RISK PROFILE

Piper methysticum extract

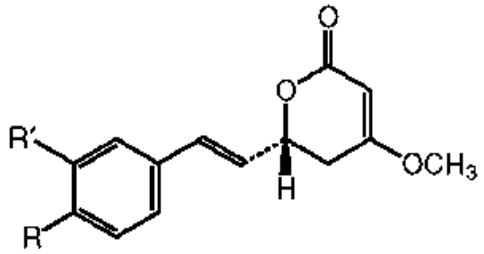
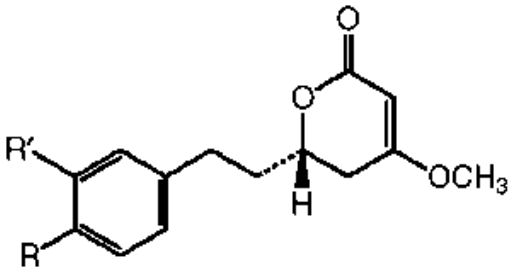
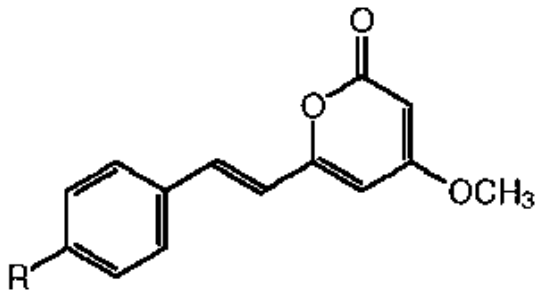
CAS No. 84696-40-2/9000-38-8

Date of reporting 03.08.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	Piper methysticum extract is an extract of the leaves, root and stem of the *Piper methysticum Forst F*. plant.
INCI	Piper methysticum leaf/root/stem extract Piper methysticum rhizome/root extract Piper methysticum root Piper methysticum root extract
Synonyms	Ava, ava pepper, awa, intoxicating pepper, kava, kava kava, kava pepper, kava root, kawa, kawa kawa, kew, rauschpfeffer, sakau, tonga, wurzelstock, and yangona.
CAS No.	84696-40-2 9000-38-8
EINECS No.	283-648-9
Molecular formula	This concerns the harmful constituents of the plant/extracts the kavalactones of which the following 6 compounds are the most abundant ones:

	 **Kawain** R = R' = H **Methysticin** R, R' = O-CH_2-O  **Dihydrokawain** R = R' = H **Dihydromethysticin** R, R' = O-CH_2-O  **Yangonin** R = OCH_3 **Demethoxyyangonin** R = H More detailed information is to be found in a recent monograph prepared by the American Cosmetic Ingredient Review panel (CIR, 2009).
Chemical structure	Confer CIR (2009)
Molecular weight	Confer CIR (2009)

<table>
<tr><td>Contents (if relevant)</td><td>The active – and potentially harmful - constituents of the extract of Piper methysticum (P. methysticum) are the ones displayed above.

The kavalactones make up 3-20 % of the root by dry weight, however, the proportion of kavalactones in the extract, depends on the extraction method. The relative concentrations of the different kavalactones will vary in the different parts of the plant, between geographic regions and with the age of the plant. Typical concentrations within extracts on a dry mass basis are (%):

<table>
<tr><td rowspan="2">compound</td><td colspan="3">Collected from CIR monograph</td><td rowspan="2">WHO (2004)</td></tr>
<tr><td>root</td><td>rhizome</td><td>Commercial powder</td></tr>
<tr><td>Kawain (1)</td><td>1.9</td><td>1.2</td><td>0.8</td><td>1.8</td></tr>
<tr><td>Methysticin</td><td>2.1</td><td>1.0</td><td>0.7</td><td>1.2</td></tr>
<tr><td>Dihydromethysticin</td><td></td><td></td><td></td><td>0.5</td></tr>
<tr><td>Demethoxyyangonin</td><td></td><td></td><td></td><td>1.0</td></tr>
<tr><td>Yangonin</td><td>1.7</td><td>0.7</td><td>0.5</td><td>1.0</td></tr>
<tr><td>Dihydrokawain</td><td></td><td></td><td></td><td>1.0</td></tr>
</table>
(1) One deliverer informed the extract contained 0.02 % Kawain (private communication with applicant august 2012)

At least 13 other lactones, two chalcones and a number of free aromatic acids are known (See reference in CIR, 2009).</td></tr>
<tr><td>Physiochemical properties</td><td>For the physiochemical properties for the different kavalactones, see CIR.

References:
(Robinson et al. 2009; (CosIng [online]).</td></tr>
</table>

2. Uses and origin

<table>
<tr><td>Uses</td><td>➢ Cosmetic products:

Function according to:

• CosIng database current
”Skin conditioning” - Maintains the skin in good condition (CosIng [online]).

• CosIng database 2006
“Anti-seborrhoeic/tonic/refreshing”

• Other
P. methysticum (kava kava) extract possesses antiseptic, soothing, and anesthetic effect (SpecialChem [online]).

One prominent supplier claims under the “SpecialChem frame” that the hydroglycolic extract possesses soothing, relaxing and anti-inflammatory properties. The extract is used in soothing, anti-stress products for reactive and sensitive skin, acne prone skin, sun. Also it is employed in after-sun products, depilatory products and after shave products (http://www.specialchem4cosmetics.com/tds/sederma-kava-kava/sederma/665/index.aspx)</td></tr>
</table>

	Galenical forms Kava kava extract is used in creams, lotions, rubs, and bath soaks (SpecialChem [online]). ***Frequency of use*** The CIR report identifies 3 products that contained kava kava extract. These were all aftershave lotions or other shaving preparation products (Robinson et al. 2009). At the databases Codecheck. and at EWG's Skin Deep a total of 13 products were identified: Shaving cream (rinse-off) (2 products) Moisturizer (5 products - body) Cleansing milk (rinse-off) (2 products) Face scrub (rinse-off) (1 product) Styling gel (1 product) Blemish Balm (3 products – explained below) (Codecheck [online]; EWG's Skin Deep [online]). An internet search primo August 2012 showed on sale internationally 50 products containing one or the other of the 4 different kava kava extracts mentioned in the CosIng database. None are mentioned in the two named databases. For the sake of illustration we picked these 50 products at random among many other such products being announced on the web at that point in time. A few “big brands” are to be seen among them. Obviously, these days the Kava Kava extracts enjoys some popularity in the international online marketplace. Out of the picked 50 products 12 are so-called Blemish Balms (BB) products which is a type of cosmetics that have become popular in recent years. These are products claiming they remove wrinkles, lighten the skin and provide moisture all at the same time. Seemingly, the Kava Kava extract have gained popularity in the BB products because of providing a soothing (calming) effect. A majority (30/50) of the 50 products are meant to be applied to the skin of the face – and are leave on products. There are a couple of face masks. There are 9 leave on hand creams, 2 shampoos and 2 leave-on hair products. Further there is one of each as to depilating (removal of body hair), body lotion, tanning lotion and acne probe skin products. In the list of ingredients the ingredient is roughly in the middle and placed higher up in the list than the preservatives in all instances. ***Concentrationsbeing applied*** According to the CIR monograph the concentrations used are for Piper methysticum leaf/root/stem extract: 0.0001 – 0.01 % Piper methysticum root extract: 0.1 % A face mask subjected to classification assessment by the Norwegian competent authorities containing 0.1 % Piper methysticum extract. The applicant wished to use more than that; 1 – 3 % and was allowed

	to do so (letter from the Norwegian medicinal product agency to applicant 18 October 2006). Currently, this mask contains 1 % extract (private communication with applicant august 2012). In 2003 a raw-material deliverer launched a Piper methysticum root extract obtained by propylene glycol extraction that the company suggested could be used in the concentration range 4 – 8 % in after-sun lotions, creams and anti-itching preparations. Claims: anaesthetic and soothing ingredient (Household & personal products industry 2003). Taking into account that one company now uses 1 %, the suggestion by one deliverer to use a high level and the placing of the extract roughly in the middle of the list of ingredients, all indicate that at least as concerns some of the Kava Kava products currently marketed much more than 0.1% is used. In a safety assessment a worst case scenario it seems reasonable to use a concentration of 1%. ➢ **Medicinal products/applications** Kava kava has been used experimentally to attenuate seizures and to treat psychotic states. Today, it is mostly used for treatment of anxiety (Ernst, 2002). It has also been used for treatment of skin disorders, asthma, lung disorders, and urologic problems in Hawaii. In Germany, before penicillin was discovered, kava kava was used to treat gonorrhea (Norton *et al*., 1994). Additionally, bactericidal and antifungal effects for kava kava extract have been reported. The kava lactones are also thought to have muscle-relaxant effects. The extract was shown to be sedative, anticonvulsive, and spasmolytic in animal studies. Some of the kava lactones have antithrombotic effect (Robinson et al. 2009). ➢ **Food and supplements** It is traditionally used in the South Pacific as a recreational drink (Ernst, 2002), where beverage is prepared by mixing crushed kava kava root with water or coconut milk (Lim et al., 2007). Outside of South Pacific islands, the primary use of kava kava occurs as an herbal supplement. Extracts of kava kava possess pharmacological properties when used in a sufficiently high concentration (Robinson et al. 2009).
Origin Natural (exo /endo) Synthetic	Natural, plant-derived. Kava kava is made from the dried rhizome of the kava kava plant (Ernst, 2002).

3. Regulation

Norway	Kava kava is currently allowed in cosmetic products at concentrations up to 3 %, and the extracts must not contain more than 70 % kava lactones. This regulation is to be lifted on the 11th of July 2013
EU	No regulation.
Rest of the world	*Piper methysticum* extracts are not permitted for use in cosmetics and personal care products in Canada (Health Canada [online]).

4. Relevant toxicity studies

Absorption Skin GI tractus	Skin: no available information. GI tractus: The absorption of six kava lactones was investigated. The kava lactones were administered orally in peanut oil to mice. The absorption rate varied greatly, from rapid to poor absorption (Robinson et al. 2009).
Distribution	The various components of kava are distributed throughout the body, including to the brain, and have been reported to have an effect on end points such as stress, addiction, muscle relaxation, and enzyme levels. (CIR i.e. Robinson *et al* 2009)
Metabolism	The metabolism of the different kava lactones has been described by Fu and co-workers and Lim and co-workers (Fu *et al*., 2008; Lim *et al*., 2007).
Excretion	The metabolites are mainly excreted in urine (Robinson et al. 2009).
Local toxic effects Irritation Sensitivity	No studies found.
Systemic toxic effects Acute Repeated dose	Taken account of in this study are only experiments that are more of recent date and those for which a well-defined protocol are described. For a full description of previous studies, it is referred to the assessment of kava kava extract done by The Cosmetic Ingredient Review (CIR) (Robinson et al. 2009). LD50 for kava kava extract have been determined to be >1500 mg/kg bw (oral) and >360 mg/kg bw (intraperitoneal) for mice and rats (ESCOP, 2003). The National Toxicology Program (NTP) assessed the toxicity and carcinogenicity of oral exposure to kava kava extract in rats and mice. NTP conducted a 14 day, 13 week and a two year study (see annex for details) (NTP, 2011). The kava lactone content in the extract used varied slightly from batch to bath, but was approximately 30 %. **13-week study rats:** Groups of 10 male and 10 female rats were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg, 5 days per week for 14 weeks. Female rats receiving 2.0 g/kg kava kava extract had a significant increase in hepatocellular hypertrophy. Occasional deaths, ataxia, lethargy, decreased body weight, and increased γ-glutamyltransferase activity occurred for the two highest doses. Male rats receiving 0.25 g/kg or greater and female rats receiving 0.5 g/kg or greater had significantly increased liver weights and increased liver and kidney weights, respectively (NTP, 2011). **13-week study mice:** Groups of 10 male and 10 female mice were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg, 5 days per week for 14 weeks. Occasional deaths occurred for the highest dose of 2.0 g/kg. Ataxia, lethargy and increased liver weight were observed for the two highest doses. 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 (NTP, 2011). Three different doses of kava kava extract, 31.25, 62.5 and 133 mg/kg, fed to Sprague-Dawley rats through diet for three months, did not cause liver injury (DiSilvestro et al., 2007). A rough estimate of the exposure from the highest dose in diet of 133 mg/kg is 13 mg/kg bw (see annex for calculation). F344 rats were administered pipermethystine (an alkaloid found in the stem and leaves) or kava kava rihzome solved in corn oil by gavage daily for two weeks, did no exhibit any significant changes in liver function or severe hepatotoxicity. However, pipermethystine and kava kava rhizome extract-treated rats did have a significant increase in hepatic glutathione, cytosolic superoxide dismutase, CYP2E1, CYP1A2 and TNF-α, suggesting adaptation to oxidative stress and possible drug-drug interactions (Lim et al., 2007). *Human data* Two studies involving more than 6000 patients found adverse effects in 2.3% and 1.5% of patients taking 120 to 240 mg of standardized extract, respectively (ref 59 and 60 in Ernst, 2002). Several cases of toxic liver damage were associated with kava kava self-medication (ref 61 in Ernst, 2002).
Mutagenicity /genotoxicity	Kava kava extract was negative in the Salmonella typhimurium, Escherichia coli, and also in *an in vivo* male and female mouse micronucleus test (*in vivo*) tests (NTP, 2011). Desmethoxyyangonin was negative in the Ames assay (Hsu et al., 1994).
Carcinogenicity	**2-year study:** Based on the two year study (mice and rats: 0-1.0 g/kg), NTP concluded with the occurrence of neoplastic lesions in the liver, forestomach, kidney, eye, and pancreas of male and female rats, liver of male and female mice, and forestomach of female mice (NTP, 2011). In detail NTP found that: Under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity* of kava kava extract in male F344/N rats based on marginal increases in the incidences of testicular adenoma. There was no evidence of carcinogenic activity of kava kava extract in female F344/N rats administered 0.1, 0.3, or 1.0 g/kg. There was clear evidence of carcinogenic activity of kava kava extract in male B6C3F1 mice based on increased incidences of hepatoblastoma and hepatocellular carcinoma or hepatoblastoma (combined). There was some evidence of carcinogenic activity of kava kava extract in female B6C3F1 mice based on increased incidences of hepatocellular adenoma or carcinoma (combined).
Reproductive toxicity / teratogenicity	No data available.

Other effects	According to the CIR monograph the Piper methysticum leaf/root/stem extract's exerts also other toxic effects. For example, there is a sedative effect in humans. Neurological effects have been found to be mediated through dopaminergic neurons of the nucleus accumbens in the mesocorticolimbic dopamine reward system. Further, as early as 1959, Klohs *et al* (ref in CIR) asserted that the main action of all kava lactones (and, presumably, those found in kava extracts) was muscle relaxation. There is also a peculiar scaly skin eruption effect in humans following heavy intake orally of the above mentioned traditional South Pacific recreational drink. In neither case, says the CIR, can the relevance to cosmetic use be determined without knowing whether kava ingredients are absorbed dermally. We, however, lay to ground that in the absence of skin penetration data the Kava lactones are taken up in the body 100 % administrated topically (SCCS guide default value).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	The NOAEL values are based on the 3-month and 2-year studies in mice and rats performed by the National Toxicology Program (NTP, 2011). NOAEL for toxicity: 125 mg/kg bw/day (based on 3-month study in mice). LOAEL for carcinogenicity: 100 mg/kg bw/day (based on 2-year study in rats). NOAEL for carcinogenicity = LOAEL/3 [1] = 100 mg/kg bw/day/ 3 = **33.3 mg/kg bw/day**
Exposure cosmetic products	• ***Shaving cream*** Amount applied (SCCS default value): 1 mg/cm^2 Surface area (SCCS default value): 305 cm^2 Body weight: 60 kg Total amount: 1 mg/cm^2 x 305 cm^2 = 305 mg Daily exposure to the product: (305 mg/60 kg) x 0.1 = 5.1 mg/kg bw/day Frequency of application: 1/day Dermal absorption, default value, SCCS: 100% = 1 Assumed concentration in product: 0.1% = 0.001 Retention factor: 0.01

[1] When making use of the Lowest Observed (Adverse) Effect Level (LO(A)EL) instead of the NO(A)EL, the SCCS usually takes into consideration an additional factor of 3 in the calculation of the MoS. Scientific Committee on Consumer Safety, The SCCS'S notes of guidance for the testing of cosmetic ingredients and their safety evaluation, the 7th revision, p 54.

	Calculation of SED: 5.1 mg/kg bw/day x 1 x 1 x 0.001 x 0.01 = **0.00005 mg/kg bw/day** • ***Moisturizer (used values for body lotion)*** Calculated relative daily exposure (mg/kg bw/day) : 123.20 Dermal absorption, default value, SCCS: 100% = 1 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 123.20 mg/kg bw/day x 1 x 0.001 = **0.12 mg/kg bw/day** • ***Cleansing milk*** Amount applied (default): 1 mg/cm^2 Surface area: 565 cm^2 Body weight: 60 kg Total amount: 1 mg/cm^2 x 565 cm^2 = 565 mg Daily exposure to the product: (305 mg/60 kg) x 0.1 = 9.4 mg/kg bw/day Frequency of application: 1/day Dermal absorption, default value, SCCS: 100% = 1 Assumed concentration in product: 0.1% = 0.001 Retention factor: 0.01 Calculation of SED: 9.4 mg/kg bw/day x 1 x 1 x 0.001 x 0.01 = **0.00009 mg/kg bw/day** • ***Face scrub*** Amount applied (default): 1 mg/cm^2 Surface area: 565 cm^2 Body weight: 60 kg Total amount: 1 mg/cm^2 x 565 cm^2 = 565 mg Daily exposure to the product: (305 mg/60 kg) x 0.1 = 9.4 mg/kg bw/day Frequency of application: 1/day Dermal absorption, default value, SCCS: 100% = 1 Assumed concentration in product: 0.1% = 0.001 Retention factor: 0.01 Calculation of SED: 9.4 mg/kg bw/day x 1 x 1 x 0.001 x 0.01 = **0.00009 mg/kg bw/day** • ***Hair styling product*** Calculated relative daily exposure (mg/kg bw/day) : 5.74 Dermal absorption, default value, SCCS: 100% = 1 Maximum concentration in product: 0.1% = 0.001 Calculation of SED: 5.74 mg/kg bw/day x 1 x 0.001 = **0.0057 mg/kg bw/day** **Overall SED:** 0.00005 + 0.12 + 0.00009 + 0.00009 + 0.0057 = **0.13 mg/kg bw/day**
Margin of Safety (MoS)	The NOAEL for carcinogenicity will be used: 33.3 mg/kg bw

	MoS for kava kava extract in shaving cream: SED: 0.00005 mg/kg bw/day MoS: 33.3/ 0.00005 = 666,000 ***MoS for kava kava extract in moisturizers:*** SED: 0.12 mg/kg bw/day MoS: 33.3/ 0.12 = 278 ***MoS for kava kava extract in cleansing milk:*** SED: 0.00009 mg/kg bw/day MoS: 33.3/ 0.00009 = 370,000 ***MoS for kava kava extract in face scrub:*** SED: 0.00009 mg/kg bw/day MoS: 33.3/ 0.00009 = 370,000 ***MoS for kava kava extract in hair styling product:*** SED: 0.0057 mg/kg bw/day MoS: 33.3/ 0.0057 = 5842 ***MoS for overall exposure for kava kava extract from cosmetic products:*** Total SED: 0.13 mg/kg bw/day MoS: 125/3.9 = 256

6. Other sources of exposure than cosmetic products

Food and supplements	Kava kava is available in tablets, capsules, cream, and powder, which can be made into tea or mixed with other drinks. For anxiety, it may be taken several times a day. For sleep, it is taken about an hour before bedtime. When used as a recreational drink, the doses can exceed over 100 times those recommended for medicinal use (Robinson et al., 2009). Medicinal extracts from kava kava are made by extracting the dried herb with an ethanol–water mixture (producing extracts containing about 30% kavalactones) or with an acetone–water mixture (producing extracts containing about 70% kavalactones) (Robinson et al., 2009). The recommended dosage for kava kava depends upon the concentration of kava lactones. Therapeutic dosages appear to be in the range of 50-70 mg of the kava lactones three times daily, or approximately 100 mg of the 70 % standardized extract. In a 30 % concentration, the dosage would be in the range of 200 mg three times daily ([No author], 1998). **Interactions:** The extract has inhibitory activity of CYP3A4, an important enzyme in the biotransformation of many pharmaceuticals (Robinson et al. 2009), which may enhance the effect of certain drugs. When kava kava is taken concomitantly with other medication that acts on the central nervous system or with alcohol, the effects of kava kava may be potentiated, leading to a temporal state of impaired vigilance or reduced consciousness; one such case has been reported (Almeida et al., 1996).

Pharmaceuticals	No registered drugs.
Other sources	
Adverse side effects - from uses other than cosmetics	Several case reports have reported adverse effects after oral intake of kava kava extract, such as neurological effects, liver toxicity and adverse dermal effects. In all cases, rather high doses had been ingested, such as 200 mg/day and more. For more details, see (Robinson et al. 2009). Repeated intake of high doses of kava kava can cause kava kava dermopathy (flakey, dry and yellow skin) (Norton et al., 1994). Severe hepatotoxicity after taking kava kava supplements have been reported, both in Europe and in the United States. This has resulted in that kava kava-containing herbal products have been banned in Germany, France, Switzerland, Australia, and Canada (Lim et al., 2007). However, in the United States, kava kava is still commercially available and can be bought at health food stores and ethnic markets (Lim et al., 2007). The Food and Drug Administration (FDA) has issued an advisory stating that the consumption of kava kava-containing dietary supplements may be associated with severe liver injury (FDA [online])..

7. Assessment

The Cosmetic Ingredient Review assessed the safety of use of piper methysticum extract in cosmetics in 2009, and concluded that the available data are insufficient to support the safety of this extract in cosmetics (Robinson et al., 2009). Since then, the National Toxicology Program have performed and published the draft of the assessment of the toxic, genotoxic and carcinogenic potential of the kava kava extract. The results show that kava kava extract have carcinogenic potential, although there are so far no indications that the kava kava extract are genotoxic, which indicates that the extract will be safe to use under a certain threshold.

There are some additional aspects that need to be taking into consideration when assessing the safety of kava kava extract in cosmetics: i) reports of severe hepatotoxicity after the use of kava kava as a herbal supplement have been reported - although this is probably not an issue at the concentrations used in cosmetic products, ii) no information exists concerning the possible teratogenicity or reproductive effects of kava kava extract.

Kava kava extracts are present in many more than 50 products being sold via the internet.

MoS for kava kava extract in shaving cream =	666,000 (when usage limit is 0.1 %)
MoS for kava kava extract in moisturizers =	278 (when usage limit is 0.1 %)
MoS for kava kava extract in cleansing milk =	370,000 (when usage limit is 0.1 %)
MoS for kava kava extract in face scrub =	370,000 (when usage limit is 0.1 %)
MoS for kava kava extract in hair styling product =	5842 (when usage limit is 0.1 %)

The concentration used may be much higher than 0.1 % in some of the products now marketed. For moisturizers containing 0.2 % and 1% the calculated MoS is down to 139 and 28 respectively.

The required margin of safety we set to 6000 (100 x 10 x 3 x 2) to account for:

i) The gravity of the carcinogenic potential of the kava kava extract present (x10)
ii) The uncertainties revolving the NOAEL that was used in the calculations, such as possible different concentrations of kava lactones (x3). The kava kava extract used in the NTP study which the NOAEL value is based upon, contains 30 % kava lactones, whereas an extract of kava kava can contain up to 70 %.
ii) Studies have showed that the absorption rate between the different kava lactones varies greatly. Since the NOAEL value is based on oral toxicity studies, it might not be representative for dermal application; meaning that a 100% skin penetration will yield a higher systemic exposure compared to the same dose of kava kava extract taken orally (x2).

The SED for the rinse-off products yields a MoS that greatly exceeds the minimum requirement of a MoS of 6000. However, this is not the case for the two leave-on products, moisturizers and hair styling product, where the MoS is below the required margin of 6000. For body lotion moisturizers of which there are some on the market the MoS is even much below the otherwise conventional safety margin of 100 in case these products contain 1 % of the extract.

When taking into consideration that there are great uncertainties for the NOAEL value that has been used in this assessment and the lack of important information as concerns for example the reprotoxic properties, it would be appropriate as a precautionary to prohibit the use of kava kava extract in leave-on products, whilst allow it in rinse-off products at a 0.1 % concentration. Since the amount of kava lactones in the extract are variable, it also important to set limit for the amount. The NTP study used a kava kava extract containing 30 %. The portion of kava lactones in the kava kava extract used in cosmetic products is not known. In respect of the high MoS for the rinse-off products containing even 1 % (~14,000), it should not present a health risk to allow a kavalactone content up to 70 % for these products.

8. Conclusion

In conclusion, we are of the opinion that kava kava extract in rinse-off cosmetic products must not exceed 1 %, and the extracts must not contain more than 70 % kava lactones. As concerns leave on products we are of the opinion kava kava extract must be prohibited. .

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10. Annexes

- **Calculation of the highest exposure dose in the experiment of DiSilvestro et al., 2007.**

Amount consumed daily (default value): 15 g
Body weight (stated by the authors): 150-174 g = 0,15-0,174 kg
Concentration in feed: 133 mg/kg = 0,133 mg/g

A rat eating 15 g of feed daily will be exposed to 2 g kava extract/day (15 g x 0,133 mg/g = 2 mg)
This corresponds to an exposure of 11.4-13.3 mg/kg depending on the body weight (2 mg/ 0.174 kg = 11.4 mg/kg; 2mg/ 0.15 kg = 13.3 mg/kg).

- **The NTP study**

Abstract for TR-571 - Kava Kava Extract

http://ntp.niehs.nih.gov/go/36127

Toxicology and Carcinogenesis Studies of Kava Kava Extract (CAS No. 9000-38-8) in F344/N Rats and B6C3F1 Mice (Gavage studies)

PLEASE NOTE: The following abstract has been extracted from the DRAFT technical report reviewed by the National Toxicology Program Technical Reports Peer Review Panel on January 26, 2011 (Actions and the full draft report will be available from the meeting page). When this report becomes final the entire report will be available in pdf format on the NTP website.

Draft Abstract

Kava beverages, made from dried roots of the shrub Piper methysticum, have been used ceremonially and socially in the South Pacific and in Europe since the 1700s. The drink is reported to have pleasant mild psychoactive effects, similar to alcoholic beverages. In the United States, kava kava is an herbal product used extensively as an alternative to anti-anxiety drugs such as Xanax® and Valium®. It has also been reported as being used to help children with hyperactivity and as a skin-conditioning agent in cosmetics. Kava kava was nominated by the National Cancer Institute for study because of its increasing use as a dietary supplement in the mainstream United States market and reports of liver toxicity among humans. Male and female F344/N rats and B6C3F1 mice received kava kava extract in corn

oil by gavage for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in Salmonella typhimurium, Escherichia coli, and mouse peripheral blood erythrocytes

2-WEEK STUDY IN RATS

Groups of five male and five female rats were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg body weight, 5 days per week for 16 days. One female rat administered 2.0 g/kg kava kava extract died on day 3 of the study. Mean body weights of all dosed groups of rats were similar to those of the vehicle controls. Clinical findings included abnormal breathing, ataxia, and lethargy in the 2.0 g/kg groups of males and females and ataxia and lethargy in the 1.0 g/kg group of females. Liver weights were significantly increased in 1.0 and 2.0 g/kg males and in 0.5 g/kg or greater females compared to the vehicle controls. Minimal hepatocellular hypertrophy occurred in all 2.0 g/kg males and in all females administered 0.25 g/kg or greater.

2-WEEK STUDY IN MICE

Groups of five male and five female mice were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg body weight, 5 days per week for 17 days. In the 2.0 g/kg group of males, one died on day 2 and one died on day 3. Mean body weights of all dosed groups of mice were similar to those of the vehicle controls. Clinical findings included abnormal breathing, ataxia, and lethargy in males and females in the 1.0 and 2.0 g/kg groups. Liver weights of 2.0 g/kg males and females were significantly increased. The incidence of hepatocellular hypertrophy in 2.0 g/kg female mice was significantly greater than that in the vehicle control group.

3-MONTH STUDY IN RATS

Groups of 10 male and 10 female rats were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg, 5 days per week for 14 weeks. Deaths attributed to kava kava extract administration included three males and four females in the 2.0 g/kg groups and one female in the 1.0 g/kg group. One 0.25 g/kg male and one vehicle control female also died before the end of the study. The mean body weights of males in the 1.0 and 2.0 g/kg groups and females in the 2.0 g/kg group were significantly less than those of the vehicle controls. Ataxia and lethargy were observed in males and females in the 1.0 g/kg groups during week 1 and in the 2.0 g/kg groups throughout the study. Increased γ-glutamyltransferase activity in 1.0 g/kg females and 2.0 g/kg males and females may represent enzyme induction. However, the hepatocellular hypertrophy observed in the 2.0 g/kg females may have contributed to the increased γ-glutamyltransferase activity. The liver weights of 0.25 g/kg or greater males and 0.5 g/kg or greater females were significantly increased compared to the vehicle controls. The kidney weights of 0.5 g/kg or greater males and females were significantly increased compared to the vehicle controls. The incidence of hepatocellular hypertrophy in 2.0 g/kg females was significantly greater than that in the vehicle controls.

3-MONTH STUDY IN MICE

Groups of 10 male and 10 female mice were administered kava kava extract in corn oil by gavage at doses of 0, 0.125, 0.25, 0.5, 1.0, or 2.0 g/kg, 5 days per week for 14 weeks. Four male and three female 2.0 g/kg mice died during week 1; these deaths were attributed to kava kava extract administration. One additional 2.0 g/kg female died during week 6 due to a gavage accident. The mean body weights of dosed males and females were similar to those of the vehicle controls. Ataxia and lethargy occurred in males and females in the 1.0 and 2.0

g/kg 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 vehicle 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.

2-YEAR STUDY IN RATS

Groups of 49 or 50 male and 50 female rats were administered kava kava extract in corn oil by gavage at doses of 0, 0.1, 0.3, or 1.0 g/kg, 5 days per week for 104 (males) or 105 (females) weeks. Survival of dosed groups of males and females was similar to that of the vehicle controls. Mean body weights of males administered 1.0 g/kg were less than those of the vehicle controls after week 65, and those of the 1.0 g/kg females were less than those of the vehicle controls after week 41. Clinical findings included ataxia and lethargy that occurred in 21 males and 14 females in the 1.0 g/kg groups during the first 4 weeks of the study. After week 5, ataxia and lethargy were noted in 10 males and eight females in the 1.0 g/kg groups and these findings were observed randomly and intermittently throughout the study. At approximately 1 year into the study, twitching and seizures were observed in males and females in all dosed groups but mainly in the 1.0 g/kg groups.

There was a dose-related increase in the incidences of interstitial cell adenoma in the testis with increased incidences of bilateral neoplasms. The incidences of hepatocellular hypertrophy in 1.0 g/kg males and females were significantly greater than those in the vehicle controls. Increased γ-glutamyltransferase activity and/or bile salt concentrations in males and females may represent a cholestatic event related to the hepatocellular hypertrophy observed in rats. Enzyme induction may have played a role in the increased γ-glutamyltransferase activity. Significantly increased incidences of centrilobular fatty change occurred in 0.1 and 1.0 g/kg males. The incidences of inflammation, ulcer, and epithelial hyperplasia in the forestomach were significantly increased in 1.0 g/kg males and females. The severity of nephropathy was increased in 1.0 g/kg male rats, and the incidence of nephropathy was significantly increased in 1.0 g/kg females. Incidences of transitional epithelial hyperplasia of the pelvis of the kidney were significantly increased in 1.0 g/kg males and 0.3 and 1.0 g/kg females. The incidences of retinal degeneration in the eye were significantly increased in 1.0 g/kg males and females. The incidences of metaplasia of pancreatic acinar cells to a hepatocytic morphology increased in 1.0 g/kg males and females, and the increase in males was significant.

Significantly decreased incidences of pars distalis adenoma in the pituitary gland occurred in 1.0 g/kg males and in 0.1 and 1.0 g/kg females. The incidence of fibroadenoma of the mammary gland in 1.0 g/kg females was significantly less than that in the vehicle control group.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice received kava kava extract in corn oil by gavage at doses of 0, 0.25, 0.5, or 1.0 g/kg, 5 days per week for 105 weeks. Survival of dosed groups of males and females was similar to that of the vehicle controls. Mean body weights of males administered 1.0 g/kg were generally similar to those of the vehicle controls until the end of the study; however, those of 1.0 g/kg females were less than those of the vehicle controls after week 21. Clinical findings included ataxia and lethargy that occurred in 13 males and 31 females in the 1.0 g/kg groups during the first week of the study. Decreasing numbers of

animals exhibited ataxia or lethargy during the remainder of the study, but these findings were observed in 1.0 g/kg females as late as week 101.

The incidences of hepatoblastoma in 0.5 and 1.0 g/kg males were significantly increased compared to the vehicle controls. The incidences of hepatocellular carcinoma or hepatoblastoma (combined) were significantly increased in 0.5 g/kg males. Incidences of hepatocellular carcinoma were increased in all dosed groups of females, and the increase was significant in the 0.25 g/kg group. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in 0.25 and 0.5 g/kg females.

In the liver, the incidences of centrilobular hypertrophy in all dosed groups of males and females were significantly greater than those in the vehicle control groups. Significantly increased incidences of eosinophilic foci occurred in 0.5 g/kg males and in 1.0 g/kg males and females, and the incidence of angiectasis was significantly increased in the 1.0 g/kg males. The incidences of hepatocellular necrosis were significantly increased in 0.25 and 1.0 g/kg males. In the forestomach, the incidences of chronic inflammation, epithelial hyperplasia, and erosion were significantly increased in 0.5 and 1.0 g/kg females, and the incidence of ulceration was significantly increased in 1.0 g/kg females.

GENETIC TOXICOLOGY

Kava kava extract was tested for bacterial mutagenicity over a broad range of concentrations in two independent assays using several strains of bacteria (S. typhimurium tester strains TA97, TA98, TA100, and TA1535 and E. coli strain WP2 uvrA/pKM101), with and without exogenous metabolic activation. No increase in mutant colonies was seen in any of the tester strains, under any activation condition. In vivo, no increases in the frequencies of micronucleated erythrocytes were observed in peripheral blood of male or female B6C3F1 mice administered kava kava extract by gavage for 3 months.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity* of kava kava extract in male F344/N rats based on marginal increases in the incidences of testicular adenoma. There was no evidence of carcinogenic activity of kava kava extract in female F344/N rats administered 0.1, 0.3, or 1.0 g/kg. There was clear evidence of carcinogenic activity of kava kava extract in male B6C3F1 mice based on increased incidences of hepatoblastoma and hepatocellular carcinoma or hepatoblastoma (combined). There was some evidence of carcinogenic activity of kava kava extract in female B6C3F1 mice based on increased incidences of hepatocellular adenoma or carcinoma (combined).

Kava kava extract administration was associated with the occurrence of nonneoplastic lesions in the liver, forestomach, kidney, eye, and pancreas of male and female rats, liver of male and female mice, and forestomach of female mice.

Synonyms: Antares, ava; ava pepper; ava pepper shrub; ava root; awa; bornyl cinnamate; cavain; (+)-dihydrokawain-5-ol; Fijian kava; flavokavines A and B; 6-dihydroyangonin; gea; gi; grog; intoxicating long pepper; intoxicating pepper; kao; kava kava extract LI 140; kava kava rhizome; kava root; kavain; kavakava; kavalactones; kavapiper; kavapyrones; kavarod; kavasporal forte; kave-kave; kawa; kawa kawa; kawa pepper; Kawa Pfeffer; kew; LI150; long pepper; Macropiper latifolium; malohu; maluk; maori kava; meruk; 11-methoxy-5, 5-

hydroxydihydrokawain; milik; olanzapine; pepe kava; piperis methystici rhizome; pipermethystine; Rauschpfeffer; rhizoma piperis methystici; rhizome di kava-kava sakaua; risperidone; sakau; tonga; WS 1490; wurzelstock; yagona; yangona; yaqona; yongona

Botanical name: Piper methysticum

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Kava Kava Extract

	Male F344/N Rats	**Female F344/N Rats**	**Male B6C3F1 Mice**	**Female B6C3F1 Mice**
Doses in corn oil by gavage	0, 0.1, 0.3, or 1.0 g/kg	0, 0.1, 0.3, or 1.0 g/kg	0, 0.25, 0.5, or 1.0 g/kg	0, 0.25, 0.5, or 1.0 g/kg
Body weights	1.0 g/kg group 10% less than the vehicle control group after week 65	1.0 g/kg group 10% less than the vehicle control group after week 41	Dosed groups generally similar to the vehicle control group	1.0 g/kg group 11% less than the vehicle control group after week 21
Survival rates	34/49, 35/50, 34/50, 31/50	34/50, 35/50, 24/50, 34/50	34/50, 33/50, 35/50, 36/50	38/50, 34/50, 45/50, 37/50
Nonneoplastic effects	Liver: hepatocyte, hypertrophy (0/49, 2/50, 2/50, 22/50); centrilobular, fatty change (1/49, 7/50, 4/50, 21/50) Stomach, Forestomach: inflammation (8/49, 4/50, 9/50, 22/50); ulcer (4/49, 0/50, 6/50, 13/50); epithelium, hyperplasia (6/49, 4/50, 11/50, 27/50) Kidney: severity of nephropathy (1.4, 1.2, 1.8, 3.1); pelvis, transitional epithelium, hyperplasia (0/49, 1/50, 1/50, 15/50) Eye: retina, degeneration (6/49, 6/50, 10/50, 16/50) Pancreas: acinus, metaplasia, hepatocyte (0/49, 0/50, 0/50, 6/50)	Liver: hepatocyte, hypertrophy (5/50, 2/50, 3/50, 33/50) Stomach, Forestomach: inflammation (5/49, 7/50, 7/50, 13/50); ulcer (1/49, 1/50, 3/50, 7/50); epithelium, hyperplasia (5/49, 6/50, 8/50, 19/50) Kidney: nephropathy (34/50, 35/50, 37/50, 43/50) Eye: retina, degeneration (5/50, 5/50, 5/50, 12/50) Pancreas: acinus, metaplasia, hepatocyte (0/49, 1/50, 0/50, 4/50)	Liver: centrilobular, hypertrophy (0/50, 34/50, 30/50, 39/50); eosinophilic focus (28/50, 32/50, 42/50, 43/50); angiectasis (3/50, 6/50, 7/50, 10/50); necrosis (3/50, 10/50, 7/50, 13/50)	Liver: centrilobular, hypertrophy (0/50, 20/50, 48/50, 49/50); eosinophilic focus (9/50, 7/50, 16/50, 26/50) Stomach, Forestomach: inflammation, chronic (3/50, 6/50, 21/50, 22/50); epithelium, hyperplasia (3/50, 6/50, 23/50, 24/50); erosion (0/50, 1/50, 14/50, 11/50); ulcer (0/50, 2/50, 3/50, 6/50)
Neoplastic effects	None	None	Liver: hepatoblastoma (0/50, 4/50, 9/50, 12/50 hepatocellular	Liver: hepatocellular carcinoma (3/50, 13/50, 8/50, 8/50); hepatocellular

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Kava Kava Extract				
	Male F344/N Rats	**Female F344/N Rats**	**Male B6C3F1 Mice**	**Female B6C3F1 Mice**
			carcinoma or hepatoblastoma (20/50, 21/50, 30/50, 25/50)	adenoma or carcinoma (10/50, 21/50, 20/50, 13/50)
Equivocal findings	Testes: interstitial cell, adenoma (37/49, 44/50, 49/50, 46/50)	None	None	None
Level of evidence of carcinogenic activity	Equivocal evidence	No Evidence	Clear evidence	Clear evidence
Genetic toxicology				
Bacterial gene mutations:		Negative in *S. typhimurium* strains TA97, TA98, TA100, and TA1535 with and without S9; negative in *Escherichia coli* WP2 *uvrA*/pKM101 with and without S9		
Micronucleated erythrocytes Mouse peripheral blood *in vivo*:		Negative in males and females		