

## Opinion on a request from the Commission related to the safety of noni juice (juice of the fruits of *Morinda citrifolia*)

(Request N° EFSA-Q-2005-236)

(adopted on 1 September 2006 by written procedure)

### SUMMARY

On the basis of the “Opinion on Tahitian Noni<sup>®</sup> juice” adopted by the Scientific Committee on Food (SCF) on 4 December 2002, the Commission authorised the use of “noni juice” (juice of the fruit of *Morinda citrifolia* L.) as a novel food ingredient to be used in pasteurised fruit drinks on 5 June 2003, under Regulation (EC) N° 258/97. On 20 June 2005, the Austrian Competent Authority informed the Commission of a case report that might be of concern with respect to the safety of noni juice. The Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (AGES) upon request of the Austrian Competent Authority delivered an opinion on this case report and on two further recently published cases. As this new information might possibly have an impact on the opinion on the safety of noni juice and because of the Community interest in this matter, the European Commission has decided to seek the opinion of the European Food Safety Authority.

In response to a request by EFSA, the manufacturer provided additional information on noni juice regarding analysis for the presence of anthraquinones, updated data on consumption, information on reports of any adverse effects associated with the consumption, data on genotoxicity and cytotoxicity and a report on a study in humans.

The Panel agrees with the conclusions of the SCF regarding the studies on acute, subacute and subchronic toxicity as well as genotoxicity and allergenicity. From a toxicological point of view noni juice has been adequately tested and the studies evaluated by the SCF as well as the additional toxicological studies provided do not raise concern. The Panel considers the SCF opinion to be appropriate.

On the basis of the available toxicological information and against the background of the data provided on consumption of noni juice without the reporting of hepatotoxic effects, the Panel considers it unlikely that consumption of noni juice, at the observed levels of intake, induces adverse human liver effects. This would also apply to the anthraquinones potentially present in the commercially produced noni juice.

The Panel concluded that there is no convincing evidence for a causal relationship between the acute hepatitis observed in the case studies reported and the consumption of noni juice.

### KEY WORDS

Noni juice, case reports, hepatotoxicity, liver, transaminases.

## BACKGROUND

On 4 December 2002, the Scientific Committee on Food (SCF) adopted the “Opinion on Tahitian Noni<sup>®</sup> juice”.

On 5 June 2003, under Regulation (EC) N° 258/97, the Commission authorised the use of “noni juice” (juice of the fruit of *Morinda citrifolia* L.) as a novel food ingredient to be used in pasteurised fruit drinks<sup>1</sup>.

On 20 June 2005, the Austrian Competent Authority informed the Commission about a case report (Millonig *et al.*, 2005) that might raise concern with respect to the safety of noni juice. The Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (AGES) upon request of the Austrian Competent Authority delivered, in the meantime, an opinion. As this new information might possibly have an impact on the opinion of the safety of noni juice and because of the Community interest in this matter, the European Commission has decided to seek the opinion of EFSA.

## TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation N° 178/2002, the European Commission requests the European Food Safety Authority:

- To consider the following reports transmitted by Austria:
  1. (Case report) Herbal hepatotoxicity: acute hepatitis caused by a Noni preparation (*Morinda citrifolia*), G. Millonig *et al.*, Eur J Gastroenterol Hepato (2005) 17: 445-447;
  2. AGES: Abschliessende Stellungnahme zu Nonisaft Produkten – Verdacht auf lebertoxische Effekte.
- Depending on the outcome of this assessment, to review the aforementioned SCF opinion on the safety of “noni juice” (juice of the fruit of *Morinda citrifolia*), in the light of new scientific elements.

## ASSESSMENT

The term “noni juice” used in this Opinion refers to “noni juice” (juice of the fruit of *Morinda citrifolia* L.), consisting of a mixture of 89% noni fruit and 11% common grape and blueberry juice concentrates and natural flavours, which has been subject to the Commission Decision 2003/426/EC.

In this Opinion, the Panel took into consideration and reviewed the following data:

- the case report by Millonig *et al.* (2005),
- the AGES opinion,

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<sup>1</sup> Commission Decision 2003/426/EC. OJ L144, 12.06.2003, p. 0012.

- three further case reports, two reported by Stadlbauer *et al.* (2005) and referred to in the AGES opinion, and one reported by Yuce *et al.* (2006),
- a letter received from AFSSA in relation to anthraquinones,
- and the additional information received from the manufacturer further to EFSA request.

## 1. CASE REPORTS

### *Case 1 (Millonig et al., 2005)*

The case report describes a 45-year-old male subject admitted to the out-patient department of a hospital with a 2-week history of malaise and non-specific thoracic discomfort. Routine laboratory blood tests revealed highly elevated transaminases (glutamate oxalacetate transferase [GOT] 604 IU/mL; glutamate pyruvate transaminase [GPT] 1.995 IU/mL [normal range <50 IU/mL]); and gamma glutamyl transferase (GGT) 539 IU/mL (normal range <66 IU/mL) and elevated LDH (419 IU/mL; normal range < 232 IU/mL). Bilirubin and other parameters of liver and kidney function were normal. Liver biopsy and a histological examination confirmed the diagnosis of acute hepatitis. Histology revealed acute hepatitis with a mixed inflammatory infiltrate with numerous eosinophils in portal tracts and lobules. Hepatocellular cholestasis was evident in zone 3 of the acinus. In addition, activated Kupffer cells and Periodic Acid Schiff (PAS) positive histiocytes were present in the sinusoids. Viral hepatitis, alcoholic liver disease and other potential causes of acute hepatitis, i.e. autoimmune aetiology, Budd-Chiari syndrome, haemochromatosis or Wilson's disease, were excluded. The patient was asked about recent dietary changes and the consumption of a glass of noni juice (*Morinda citrifolia*) every day for the previous three weeks was mentioned. Two days after ceasing consumption of noni juice, transaminase levels began to fall, ten days later they had decreased considerably and were only slightly above normal, and one month later, they were completely normalised.

The Panel noted that the patient was an apparently healthy subject without history of liver disease or other conditions. There was a temporal relationship between stopping the consumption of noni juice and the decline of transaminase levels. However, the identity and the exact dose of noni juice ingested by the patient remained unclear. No samples of the juice actually consumed were available for chemical analysis.

### *Cases 2 and 3 (Stadlbauer et al., 2005)*

Case 2 (Stadlbauer *et al.*, 2005) is a 29-year old male patient readmitted with acute liver failure approximately one year after having developed acute hepatitis owing to treatment with paracetamol. During the three weeks prior to readmission, he had ingested 1.5 L noni juice (in total), and for 9 days prior to admission approximately 7 g/day of a Chinese herbal mix (containing bupleuri, pinellia, scutellaria, codonopsis, glycyrrhizae, schizonepeta, and paeonia). In addition, he admitted having treated himself with various homeopathic preparations for 14 months prior to readmission. On readmission, he showed grade 1 hepatic encephalopathy, GOT 1557 U/L [normal <35 U/L], GPT 1626 U/L [normal < 45 U/L], bilirubin 45.3 mg/dL [normal range = 0.1-1.2 mg/dL]. Histology revealed acute hepatitis with centrolobular necrosis consistent with acute drug-induced hepatotoxicity of idiosyncratic type. Liver failure progressed rapidly requiring emergency liver transplantation.

Other potential causes for acute liver failure such as virally induced hepatitis A or B, Wilson's disease and Budd-Chiari syndrome were ruled out. Causality of liver injury by noni juice was

assessed by the authors as “possible”. However, the authors could not exclude concomitant pre-existing liver damage by paracetamol and/or additional hepatotoxic effects of the components of the Chinese herbal mix.

The Panel noted that the patient had a documented history of drug-related hepatotoxicity before the episode of acute liver failure. The concomitant intake of a Chinese herbal mix could also have contributed to aggravate a pre-existing liver damage (induced by paracetamol), and therefore it is not possible to identify the cause of the liver injury.

Case 3 (Stadlbauer *et al.*, 2005) is a 62-year-old woman admitted to the hospital with vomiting and diarrhoea. Routine laboratory tests and liver biopsy revealed acute hepatitis (GOT 1415 U/L [normal <35 U/L], GPT 2381 U/L [normal < 45 U/L], GGT 241 U/L [normal < 55 U/L], alkaline phosphatase 292 U/L (normal range = 40-130 U/L), bilirubin 2.9 mg/dL [normal range = 0.1-1.2 mg/dL]). Four years before admission, she was diagnosed with chronic B-cell leukaemia which had been treated one year previously with fludarabine resulting in remission. Until two months before admission the patient had ingested 2 L of noni juice (in total) over a period of 3 months. Laboratory values peaked and gradually improved over the next 30 days. Nine months later, aminotransferases and bilirubin normalised.

Viral hepatitis, auto-immune hepatitis, haemochromatosis,  $\alpha_1$ -antitrypsin deficiency, Wilson’s disease and Budd-Chiari syndrome were ruled out. Causality of liver injury by noni juice was assessed by the authors as “probable”. A liver biopsy revealed acute hepatitis showing centrolobular liver cell necrosis, ballooned hepatocytes and mild inflammatory infiltrate which, according to the authors was consistent with an idiosyncratic drug reaction.

The Panel noted that in the Case 3 report no reference was made as to the consumption of alcohol or to the type of antibody tests performed. Therefore, both conditions (i.e. alcoholic liver disease or autoimmune hepatitis) cannot completely be ruled out. Moreover, the Panel pointed out that acute hepatitis was diagnosed two months after the discontinuation of the noni juice, and that it took nine months for the transaminases and bilirubin to normalize completely. This pattern might suggest that factors other than noni juice such as alcohol or autoimmune aetiology cannot be ruled out.

#### **Case 4 (Yuce *et al.*, 2006)**

In addition to the previous three cases, the Panel has been made aware of a new case report by Yuce *et al.* (2006).

Case 4 is a 24-year-old female admitted to the hospital with jaundice (on admission: ALT 1,538 U/L; GGT 110 U/L; bilirubin 5.25 mg/dL). She had been treated with interferon (IFN) beta-1a for 10 weeks after diagnosis of multiple sclerosis. Routine laboratory examination had revealed normal liver enzyme values after 4 weeks of IFN therapy. Nevertheless, after exclusion of viral hepatitis A-E by serological testing, IFN was suspected of having caused the hepatitis and was therefore withdrawn. One week after IFN withdrawal, the patient was examined again showing a further increase of her liver enzyme levels (AST 2,818 U/L; ALT 3,648 U/L; bilirubin 43.5 mg/dL). Further to extended medical history, the patient reported she had drunk a total of 1-1.5 litres of noni juice over the previous 4 weeks. The exact amount of noni juice consumed per day was not indicated. After stopping the ingestion of noni juice, transaminase levels fell rapidly and were reported to be within the normal range one month later.

Ultrasound scan of the liver ruled out intra- or extra-hepatic bile duct obstruction as well as vascular abnormalities or focal lesions. Alcoholic hepatitis, Budd-Chiari syndrome, haemochromatosis, or Wilson's disease, were ruled out. Laboratory examinations revealed an increased titer for liver-kidney microsomal antibody type 1 (1:3,840), with no other autoantibodies detectable. According to the authors, liver biopsy did not reveal evidence for an autoimmune disease, but did reveal confluent necroses of periportal and intralobular hepatocytes, lymphoplasmacellular and neutrophil inflammation, canalicular cholestasis and moderate fibrosis, a pattern that was considered highly suspicious for drug-induced hepatitis. The authors concluded that noni juice induced an idiosyncratic hepatitis, possibly by worsening a pre-existing liver damage due to IFN.

The Panel noted that the patient had an autoimmune disease treated with IFN beta-1a for 10 weeks. The exact dosage and brand-name of IFN were not given nor whether concomitant medications other than IFN were taken. Elevation of serum transaminases is a common finding in patients treated with IFN beta (EMEA, 2006). Interferon beta has also a potential for causing severe liver injury including acute hepatic failure, the majority of the cases occurring within the first six months of treatment (Tremlett and Oger, 2004 a and b; Tremlett *et al.*, 2004; Francis *et al.*, 2003; Durelli *et al.*, 2001). Although in some cases the liver injury may continue to evolve even after 2-3 weeks after discontinuation of IFN, in most cases transaminase levels start decreasing following IFN withdrawal and normalize completely (Byrnes *et al.*, 2006). The mechanism of IFN beta-induced hepatotoxicity in multiple sclerosis patients is unknown.

## **2. AGES OPINION**

The authors of the above case reports considered that anthraquinones may have been responsible for the reported hepatotoxicity (Millonig *et al.*, 2005; Stadlbauer *et al.*, 2005; Yuce *et al.*, 2006). The AGES performed microbiological and chemical analyses of the sample from Case 2 (the only available suspect sample) and of three other batches of noni juice. According to the report, the anthraquinones rubiadin and lucidin (limits of determination: 0.01 mg/kg) were not present. Patulin (limit of determination: 0.004 mg/kg), and pyrrolizidine alkaloids and N-oxides (calculated as senecionine, limit of detection: 0.05 mg/kg) and senkirkine (limit of detection: 0.02 mg/kg) were not detected in the samples investigated. The methods applied for analyses were not described.

The AGES concluded that on the basis of the presently available data hepatotoxic effects of noni juice, particularly as a result of the anthraquinones in question, are extremely unlikely. It pointed out that hepatotoxicity can be caused by a number of substances and that on the basis of single case reports, in which potential exposure to other hepatotoxic compounds cannot be reliably excluded, firm conclusions cannot be drawn. The Panel agrees with these conclusions.

## **3. ANTHRAQUINONES**

### **3.1. Isolation and structural elucidation of anthraquinones in fruits of *Morinda citrifolia***

In recent publications (Kamiya *et al.*, 2005; Sung-Woo Kim *et al.*, 2005; Pawlus *et al.*, 2005) referred to by AFSSA, several anthraquinones have been reported to occur in the fruits of

*Morinda citrifolia*. No explicit anthraquinone concentrations are given in these papers. They may only be estimated by considering the amounts of dried *Morinda citrifolia* fruits used as starting material and the amounts of anthraquinones actually obtained after extraction and purification. On the basis of the data reported by Kamiya *et al.* (2005), the concentration of one of the anthraquinones identified would be around 1 mg/kg juice, for the other five anthraquinones the estimated concentrations range between 0.1 and 0.5 mg/kg juice.

The Panel noted that the (freeze)-dried fruit materials used for the isolations of anthraquinones were not specified. In particular, the presence of skin and seeds, which are mechanically separated from the pureed fruit in the course of the production process of noni juice, cannot be ruled out. Considering the obvious variability of anthraquinone distribution in *M. citrifolia* depending on the plant tissue, the data regarding presence and contents of anthraquinones cannot be unconditionally extrapolated to commercially produced noni juice.

### **3.2 Analytical data provided by the manufacturer**

Additional analyses of noni juice for the presence of anthraquinones were performed. The method applied was based on extraction with ethyl acetate, separation of the compounds by reversed phase HPLC and detection using a diode array detector. Based on the characteristic UV spectra of hydroxyanthraquinones exhibiting a maximum absorption between 400 and 420 nm, the HPLC chromatograms were monitored at a wavelength of 410 nm.

To demonstrate the suitability of the method, an extract of the roots of *Morinda citrifolia* collected on the island of Tahiti was investigated. It was demonstrated that the procedure was able to isolate and to detect free hydroxyanthraquinones (lucidin and rubiadin) as well as hydroxyanthraquinones bound as glycosides (lucidin primveroside).

Data on noni juice were provided for three batches of juice. The juices were extracted with ethyl acetate to result in a 50-fold concentration with respect to the original juices. No peaks with absorption spectra typical for anthraquinones could be observed in the noni juice samples. To determine the detection limit for anthraquinones, the juices were spiked with 1 mg/kg of the anthraquinones lucidin, alizarin and rubiadin. The superposition of the HPLC chromatograms of the spiked and non-spiked samples showed the absence of these anthraquinones in the original samples. The spiked amounts of lucidin, alizarin and rubiadin were easily detectable in the chromatograms. Therefore, the detection limits for these anthraquinones for the method applied are considerably below 1 mg/kg.

The Panel noted that a comprehensive analysis of anthraquinones potentially present in noni juice at trace levels would require a very specific and targeted analytical approach (going beyond the mere detection via UV at a single wavelength) which would also have to cover glycosidically bound forms.

## **4. CONSUMPTION OF NONI JUICE IN EUROPE**

According to sales data obtained in Europe provided by the manufacturer upon request of EFSA, the majority of consumers (79%) purchased 4 bottles (4 L) of noni juice per month. Based on the assumption that the purchaser is the only consumer, this corresponds to a daily intake of 133 mL. The second largest group of consumers (9.5%) purchased 8 bottles (8 L) of noni juice per month corresponding to a daily intake of 267 mL. The total number of purchasers covered by these sales data has not been provided.

A 2005 survey of 1145 noni juice consumers conducted in five European countries resulted in the data shown in Tables 1 and 2. In the five European countries approximately 90% of noni juice consumers drank between 30 and 90 mL per day. No details about the procedure of the survey have been provided by the manufacturer.

**Table 1.** Average consumption quantities of noni juice (by country)

Country (n)	Average daily intake (mL)
All (1145)	52.3
Germany (303)	51
Sweden (325)	48
Norway (206)	65
Denmark (98)	42
Hungary (95)	44

**Table 2.** Distribution of average daily intakes of noni juice in five EU countries

Daily intake of noni juice (n=1145)		
Daily amount	Number	%
Less than 30 mL	8	0.7
30 to 60 mL	473	41.3
60 to 90 mL	577	50.4
120 mL and more	87	7.6

## 5. INFORMATION RELATED TO ADVERSE EFFECTS IN HUMANS ASSOCIATED WITH NONI JUICE CONSUMPTION

Several ethnobotanical studies from tropical regions refer to raw or cooked *Morinda citrifolia* L. fruit (noni fruit) as part of the diet of aboriginal populations of Polynesia and Australia. According to some references, the consumption was limited to times of famine due to the rather unpleasant taste and foul odour of the ripe fruits (SCF, 2002). Relevant adverse effects were not reported in these studies.

The US Food and Drug Administration (FDA) has established an adverse event reporting system (MedWatch) through which voluntary reporting of drug, dietary supplement, biologics, and medical device adverse events by consumers and medical professionals is possible.

The manufacturer has been notified by the FDA of one adverse event report initiated for a multivitamin-mineral supplement in which noni juice was mentioned. The MedWatch report notes that the consumer had been drinking noni juice during the time of the adverse event, which was a seizure. The MedWatch report also noted that the patient had a previous history of seizures. The manufacturer stated that it is unaware of any other adverse events reported to other government entities. However, the Panel pointed out that under-reporting cannot be ruled out.

The manufacturer has compiled consumer complaint data relative to noni juice. This information is catalogued by the manufacturer and monitored by the quality assurance

department. Complaints are catalogued regardless of the authenticity of the reported event, an actual diagnosis by a physician, or receipt of valid medical records. In most instances, a complaint is made without any documentation of its veracity.

The number of bottles of noni juice sold since July 1996 amounts to more than 80 million. Up to 31 January 2006, 304 health-related complaints were received from consumers, corresponding to approximately one health-related complaint for about every 250,000 bottles sold. The category and number of health related complaints were as follows: allergic reactions, 71; diarrhoea, 37; nausea, 57; skin rash, 42; and uncategorized, 97. The uncategorized groups include many different types of reported events, where no specific condition/symptoms can be determined or verified.

## **6. TOXICOLOGICAL INFORMATION**

### **6.1 Evaluation by the SCF**

In the safety evaluation of noni juice the SCF considered studies on acute toxicity, subacute toxicity and subchronic (13 weeks) toxicity in rats, studies on genotoxicity (gene mutations in mammalian cells [V79-HPRT-test], *in vivo-in vitro* UDS assay in rat hepatocytes and a mouse micronucleus test) and studies on allergenicity.

The SCF concluded that noni juice given daily to rats for 13 weeks at oral doses up to an equivalent of 80 mL/kg body weight/day caused no signs of toxicity. There was a considerable margin between the highest dose, which was without any effects, and the manufacturer's recommended daily serving size of 30 mL (equivalent to approximately 0.5 mL/kg body weight/day for a 60 kg adult). For consumers with higher consumption (say up to 600 mL/day, equivalent to 10 mL/kg body weight/day) the margin was considered smaller but compatible with margins of exposure for other whole foods. The SCF noted some limitations of the *in vivo* assay on genotoxicity but considered the results of the genotoxicity tests as an indication of lack of genotoxic potential for the materials tested. At that time, noni juice had been marketed for several years in a number of countries. While there were no formal tolerance trials or systematic post-launch monitoring, few untoward reactions were reported. Against this background the SCF considered noni juice, at the observed levels of intake, as acceptable (SCF, 2002).

### **6.2 Additional information provided by the manufacturer**

In response to the request by EFSA for additional toxicological or (pre-)clinical data that had become available since the SCF Opinion, the manufacturer of noni juice has provided further information on genotoxicity and cytotoxicity and the report of a study in humans.

#### ***Genotoxicity***

According to the manufacturer, extracts of noni juice caused no increase in DNA strand breaks in the Comet Assay and no enhancement of DNA adducts in rat hepatocytes *in vitro* and *in vivo* using the <sup>32</sup>P-post labelling method for detection.

In the mammalian microsome reverse mutation assay with *S. enterica* Typhimurium (Ames Test) an extract of noni juice, but not an extract of concentrated pure syrup of noni fruit, gave positive results in strain TA1537 with metabolic activation (S9-mix). According to the manufacturer, flavonoids in red grape juice, which is a constituent of noni juice, might have

caused this effect. The study report was not provided. However, since tests on gene mutations in mammalian cells gave negative results (SCF, 2002), this positive result in a bacterial test is considered irrelevant by the Panel.

### ***Cytotoxicity***

Cytotoxicity of noni juice and ethyl acetate extracts obtained from noni juice to primary rat hepatocytes was studied using the Neutral Red Assay. In addition, the influence on the plating efficiency of Reuber hepatoma cells (H4IIE cells) was examined. According to the author, the experiments do not support the hypothesis of a hepatotoxic action of noni juice. In the opinion of the Panel, however, the relevance of these results to the *in vivo* situation is unclear.

### ***Human data***

A single centre, double-blind, three dose level, parallel group, placebo-controlled safety study with noni juice in healthy subjects was carried out (BIBRA, 2003). A total of 96 subjects (age 18-64, 28 males and 68 females) were randomly assigned to one of four treatment groups. Each group was balanced according to sex, age and body mass index. The groups consumed 30 (group 2), 300 (group 3), or 750 (group 4) mL noni juice (containing 11% (v/v) grape and blueberry juice) per day for four weeks. The control group (group 1) consumed 750 mL water containing 11% (v/v) grape and blueberry juice. According to the study report, all subjects satisfied the defined inclusion and exclusion criteria. At screening there was no evidence of any difference between the groups as regards demographic and lifestyle data (including drinking habits), vital signs, electrocardiogram, medical history or medication used.

Adverse events were recorded over the whole of the study period. Blood samples were obtained before study commencement and at week 0 (base-line), week 2, week 4 and week 6 (follow-up) and analysed for haematology and biochemistry parameters. Urine samples were taken for analysis at the same time points. In the statistical analyses, the variables obtained at week 2, 4 and 6 were compared against week 0. Treatment groups were also compared against the control group.

Of the 96 subjects, 93 completed the study and the remaining three were withdrawn because of adverse events. Among them was a high-dose female showing elevated (about 2 to 3 times normal) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at week 2. This subject had mildly elevated levels of these liver enzymes at baseline also, but was none the less considered suitable for inclusion. According to the author a direct relationship with consumption of noni juice could not be ruled out. However, the increase was considered to be most likely related to the subject's life style, i.e. alcohol consumption. The Panel does not agree with this explanation since alcohol consumption normally causes an increase in  $\gamma$ -glutamyl transferase (GGT), which was not seen. However, the elevated transaminase levels at baseline suggest that an increase was already induced before the start of noni juice consumption. The other two withdrawals were a female, who stopped taking the product after 6 days because of intermittent increased bowel movement, and a male following high total and LDL cholesterol levels seen at week 2 (also present to some extent at week 0).

Statistical analyses were carried out to compare the values for each of the treatment groups 2, 3 and 4 with the control group 1, and also to test for dose-related trends over all four groups. Interpretation was mainly based on the results of the tests on dose-related trends, taking into account the level of statistical significance and consistency of findings at the various time points. According to the report, for some blood biochemistry and haematology parameters there was strong evidence of variation over time in all control and intervention groups.

However, there was no clear evidence of treatment-related effects. Dose-related trends significant at  $p < 0.01$  were never seen, and trends significant at  $p < 0.05$  were only evident at single time points. Changes from week 0 that were most suggestive of a possible effect of noni juice were an increase in AST activity seen at week 2 in groups 2 ( $p < 0.1$ ), 3 ( $p < 0.05$ ) and 4 ( $p < 0.05$ ) with the trend significant (trend  $p < 0.05$ ) and decreases in glucose levels seen at week 2 (trend  $p < 0.05$ ) and week 4 (trend  $p < 0.05$ ). The changes were small and all values were within normal ranges for these parameters. Therefore, the author of the study report did not regard these effects as clinically relevant. The Panel agrees with this conclusion.

However, the study report does not contain information whether power calculations to determine the necessary sample size of the study groups have been performed. Therefore, the statistical power of the study cannot be evaluated.

## **DISCUSSION**

Considering the question of potential hepatotoxicity, the Panel notes that administration of noni juice at a dose up to an equivalent of 80 mL/kg body weight/day for 13 weeks to rats did not induce adverse effects. This dose is equivalent to 4800 mL/day for a 60 kg adult. In the clinical study, administration of up to 750 mL/day for four weeks did not induce liver toxicity in apparently healthy subjects.

On the basis of the available toxicological information and against the background of the data provided on consumption of noni juice without reporting of hepatotoxic effects, the Panel considers it unlikely that consumption of noni juice, at the observed levels of intake, induces adverse human liver effects. This would also apply to the anthraquinones potentially present in the commercially produced noni juice.

The Panel concludes that, on the basis of the available information, a causal relationship between the occurrence of acute hepatitis in the four cases reported and the consumption of noni juice cannot be established.

## **CONCLUSION**

The Panel agrees with the conclusions of the SCF regarding the studies on acute, subacute and subchronic toxicity as well as genotoxicity and allergenicity (SCF, 2002). From a toxicological point of view noni juice has been adequately tested and the studies evaluated by the SCF as well as the additional toxicological studies provided do not raise concern. The Panel considers the SCF opinion to be appropriate.

The Panel concluded that, on the basis of the available information, it is unlikely that consumption of noni juice, at the observed levels of intake, induces adverse human liver effects. There is no convincing evidence for a causal relationship between the acute hepatitis observed in the case studies reported and the consumption of noni juice.

## DOCUMENTATION PROVIDED TO EFSA

Communication of the Bundesministerium für Gesundheit und Frauen (Austria) including AGES opinion to the Commission, 20 June 2005.

Letter from Agence Française de Sécurité Sanitaire des Aliments (AFSSA) in relation to anthraquinones, 13 October 2005.

Manufacturer's reply to EFSA request for additional information, 14 February 2006.

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