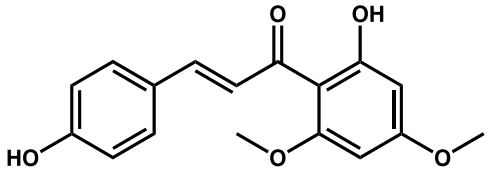
Appendix 2: Chemical constituents in kava extracts

Constituent	Chemical Structure	References
11-Hydroxy-12-methoxydihydrokavain CAS: 38146-59-7 MW: 278.30 LD50: *Unavailable* [1] XLogP3: 2.4		Bilia et al., 2004
7,8-Dihydro-5-hydroxykavain CAS: 52247-81-1 MW: 248.27 LD50: *Unavailable* XLogP3[1]: 1.6		Bilia et al., 2004
11,12 Dimethoxydihydrokavain CAS: 38146-60-0 MW: 293.33 LD50: *Unavailable* XLogP3: 2.7		Bilia et al., 2004
Methysticin (Major) CAS: 495-85-2 MW: 274.27 LD50: *Unavailable* XLogP3: 2.4		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018
Dihydromethysticin (Major) CAS: 19902-91-1 MW: 276.28 LD50: 1050 mg/kg bw (mouse, oral) XLogP3: 2.6		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018
Kavain (Major) CAS: 500-64-1 MW: 230.26 g/mol LD50: 1130 mg/kg bw (mouse, oral) XLogP3: 2.5		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018

7,8-Dihydrokavain (Major) CAS: 587-63-3 MW: 232.27 LD50: 920 mg/kg bw (mouse, oral) XLogP3: 2.8		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018
5,6-Dehydromethysticin CAS: 3129-60-0 MW: 272.25 LD50: *Unavailable* XLogP3: 2.6		Bilia et al., 2004
Desmethoxyyangonin (Major) CAS: 15345-89-8 MW: 228.24 LD50: >800 mg/kg (mouse, oral) XLogP3: 2.8		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018
Yangonin (Major) CAS: 500-62-9 MW: 258.27 g/mol LD50: >1500 mg/kg (mouse, oral) XLogP3: 2.7		Meyer, 1962; Bilia et al., 2004; Dentali et al., 2018
5,6,7,8-Tetrahydroyangonin CAS: 49776-58-1 MW: 262.30 g/mol LD50: *Unavailable* XLogP3: 2.7		Bilia et al., 2004
5,6-Dihydroyangonin CAS: 3328-60-7 MW: 260.279 g/mol LD50: *Unavailable* XLogP3: 2.5		Bilia et al., 2004
7,8-Dihydroyangonin CAS: 3155-52-0 MW: 260.279 g/mol LD50: *Unavailable* XLogP3: 2.7		Bilia et al., 2004

10-Methoxyyangonin CAS: 77900-32-4 MW: 288.29 g/mol LD50: *Unavailable* XLogP3: 2.7		Bilia et al., 2004
11-Methoxyyangonin MW: 288.29 g/mol LD50: *Unavailable* XLogP3: 2.7		Bilia et al., 2004
11-Hydroxyyangonin CAS: 77900-30-2 MW: 274.27 g/mol LD50: *Unavailable* XLogP3: 2.4		Bilia et al., 2004
Hydroxykavain MW: 246.26 g/mol LD50: *Unavailable* XLogP3: 2.2		Bilia et al., 2004
11-Methoxy-12-hydroxydehydrokavain MW: 274.27 g/mol LD50: *Unavailable* XLogP3: 2.4		Bilia et al., 2004
5,6-dihydro-5,6-dehydrokavain LD50: *Unavailable*		Wang et al., 2021

Pipermethystine CAS: 71627-22-0 MW: 287.31 g/mol LD50: *Unavailable* XLogP3: 1.4		Dragull et al., 2003
1-cinnamoylpyrrolidine CAS: 52438-21-8 MW: 201.26 g/mol LD50: *Unavailable* XLogP3: 2.4		Achenbach & Karl, 1970
1-(m-methoxycinnamoyl)pyrrolidine CAS: 29647-01-6 MW: 231.29 g/mol LD50: *Unavailable* XLogP3: 2.3		Achenbach & Karl, 1970
3α, 4α-epoxy-5β-pipermethysticine MW: 303.31 g/mol LD50: *Unavailable* XLogP3: 0.9		Dragull et al., 2003
Awaine MW: 231.29 g/mol LD50: *Unavailable* XLogP3: 1.3		Dragull et al., 2003
Flavokawain A CAS: 37951-13-6 MW: 314.3 g/mol LD50: *Unavailable* XLogP3: 3.8		Bilia et al., 2004; Dentali et al., 2018

Flavokawain B CAS: 1775-97-9 MW: 284.31 g/mol LD50: *Unavailable* XLogP3: 3.8		Bilia et al., 2004; Dentali et al., 2018
Flavokawain C CAS: 37308-75-1 MW: 300.30 g/mol LD50: *Unavailable* XLogP3: 3.5		Bilia et al., 2004; Dentali et al., 2018

[1] Computed by PubChem XLogP3 3.0 (Release 2021.05.07) https://pubchem.ncbi.nlm.nih.gov. Accessed: September 2021