

**U.S. Food and Drug Administration
Premarket Notification of New Dietary Ingredient**

KiwiBerry Extract

Submitted to:

SEP 27
AB/KON

Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
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September 26, 2005

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New Dietary Ingredient Notification for KiwiBerry Extract

September 26, 2005

1. Manufacturer and distributor of the new dietary ingredient

Efficas, Inc.
7007 Winchester Circle, Suite 120
Boulder, CO 80301

2. The name of the new dietary ingredient

KiwiBerry Extract: *Actinidia arguta* (Sieb. & Zucc.) Planch. ex Miq.

Full taxonomic description is in Annex 1.

The ingredient is manufactured from the KiwiBerry fruit. The fruit are cooked in water, insoluble components are removed by filtration, and the resulting material is dried. Manufacturing is described in more detail in Section 7 below.

3. The dietary supplement containing the new dietary ingredient

The dietary supplement product is comprised of capsules containing dried powdered KiwiBerry extract (50% by weight KiwiBerry extract concentrate, 50% by weight microcrystalline cellulose [MCC]).

The level of the new dietary ingredient in the dietary supplement

Each 600 mg capsule of KiwiBerry Extract contains 300 mg of the KiwiBerry extract concentrate plus 300 mg of MCC.

The conditions of use recommended or suggested in the labeling of the dietary supplement

Adults. Suggested use is 2 – 4 capsules per day. This suggested use provides a daily intake of 600 mg – 1200 mg of KiwiBerry extract concentrate. This daily intake is produced from 15 (fifteen) grams or 30 grams, respectively, of the fresh, grape-sized KiwiBerry fruits, or approximately 3 (three) – 6 (six) KiwiBerry fruit. In contrast, one kiwifruit (*A. deliciosa*) weighs 80 – 90 grams.

Children weighing at least 20 kg or 44 pounds. Suggested use is 1 capsule per day.

KiwiBerry extract may be used daily by adults and by children weighing at least 44 pounds. With a No Observed Adverse Effect Level > 2,000 mg/kg, KiwiBerry extract is safe enough for daily (chronic) use at ≤ 20 mg/kg (see Section 5).

4. History of use of KiwiBerry fruit as food

Throughout the native range of *A. arguta* in Asia, it is known as a common plant and has been described as such in scientific publications both before 1958 and in modern times (Annex 2). Publications in English, Chinese, Japanese and Russian describe the species, its distribution and the common use of *A. arguta* fruit by local populations. The documented use includes fresh, dried, cooked, preserved, fermented and decocted (water extracted) forms. Evidence that the food status of the fruit is accepted within the United States comes from the fact that the crop is being promoted for cultivation by agricultural scientists within several state University systems and that the USDA lists the economic importance of *A. arguta* as human food (USDA, ARS, 1999).

Currently, *A. arguta* is cultivated in USA, Canada, Chile and New Zealand (the primary producers for the export market) as well as Russia, China, Japan, Korea, France, Italy, Germany, Switzerland and Australia (Berry, 2003; Boyes et al., 1997a; Okamoto and Goto, 2005; Strik and Cahn, 1996; Kolbasina, 2000; Zhang et al., 1992).

5. Safety Studies

Statement of the Basis for a Determination of Safety

Efficas has determined that KiwiBerry extract is safe for consumption under the suggested conditions of use based the following information:

1. The compositional equivalence of KiwiBerry, KiwiBerry extract and kiwifruit (*A. deliciosa*).
2. Documented acceptance of the KiwiBerry fruit as food in the United States.
3. The published evidence of a history of use of KiwiBerry fruit as food in fresh, dried, cooked, fermented and decocted (water extracted) forms.
4. Data from the Ames test demonstrating no mutagenic effect of the KiwiBerry extract.

All other data, including the *in vivo* preclinical studies, are viewed as supplemental, rather than primary, evidence of safety.

Clinical Study

The safety of 600 mg/day KiwiBerry extract concentrate was evaluated during a double-blind, randomized, placebo-controlled clinical trial. The study was conducted in accordance with ICH/GCP guidelines. Adult subjects were instructed to take 2 capsules per day of KiwiBerry extract or placebo (MCC) for 42 days. The study achieved a total enrollment of 51 subjects at three established clinical research study centers in the United States. Twenty-five subjects were randomized to the test article and 26 were randomized to placebo. The intent to treat (ITT) analysis encompassed all 51 subjects who were enrolled while 43 subjects satisfied the per protocol (PP) analysis criteria, which included a minimum threshold of 90% dosing compliance (21 test article and 22 placebo).

Safety was assessed using data on adverse events, standard urinalysis, hematology and clinical chemistry on Day 1, Day 14 and Day 42. Safety variable and parameters were evaluated by an independent Medical Monitor not employed by Efficas. There were no serious adverse events reported in the clinical trial. The number of adverse events reported in both the test article and placebo groups were comparable, 12 in the test article group versus 13 in the placebo group. The attribution to test article as well as severity ratings of the adverse events were also unremarkable between the two cohorts. There were no safety concerns detected in the clinical laboratory values.

Preclinical Studies

One *in vitro* and 5 *in vivo* safety studies have been conducted with KiwiBerry extract. These are summarized briefly below. A more complete description of the GLP-compliant *in vivo* study is in Annex 3.

In vitro assessment of mutagenicity (Ames test).

KiwiBerry extract concentrate (not containing MCC) was tested for mutagenic activity in an Ames test conducted at an independent laboratory. The test utilized 5 strains of *Salmonella typhimurium*, with and without metabolic activation (pre-incubation method). Test article concentrations ranged from 5 – 5000 µg/plate (11 concentrations tested). There was no mutagenic effect.

In vivo studies (Table 1). Five studies were conducted in rodents to assess potential toxicity of KiwiBerry extract concentrate (not containing MCC). The juvenile rat study was conducted in the US under GLP. The remaining studies, conducted by another company overseas, are not GLP-compliant (Efficas has only brief summaries of these studies, and this information is included in the Notice only for the sake of completeness).

Table 1. Description of *in vivo* safety studies conducted with KiwiBerry extract.

	Juvenile Rat Study	28-day Mouse	28-day Rat	3 month Mouse	6 month Rat
GLP	Yes	no	no	no	no
Animal species	SD rat	Balb/c Mouse	SD rat	Balb/c Mouse	SD rat
Age	PND 8 - PND 85	Not specified	5 weeks old at start	5 weeks old at start	5 weeks old at start
# female /tmt	20	10	7	7	7
#male/tmt	20	0	7	7	7
Doses	0, 500, 1000, 2000 mg/kg	0, 150 mg/kg	0, 100, 300, 1000 mg/kg	0, 150 mg/kg	0, 300 mg/kg
Administration	Gavage	Gavage	Oral	Gavage	Oral
Duration	76 days	28 days	28 days	3 months	6 months
Microscopic examination	No test article related adverse effects in any organ or tissue	Kidney, spleen, thymus & liver examined. No adverse effects seen.	Heart & liver examined. No adverse effects seen.	ND	ND
Treatment related adverse findings	None clinically significant	None clinically significant	None clinically significant	None clinically significant	None clinically significant

ND – not done.

6. Allergenicity studies

There are several recent reports of allergy to common kiwi fruit, *Actinidia deliciosa* (reviewed in Lucas et al., 2003). Various symptoms have been reported, including localized oral symptoms and anaphylaxis. Allergy to kiwi fruit has been considered rare but may be increasing in prevalence (Fiocchi et al., 2004; Lucas et al., 2004).

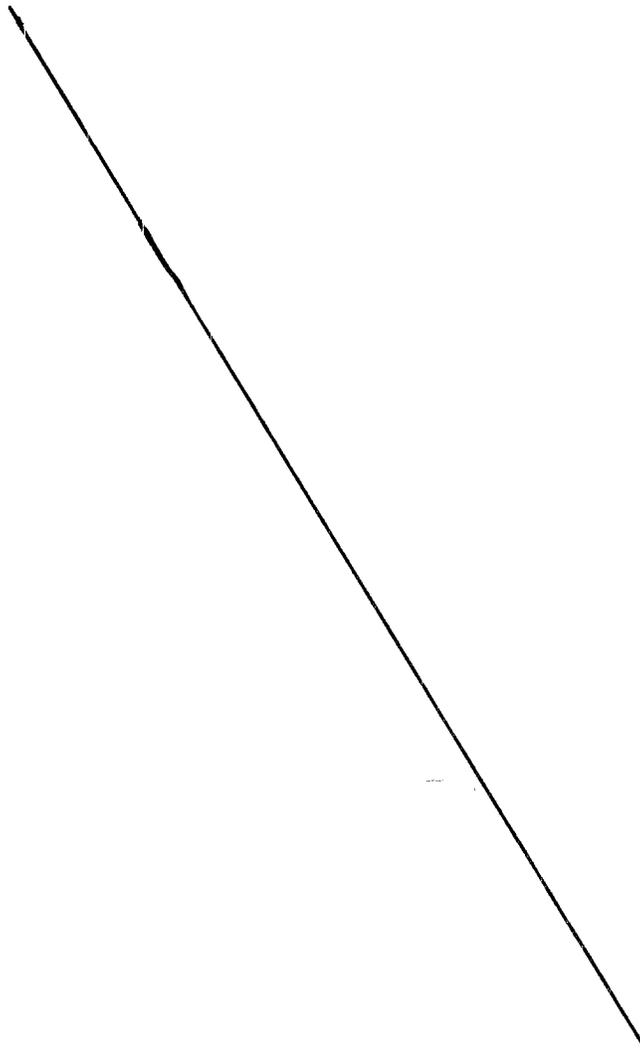
Allergens in kiwifruit, particularly actinidin, are heat labile (Lodge and Perera, 1992). Heat processed kiwifruit may be less allergenic than fresh kiwifruit (Fiocchi et al., 2004). Of 20 kiwi allergic children tested, none had an allergic reaction to a commercial preparation of heat treated homogenized kiwifruit during a double-blind placebo-controlled food challenge study (Fiocchi et al, 2004).

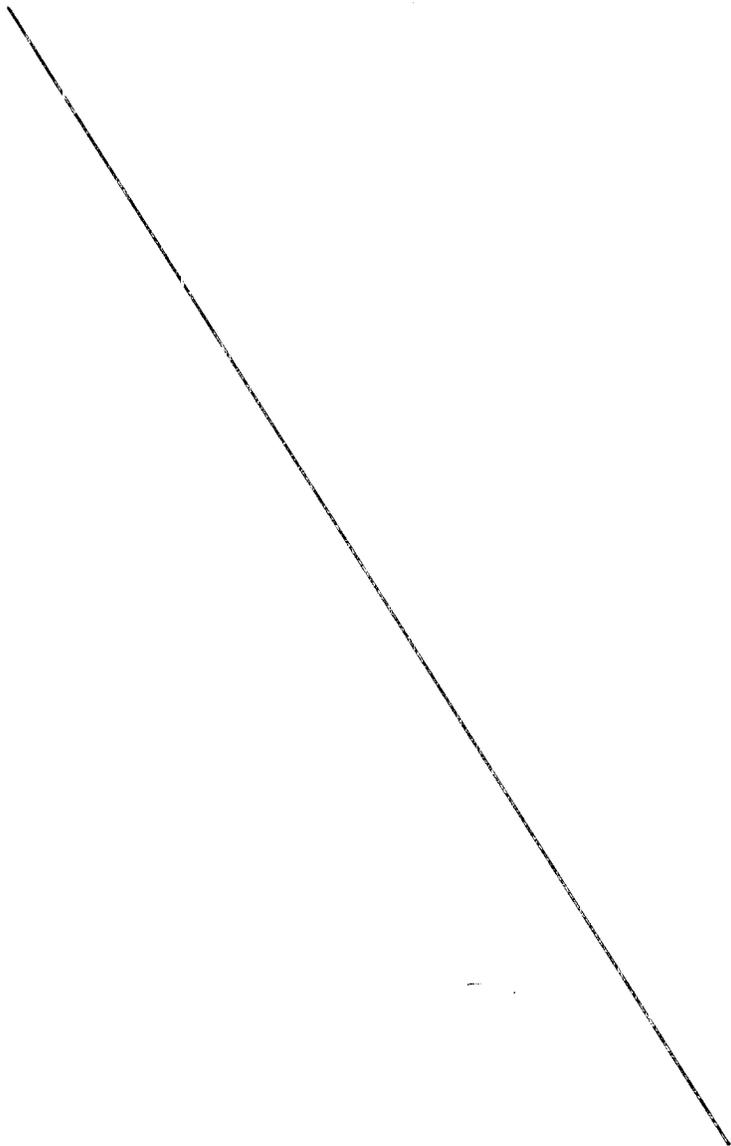
KiwiBerry extract is manufactured using prolonged heat processing (see Section 7 below). Experiments were conducted at the Food Allergy Research and Resource Program of the University of Nebraska, with a grant from Efficas, to evaluate the potential allergenicity of KiwiBerry extract concentrate (Chen et al., 2005. Manuscript submitted). Results of the study were that “sera obtained from this population of kiwifruit-allergic subjects did not bind to heat-processed hardy kiwifruit concentrate.”

Chen et al. (2005) write: “In this study we have used 12 well-characterized green kiwifruit-allergic subjects to evaluate potential cross-reactivity. Eight of the subjects tested positive by the “gold standard”, DBPCFC, performed in a controlled clinical setting with full resuscitation capabilities. The remaining four subjects had the most severe historical reactions to kiwifruit and were not asked to accept food challenge, but had clear ImmunCAP positive results to f84 (green kiwifruit). The results demonstrate that IgE from sera obtained from this population of kiwifruit-allergic subjects did not bind to heat-processed hardy kiwifruit concentrate. These results imply that heat-processed hardy kiwifruit concentrate is unlikely to cause a reaction in someone with allergy to raw green kiwifruit. These results were based only on *in vitro* data using sera from 12 kiwifruit-allergic individuals so caution must be exercised with respect to any broad recommendations regarding the allergenicity of heat-processed hardy kiwifruit concentrate for the entire population of kiwifruit-allergic consumers.”

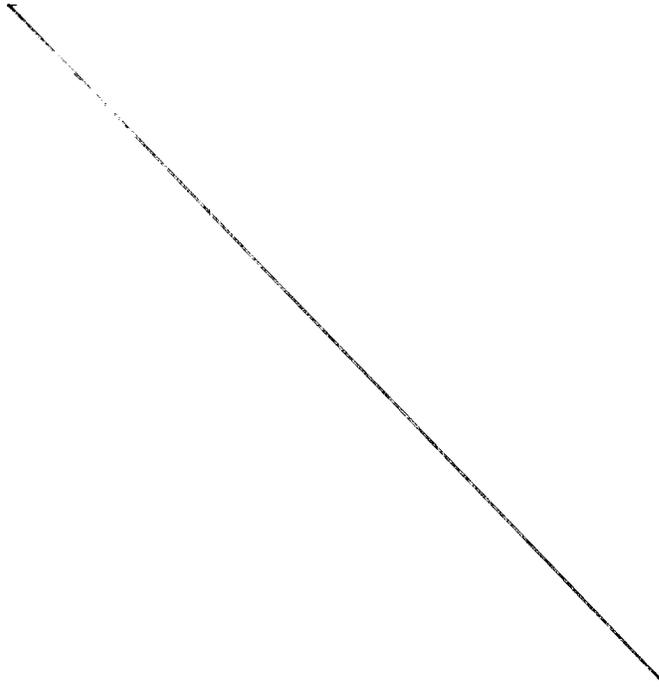
The ingredient name, KiwiBerry extract, should alert kiwi allergic consumers to the potential allergenicity of the dietary supplement product.

7. Description of Manufacturing





KiwiBerry Extract Process Overview



8. Compositional analysis

A comparison was made of the major nutritive and nonnutritive components of *A. arguta*, *A. deliciosa* and KiwiBerry extract concentrate (i.e. KiwiBerry extract not containing MCC) based on published literature references and analytical studies conducted by independent laboratories. The KiwiBerry extract was manufactured using Oregon-sourced fruit from 2 years of harvest. A summary of the findings are given below, followed by tabular data.

Methods

Proximate analysis, mineral analyses and microbial analyses were performed by The National Food Laboratory, Inc. using their internal standard methods. Carbohydrate was calculated by difference (100% minus SUM[fat + protein + ash]).

Sugars were measured by Medallion Laboratories using HPLC.

Starch and fiber were measured by Shuster Laboratories, Inc. using AOAC Method 920.44 and AOAC Official Methods of Analysis, 17th Edition, 2000, CH45, p 78, respectively. Organic acids were measured by Shuster Laboratories, Inc. using USP method 28 2005 p.2074. Vitamin C was measured by Shuster Laboratories, Inc using AOAC Official Methods of Analysis, 17th Edition, 2000, CH45, p 16.

Flavonoid assays, anthocyanin assays and catechin assays were conducted by ChromaDex, Inc. using HPLC.

Results

Proximate analysis demonstrates that fruits of both species are approximately 80% moisture (Table 2). On a dry weight basis, fruits of both species are predominantly comprised of carbohydrate (ca. 80%), with low amounts of fat, protein and ash. The manufacture of KiwiBerry extract concentrate does not have a significant impact on the results of proximate analysis.

The total carbohydrate content of the two species is comparable (Table 3). Starch is a very minor component of the ripe fruit tested. Fiber levels are greater in fresh fruit than in KiwiBerry extract, most likely due to the filtration step that removes insoluble fiber. Sugar composition is impacted by the degree of ripeness of the fruit in both species (Klages et al., 1998). Myo-inositol composition tends to be greater in *A. arguta* than *A. deliciosa*, but also declines during ripening. *A. arguta* cultivated in New Zealand is consistently reported to have greater sucrose: monosaccharide ratio than that of *A. deliciosa* (Boldingh et al., 2000; Boyes et al., 1997b; Klages et al. 1998) however this was not the case for fruit harvested in China (Zhang et al., 1992). These differences may be varietal, due to growing conditions or ripeness, or a combination of these factors. Alternatively, the reported differences in sucrose : monosaccharide ratio in Chinese versus New Zealand samples may be partially due to sample handling; samples from New Zealand were frozen immediately after harvest to preserve sucrose. Compositional differences of individual sugars do not constitute a hazard as the monosaccharides are dietary components and also metabolites of sucrose. Fruit that is stored before being consumed would be expected to have low sucrose content due to the activity of the enzyme invertase, which cleaves sucrose to glucose and fructose. The very low sucrose

content reported for the grocery store sourced fruit samples in Table 3 is most likely due to the activity of invertase. These samples are likely more representative of the sugars content of kiwi fruits as consumed than are reports from the literature.

There is very little published data on the organic acid content of *A. arguta* (Table 4). Data from grown fruit in New Zealand, China and Japan suggest that the organic acid composition of *A. deliciosa* and *A. arguta* are very similar (Boyes et al., 1997b; Okamoto and Goto, 2005; Zhang et al., 1992). These similarities are also evident in KiwiBerry concentrate.

We did not find any published data on the flavonoid composition of *A. arguta* fruit, although one study has compared the flavonoid composition of leaves of *A. arguta*, *A. deliciosa* and other members of the genus (Webby et al., 1994). Flavonoids detected in KiwiBerry extract concentrate were also detected in *A. deliciosa* (Table 5). Quercetin levels in individual lots of KiwiBerry extract ranged from 21.5 to 82.4 ppm, and were 36.07 ppm and 16.71 ppm in the single samples of *A. arguta* and *A. deliciosa* fruit tested, respectively.

We did not find any published data on the anthocyanin composition of *A. arguta* fruit. The major anthocyanin in *A. arguta*, cyanidin, was apparently degraded during the manufacturing of KiwiBerry extract concentrate, as were most of the other anthocyanins (Table 5). Malvidin, which was found in comparable levels in *A. arguta* and *A. deliciosa*, apparently was not degraded during the manufacturing of KiwiBerry extract concentrate.

Catechins were not detected in *A. arguta* fruit or in KiwiBerry extract (Table 5).

KiwiBerry extract concentrate contains low sodium levels, modest amounts of calcium, magnesium, and phosphorus, and high levels of potassium (Table 6). These findings are consistent with the composition of *A. arguta* fruit from Oregon and published data from Japan (Okamoto and Goto, 2005).

KiwiBerry extract concentrate and powder contains no detectable bacteria, mold or yeast contaminants (Table 7).

Conclusions. The major components of *A. arguta* and KiwiBerry extract concentrate are present in the common kiwifruit *A. deliciosa*. Minor differences in relative amounts of the various constituents do not pose a hazard. Processing of *A. arguta* to produce KiwiBerry extract concentrate does not disproportionately concentrate any particular component that would be a cause for concern.

Table 2. Proximate analysis of KiwiBerry extract concentrate, *A. arguta* and *A. deliciosa* fruit. All measures are expressed on a dry weight basis except for moisture.

	KiwiBerry Extract^a	<i>A. arguta</i> (Oregon^b)	<i>A. deliciosa</i> (grocery^b)
	Mean \pm SD		
Moisture %	33.28 \pm 6.1	76.82	83.3
Ash %	4.64 \pm 0.5	3.28	5.27
Protein %	5.91 \pm 0.58	6.17	6.65
Fat %	4.32 \pm 2.14	7.38	11.08
Carbohydrate %	85.75 \pm 2.83	83.18	77.13
Calories per 100 g	399.7 \pm 12.98	422.78	437.13

^a Mean \pm standard deviation of 7 independent lots of manufactured extract. Raw material was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

Table 3. Carbohydrate components of KiwiBerry extract concentrate, *A. arguta* and *A. deliciosa* fruit. All measures are expressed on a dry weight basis.

	KiwiBerry Extract^a	<i>A. arguta</i> (Oregon^b)	<i>A. arguta</i> (literature range^c)	<i>A. deliciosa</i> (grocery^b)	<i>A. deliciosa</i> (literature range^c)
	Mean \pm SD				
Sugars %	55.06 \pm 3.44	23.99	23.3 – 46.2	52.8	13.4 – 38.8
Fructose	26.71 \pm 2.13	10.05	5.5 – 8.5	27.0	5 – 16.5
Glucose	23.06 \pm 1.62	11.09	5.0 – 8.5	24.9	4.7 – 12.5
Inositol	4.99 \pm 0.42	2.85	1.4 – 2.5	0.9	0.8
Sucrose ^d	0.30 \pm 0.35	0.00	2.5 – 27.5	0.00	2.7 – 2.8
Starch %	0.13 \pm 0.01	0.45	DNR ^e	0.52	DNR
Total Fiber %	4.88 \pm 1.20	25.02	DNR	13.17	DNR

^a Mean \pm standard deviation of 7 independent lots of manufactured extract. Raw material was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

^c Literature values reported for ripe fruit at harvest (calculations were made when necessary to standardize units). Boldingh et al., 2000; Klages et al., 1998; Zhang et al, 1992; Boyes et al, 1997b.

^d Reported sucrose content may be influenced by ripeness and length of storage before analysis due to the activity of invertase enzyme in kiwi fruit. No attempt is made to inactivate invertase during the manufacturing of KiwiBerry extract.

^e Did not research this topic.

Table 4. Organic acid components of KiwiBerry extract concentrate, *A. arguta* and *A. deliciosa* fruit. All measures are expressed on a dry weight basis.

	KiwiBerry Extract ^a	<i>A. arguta</i> (Oregon ^b)	<i>A. arguta</i> (literature range ^c)	<i>A. deliciosa</i> (grocery ^b)	<i>A. deliciosa</i> (literature range ^c)
Organic acids, mg/g	Mean ± SD				
Citric	74.41 ± 8.67	35.33	60 – 60.9	38.3	33.9 - 51
Malic	15.96 ± 4.02	22.86	11.5 – 13.15	29.4	5 - 13
Quinic	37.67 ± 4.85	21.18	25.95 – 75.5	44.05	32.5 – 41.8
Vitamin C ppm	12.53 ± 20.83	149.70	DNR ^d	452.50	DNR

^a Mean ± standard deviation of 7 independent lots of manufactured extract. Raw material was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

^c Literature values reported for ripe fruit were on a fresh weight basis. These values were multiplied by 5 to estimate dry weight values. Zhang et al, 1992; Boyes et al, 1997b; Okamoto and Goto, 2005.

^d Did not research this topic.

Table 5. Microcomponents of KiwiBerry extract concentrate, *A. arguta* and *A. deliciosa* fruit. All measures are expressed on a dry weight basis.

Flavonoids, ppm	KiwiBerry Extract ^a		<i>A. arguta</i> (Oregon ^b)	<i>A. deliciosa</i> (CA grocery ^b)
	Mean ± SD	Range		
Quercetin	62.38 ± 22.57	21.5 – 82.4	36.07	16.71
Isorhamnetin	25.23 ± 3.22	ND – 31.4	ND	15.87
Kaempferol	23.74 ± 3.07	ND – 27.7	ND	12.1
Anthocyanins, ppm				
Cyanidin	1.13 ^c	ND – 1.13	130.07	ND
Delphinidin	0.20 ± 0.07	ND – 0.32	9.15	0.18
Malvidin	5.9 ± 5.89	ND – 15.06	11.22	11.68
Pelargonidin	ND	ND	0.69	ND
Peonidin	0.18 ± 0.14	ND – 0.35	0.99	ND
Catechins	ND	ND	ND	Not tested

^a Mean ± standard deviation of 7 independent lots of manufactured extract with the exception of catechins (1 lot tested). Raw material was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

^c Cyanidin detected in only 1 of 7 lots tested.

ND – none detected

Table 6. Mineral and metal components of KiwiBerry extract concentrate, *A. arguta* and *A. deliciosa* fruit compared to published values. All measures are expressed on a dry weight basis.

	KiwiBerry Extract^a	<i>A. arguta</i> (Oregon^b)	<i>A. arguta</i> (Publ.^c)	<i>A. deliciosa</i> (grocery^b)	<i>A. deliciosa</i> (Publ.^c)
Minerals, ppm	Mean ± SD				
Calcium	1267.9 ± 365	3623	2160	2455	1210
Magnesium	1131.9 ± 241	906	930	1018	800
Phosphorus	1993 ± 527	2066	No data	3180	No data
Potassium	21,204 ± 1062	11,260	13,840	22,215	12,710
Sodium	338 ± 140	25.02	No data	77.84	No data
Metals					
Heavy metals as lead, ppm. MDL = 10	7 Passed	1 Passed	No data	1 Passed	No data

^a Minerals are expressed as mean ± standard deviation of 7 independent lots of manufactured extract. Heavy metals are expressed as the number of samples with less than detectable heavy metals by the assay. Raw material for the KiwiBerry extract was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

^c Okamoto and Goto, 2005.

ND – none detected

Table 7. Microbiological components of KiwiBerry extract concentrate and powder, *A. arguta* and *A. deliciosa* fruit. All measures are expressed on a fresh weight basis.

	KiwiBerry Extract^a	KiwiBerry Extract Powder	<i>A. arguta</i> (Oregon^b)	<i>A. deliciosa</i> (grocery^b)
Microbiological				
Total aerobic, CFU/g	< 10	< 10	20	<10
Coliforms, MPN/g	< 3	< 3	< 3	< 3
<i>E. coli</i> , MPN/g	< 3	< 3	< 3	< 3
Fecal coliforms, MPN/g	< 3	< 3	< 3	< 3
Salmonella per 25 g	Negative	Negative	Negative	Negative
Mold, CFU/g	< 10	< 10	< 10	< 10
Yeast, CFU/g	< 10	< 10	< 10	< 10

^a Results are from tests of 7 independent lots of manufactured extract. Raw material was Oregon-sourced fruit from 2 years harvest.

^b One lot of fruit was tested.

9. Product specification

KiwiBerry Extract Powder

Manufacturer:

Efficas, Inc.
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Boulder, CO 80301
Tel: (303) 381-2070
FAX: (303) 381-2074

Product Specification:

Description

KiwiBerry Extract Powder is obtained from the hot water extraction of sliced, dried KiwiBerry fruit (*Actinidia arguta*), followed by filtration to remove insoluble components, and concentration. The concentrate is dried with an inert carrier to form the flowable powder.

Functional Use in Dietary Supplements: KiwiBerry Extract Powder is used as a source of nutrients.

Requirements

Moisture	< 6 %
Ash	< 4 %
Carbohydrate	> 75%
Protein	< 5%
Total organic acids	> 25 mg/g
Heavy metals	< 10 ppm
Microbiology	Total aerobic ≤ 10,000 CFU/g
	Coliforms: < 3 MPN/g
	Salmonella: Negative to test
	Molds: ≤ 500 CFU/g

10. Product stability

Methods

Merlin Development, Inc. coordinated the storage study on the KiwiBerry extract powder. Sensory analysis was conducted by Merlin Development, Inc. Sample storage and analytical testing were conducted by Medallion Laboratories.

The dried, powdered KiwiBerry extract was packaged in double poly bags for shelf life testing. Samples for testing were stored at three conditions: 70 degrees F./38% RH, 40 degrees F./ambient RH and 100 degrees F. /20% RH. Samples were pulled for evaluation monthly up to three months. At each interval samples were evaluated for:

- Sensory characteristics: color, clumping and aroma
- Analytical: pH, moisture, Aw, total sugars and microbial content

Results

Analytical (Table 8). Analytical characteristics were quite stable at all conditions of storage. pH and sugars content were stable, and there was no indication of microbial growth during the study. Moisture, an indicator of the impermeability of the packaging, increased only slightly during the 3 months incubation.

Sensory (Table 9). Sensory characteristics were quite stable at all conditions of storage. There was some loss of aroma at ambient and elevated temperatures, but no increase in off aroma.

Conclusion

The KiwiBerry extract powder is very stable at room temperature (70 degrees F) and under accelerated conditions.

Table 8. Stability Study on KiwiBerry Extract Powder : Analytical Tests

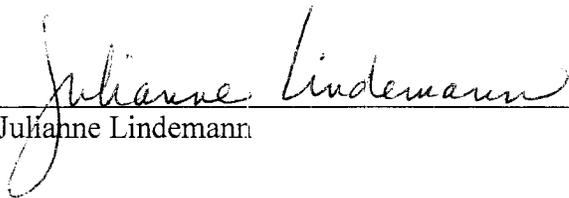
		Analytical Parameter						
Conditions/Time	pH	Moisture %	Aw	Total % sugars (HPLC)	% Fructose	% Glucose	% Sucrose	Total aerobic microbes (CFU/g)
70 F, 38% RH								
Time 0	3.72	1.24	0.166	16.3	8.84	7.46	0	< 10
1 month	3.63	1.36	0.189	16.5	9.01	7.5	0	< 10
2 months	3.73	1.36	0.178	19.6	8.88	7.48	0	< 10
3 months	3.63	1.36	0.244	16	8.88	7.07	0	< 10
40 F, ambient RH								
1 month	3.63	1.28	0.183	16.3	8.88	7.46	0	< 10
2 months	3.72	1.20	0.196	19.6	8.82	7.45	0	< 10
3 months	3.64	1.28	0.209	16	8.92	7.05	0	< 10
100 F, 20% RH								
1 month	3.63	1.20	0.157	16.3	8.9	7.42	0	< 10
2 months	3.74	1.28	0.161	19.5	8.62	7.36	0	< 10
3 months	3.65	1.36	0.221	16.5	8.76	7.78	0	< 10

Table 9. Stability Study on KiwiBerry Extract Powder : Sensory Assessment

		Sensory Characteristics								
		Hunter Color								
Conditions/Time		L	a	b	Light/Dark	Red/Brown	Clumping	Particle size	Dried Fruit Aroma	Off Aroma
70 F, 38% RH										
	Time 0	56.8	10.7	25.9	40	25	5	20	30	2.5
	1 month	55.5	10	24.9	40	25	5	20	30	2.5
	2 months	56.4	9.82	24.6	40	26	5	20	30	2.5
	3 months	54.5	10.1	25	41	27	5	20	25	2.5
40 F, ambient RH										
	1 month	56	9.99	25	40	25	5	20	30	2.5
	2 months	55.3	10.2	25.3	40	26	5	20	30	2.5
	3 months	50.2	9.63	22.8	40	25	5	20	30	2.5
100 F, 20% RH										
	1 month	56.3	10.7	25.6	40	25	5	20	30	2.5
	2 months	56.5	10.7	25.4	40	26	5	20	30	2.5
	3 months	56.3	11.1	26	45	28	5	28	22	2.5

If there are questions about this New Dietary Ingredient Notification, please contact:

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Julianne Lindemann

Annex 1. Taxonomic Characterization of *Actinidia arguta*

Taxonomic Designation and Description of the Source Plant

Actinidia arguta (Sieb. & Zucc.) Planch. ex Miq. is a dicotyledonous, perennial, deciduous, flowering plant with a vining growth habit. The current taxonomic designation is as follows:

Kingdom: Plantae
Subkingdom: Tracheobionta (vascular plants)
Superdivision: Spermatophyta (seed plants)
Division: Magnoliophyta (flowering plants)
Class: Magnoliopsida (dicotyledons)
Subclass: Dilleniidae
Order: Theales
Family: Actinidiaceae
Genus: *Actinidia* Lindl.
Section: *Leiocarpae* (Dunn) Li
Series: *Lamellatae* C.F. Liang
Species: *Actinidia arguta* (Sieb. & Zucc.) Planch. ex Miq.

Synonyms (Compiled in Mansfeld's Database, 2002):

Trochostigma arguta
Trochostigma rufa
Actinidia rufa
Actinidia cordifolia
Actinidia platyphylla
Actinidia arguta var. *rufa*
Actinidia callosa var. *rufa*
Actinidia giraldii

Actinidia arguta is a vigorous, perennial, woody climbing vine reaching 7 m or more in height. Within its natural range it is a common plant and can be found growing in thickets (Dunn, 1911; Nakai, 1933; Li, 1952; Kolbasina, 2000). Flowers are white, with 5 sepals and 5 petals, and functionally dioecious. Stems and leaves are smooth. Leaves are ovoid, dark green, 8-12 cm long with serrated edges. The fruit are edible, with green skin and pulp, smooth-skinned (lacking hairs or fuzz), unspotted, borne in clusters, and are ovoid or oblong, 2 -- 2.5 cm long. In botanical nomenclature, the fruits are berries (Li, 1952) and contain many tiny dark seeds in a circular pattern within the green flesh.

The genus *Actinidia* contains more than 60 species. The genus has been subdivided into 4 Sections based on morphological features of stems, leaves and fruit; the structure of leaf hairs, extent of pubescence on stems, leaves and fruit, and the presence or absence of lenticels (spots) on the fruit (Li, 1952; Ferguson, 1990a). The extremes of this variability are represented by the sections *Leiocarpe*, containing *A. arguta* and other taxa with

smooth skinned fruit lacking lenticels, and Stellatae, containing *A. chinensis* and *A. deliciosa*, whose stems, leaves and fruit are covered with stellate hairs.

While these divisions are generally accepted, it has also been noted that there is a high degree of morphological variability within each species (Ferguson, 1990b). Some of this intraspecies variability may be due to natural hybridization between species (Huang et al., 2002). In other cases variability may result from there being multiple ploidy levels. *A. arguta* for example has been found in diploid ($2n=58$), tetraploid ($2n=116$) and hexaploid ($2n=174$) forms (Ferguson et al., 1996), displays a high degree of morphological variability and may still be differentiating or undergoing speciation (Huang et al., 2002). The common kiwifruit, *A. deliciosa*, is hexaploid, whereas the closely related *A. chinensis* is diploid.

While the identity of macrocomponents of fruits are the same in *A. arguta* and *A. deliciosa*, the relative amounts of these components may differ. Compositional studies have generally confirmed the placement of individual species within the different Sections. For example, *A. arguta* has been distinguished from *A. deliciosa* based on leaf flavonoids (Webby et al., 1994) and relative proportions of common fruit sugars and organic acids (Klages et al., 1998; Boldingh et al., 2000; Boyes et al., 1997b). Such studies relied on few individual plants of each species due to the relative paucity of varieties under cultivation and available for study. Extensive compositional data are not available for *A. arguta* representing all 3 ploidy levels. Compositional data from New Zealand (Boyes et al., 1997b) differ significantly from that published in China (Zhang et al., 1992) particularly in regard to sugars composition. Virtually all of the information available on *A. deliciosa* is derived from the cultivar "Hayward" (Ferguson, 1990b). Among the cultivars which were studied, the fruit of *A. arguta* tend to be sweeter and firmer than those of *A. deliciosa* (Ferguson, 1991).

Based on morphology, DNA (RAPD) markers, and isozyme polymorphism studies, *A. arguta* and *A. deliciosa* are regarded as relatively dissimilar species (Ferguson, 1990a; Huang et al., 2002; Testolin and Ferguson, 1997). In addition to the morphological differences noted above, *A. deliciosa* bears fruit the size of a hen's egg weighing 80 - 90 g, whereas fruit of *A. arguta* are the size of a grape weighing 5 - 14 g (Strik and Cahn, 1996; Ferguson, 1991). In spite of these dissimilarities, genetic compatibility between the species is high. Intentional crosses between *A. arguta* and *A. deliciosa* have been successful (summarized in Ferguson et al., 1996; Ferguson, 1990b), natural cross-pollination under adjacent cultivation has been documented (Webby et al., 1994) and crosses probably have also occurred in the wild where the species' distributions overlap (Ferguson, 1990a). *A. arguta* can also be grafted onto *A. deliciosa* (Boyes et al., 1997a,b).

Geographic Distribution

The genus *Actinidia* is native to eastern Asia, with the center of development in China (Li, 1952; Ferguson, 1990a). *A. arguta*, *A. polygama* and *A. chinensis*, in particular, are noted for their wide distribution in east Asia where they are common plants (Dunn, 1911; Li, 1952; Ferguson, 1990b). The distribution of *A. arguta* extends from Japan through

northeastern Asia (Korea, eastern Siberia, Manchuria) and through much of China (Mansfeld's Database, 2002; Ferguson, 1991).

In northern China and Japan, *A. arguta* is the most abundant *Actinidia* species, and has been an important source of fruit in the human diet (Li, 1952; Anetai et al., 1996). The English botanist Stephen Dunn (1911) who studied, collected and published on Actinidias in China and served as Superintendent of The Botanical Forestry Dept. in Hong Kong, wrote the following:

“The Actinidias hold somewhat the same position in the vegetation of the Far East that the brambles do in this country¹ – that is to say, they provide a large part of the shrubby growth in wood borders and in hedges, in districts in which they abound, climbing over small trees when occasion offers or forming large straggling bushes on the hill-sides.”

Similarly, American *Actinidia* taxonomist Li (1952), of the Smithsonian Institution, describing the distribution of *Actinidia* in Asian countries, writes “the species are generally common plants in the thickets of the region and occupy fairly broad ranges” and that “those of wider ranges” include “*A. arguta*”. The Japanese taxonomist Nakai (1933) writes “*Actinidia arguta* is found nearly everywhere in Japan”. In spite of urbanization, this wide distribution has persisted into modern times, as attested by Okamoto and Goto (2005): “Wild vines of *Actinidia arguta* are commonly found in mountainous areas of the Japanese Islands.” Russian botanist E. Kolbasina (2000) writes of *A. arguta* “In forests in the Far East, it forms continuous overgrowth, winding around the trunks of supporting trees like braids”.

¹ Referring to England, the place of publication

Annex 2. History of Use of KiwiBerry as Food

Fruit of *A. arguta*, primarily harvested from the wild but also cultivated, have a documented history of human consumption in China, Japan and Siberia (Dunn, 1911; Michurin, 1949; Li, 1952; Titlyanov, 1963; Kolbasina, 2000; Anetai et al., 1996; Mansfeld's Database, 2002; Zhang et al., 1992; Boyes et al., 1997a). Populations commonly using this fruit in Siberia are primarily of European heritage. More recently, *A. arguta* have been recognized as a source of edible fruit in the United States, Canada, western Europe, Australia and New Zealand. Recorded evidence suggests that *A. arguta* has historically been a more important part of the human diet than *A. deliciosa*, the fuzzy kiwi known in the United States, and given that *A. arguta* is more widely adapted to northern climates (being frost hardy), this should not be surprising.

Dunn (1911) notes of the Actinidias in Japan and China: "The fruits, which in several species have a greenish pulp of pleasant acid taste, somewhat resembling gooseberries, are collected and eaten in many parts of those countries." Since *A. arguta* is the most abundant of the *Actinidia* species in Japan and northern China, this reference most likely includes *A. arguta*. Dunn also notes specifically of *A. rufa*² (a species that contains *A. arguta* in Dunn's description and which is treated in Mansfeld's Database as synonymous with *A. arguta*) "Its fruits are eaten and its sweet sap is used as a drink." Further corroboration of this interpretation of Dunn can be found in Okamoto and Goto (2005), Anetai et al (1996) and Li (1952).

Anetai et al. (1996) describe the use of *A. arguta* and other native food plants by the Ainu people of Japan, particularly previous to the Showa era (pre-1930). *A. arguta* is currently cultivated for food use in northern Japan (Okamoto and Goto, 2005). Japanese use the fruit for eating fresh, for wine making, and in heat processed forms such as jam.

Regarding the food use of *A. arguta* fruit in China, American *Actinidia* taxonomist Li (1952) comments:

"Actinidia is of economic importance because of the fruits. *Actinidia chinensis* and *A. arguta*, well known as Yang-tao in China, have long been used for their edible fruits, which have a greenish pulp of pleasant acid taste. The fruits are collected from wild plants. *Actinidia arguta* is common in northern China while *A. chinensis* is especially common along the Yangtze valley. Recent efforts in introducing these species into cultivation and in improving their products are highly desirable and commendable."

More recently in China it was claimed that 2,000 tons of fruit of *Actinidia kolomikta*, *A. arguta* and *A. polygama* are harvested annually for use as food (Zhang et al., 1992).

² Dunn (1911) describes *A. arguta* as a variety of *A. rufa*, whereas Li (1952) put forth that the name *A. arguta* preceded *A. rufa* and thus treated *A. rufa* as a variety of *A. arguta*. In both cases, the species are described as morphologically very similar to overlapping. Several recent studies, reviewed by Huang et al., (2002), support the placement of *A. rufa* and *A. arguta* in separate species.

These same authors mention that the fruit extracts prepared by boiling dried fruits are used traditionally to improve digestion and general health: “Decocted³ Actinidia dried fruits can stimulate the appetite, promote digestion, and enrich and strengthen the body” (Zhang et al., 1992).

Selections of *A. arguta* for food use were made over a period of several decades by the Russian scientist Michurin beginning in 1930 (Titlyanov, 1963; Mansfeld’s Database, 2002). He used seed obtained from southeastern Siberia, an area called Primor’e or Primorskiy Kray. Michurin writes in 1949 that “The large-fruit variety of *Actinidia arguta* has been growing in my nursery for over twenty-five years” but goes on to describe 3 newer selections of improved quality (Michurin, 1949).

The local populations in Primorskiy Kray were harvesting fruit from the wild and also from plantations established prior to 1955, calling the berries of *A. arguta* “big kishmish” (Titlyanov, 1963). This area of Siberia was settled by Europeans (Russians and Ukrainians) beginning in the 19th Century. The population of Europeans in this region, which includes the port city of Vladivostok, the inland city Ussuriysk (where Titlyanov worked) and numerous smaller cities, was approximately 1.7 million in 1970 (Sasaki, 2004). Fruits are eaten fresh, dried or in cooked form, including jam (Titlyanov, 1963). Fruits are also used to make wine (Titlyanov, 1963).

“The characterization of the *Actinidia* species will be far from complete unless they are also described as fruit-bearing plants of nutritional significance. The fruits of *Actinidia* species are large and have an attractive appearance. Their outer skin is soft, does not have fuzz, and is sometimes translucent in the sun. The flesh of the fruit is tender, melts in the mouth, and is similar in consistency to the flesh of figs” (Titlyanov, 1963).

“The local population has long been using *Actinidia* fruits in the fresh form for preparing fruit gels and compotes and as a filling for pies. When dried, the fruits have the pleasant aroma of other dried fruits and a sweeter taste than they do when fresh, and in this regard are reminiscent of seedless grapes, currants or raisins, which is why they were so named by the first settlers in the Primor’e region” (Titlyanov, 1963).

Regarding the use of *A. arguta* as an edible fruit in modern times, researchers in New Zealand (Boyes et al., 1997a) note the following:

“*Actinidia arguta* is widely grown, occupying areas in the Northern Hemisphere where kiwifruit does not survive, as far north as Eastern Siberia. For this reason it is sometimes known as the “hardy kiwifruit”. The geographical distribution of *A. arguta* results in a wide variation in physiological characteristics such as time of flowering, yield, size, colour of fruit and harvest time. The edible green skin and a distinctively sweeter taste than kiwifruit are desirable characteristics for the commercialisation of *A. arguta*.”

³ Decoct: To prepare by boiling; to digest in hot or boiling water; to extract the strength or flavor of by boiling; to make an infusion of.

Numerous agricultural scientists in the U.S. acknowledge that *A. arguta* is cultivated in the United States and produces edible fruits. University publications describe where to purchase plants, and how to grow *A. arguta* for best fruit yields. Examples include the following:

1. The Oregon State University Extension Service publication "Growing Kiwifruit" (Strik and Cahn, 1996) states of *A. arguta*:

"*A. arguta*, known as the hardy kiwi or arguta (marketed as baby kiwi in Oregon and grape kiwi in British Columbia)."

"Hardy kiwi plants are very vigorous and produce a good quality, highly aromatic fruit that is quite different from the fruit of *A. deliciosa*. Fruit are smooth skinned (skin can be eaten), generally green in color, and much smaller than the fuzzy types. The flavor is excellent, but varies by cultivar."

Regarding the *A. arguta* variety Ananasnaya which is cultivated in Oregon "Fruit are of very good quality with a good aroma and sweet intense flavor".

2. The Ohio State University Extension Service Publication "Kiwifruit and Hardy Kiwi" (Strang and Funt, 1993) states:

"*A. arguta* is more cold hardy than the kiwifruit and is reported to survive temperatures of -25 degrees F. This is the species that has been purchased and planted by many backyard fruit growers in the midwest. Fruit size is considerably smaller than that of 'Hayward' and is about the size of a large sweet cherry. The skin of *A. arguta* is smooth and consumed with the fruit. Fruit are greenish-yellow in color and acidic until ripe. When ripe they are very sweet and juicy and the flavor is considered to be better than that of the kiwifruit."

3. The Pennsylvania State University College of Agricultural Sciences publication "Small Scale Fruit Production" (Penn State, 1997) states:

"A cousin of this kiwi, though, the hardy kiwi (*Actinidia arguta*, *Actinidia kolomikta*), is much more cold hardy than the plant of the commercially available fruit. It is the subject of considerable interest in our region due to its lovely flavor, relatively smooth (and edible) skin, "out of hand" eating size (about the size of a large grape), and its good shelf life."

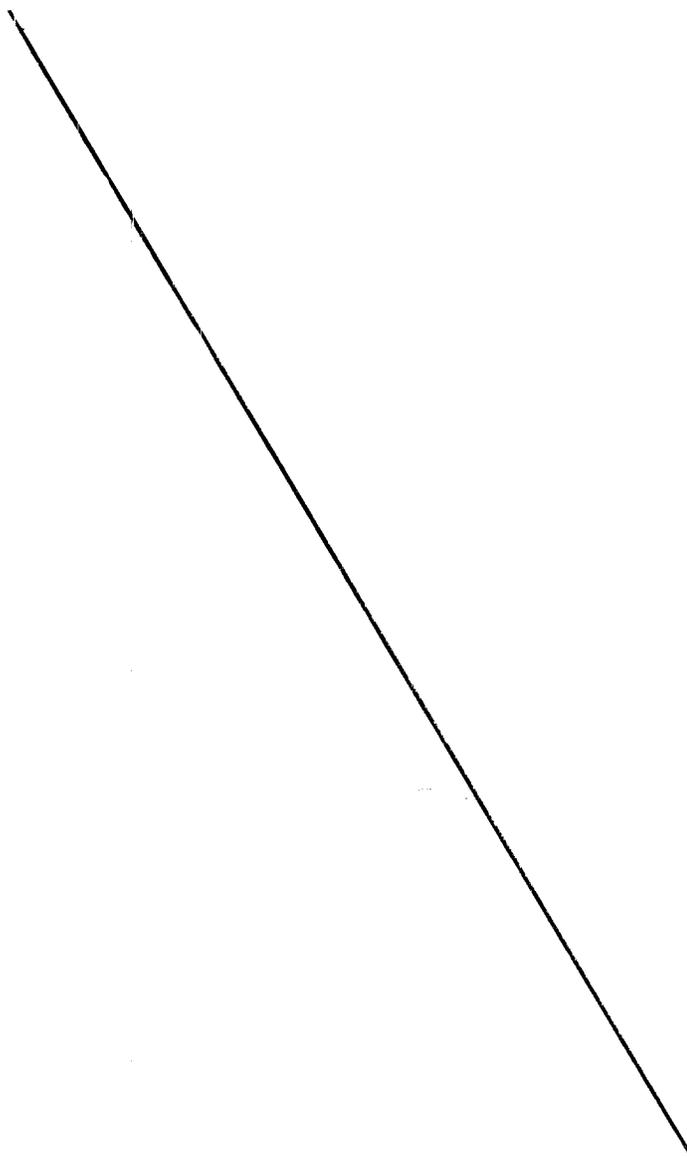
The United States Department of Agriculture, Agricultural Research Service maintains 81 accessions of *A. arguta* at the National Germplasm Repository, Corvallis, Oregon. USDA, ARS (1999) lists the economic importance of *A. arguta* as "Human food: fruit".

Conclusions

Throughout the native range of *A. arguta*, it is known as a common plant and has been described as such in scientific publications both before 1958 and in modern times. Publications in English, Chinese, Japanese and Russian describe the species, its distribution and the common use of *A. arguta* fruit by local populations. This documented use includes fresh, dried, cooked, preserved, fermented and decocted (water extracted) forms. Evidence that the food status of the fruit is accepted within the United States

comes from the fact that the crop is being promoted for cultivation by agricultural scientists within several state University systems and that the USDA lists the economic importance of *A. arguta* as human food.

Annex 3. Safety Studies



PAGES 29 THROUGH 31

REDACTED IN ITS
ENTIRETY
CONTAINS
TRADE SECRET
CONFIDENTIAL
COMMERCIAL
INFORMATION

Annex 4. Literature Cited

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Efficas

OCT - 6
AB/FOA

October 5, 2005

Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

ATTN: Dr. Linda Pellicore

Re: Premarket Notification of New Dietary Ingredient, Kiwiberry Extract

Dear Dr. Pellicore,

Per our telephone discussion October 5, 2005, enclosed are three copies of supplemental information for the Premarket Notification of a New Dietary Ingredient, KiwiBerry Extract. The supplemental information includes a statement of the basis for a determination of safety, expanded Table of Contents, more explicit description of results from a toxicology study, a copy of the manuscript by Chen et al., and data from the Ames test.

Enclosed pages 2, 5, 6 and 31 are to replace those pages from the original submission. All other pages are supplemental to the initial submission.

Please do not hesitate to contact me if you require additional information.

Sincerely,



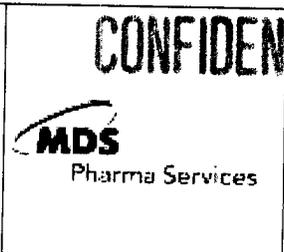
Julianne Lindemann, Ph.D.
Consultant to Efficas
Tel: (925) 998-1658
FAX: (510) 669-9951

005-6700
AMS

Annex 5. Ames Test With KiwiBerry Extract

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

Tabulated Summary
Report
Page / Number
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MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening (5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Test cells:
Mutants of *Salmonella typhimurium* LT2: strains TA98, TA100, TA1535, TA1537 and TA102.

Test for induction of:
Reverse mutation to histidine independence (Hist⁻ → Hist⁺)

Metabolizing system:
Aroclor 1254-induced rat liver S9Mix (fraction); 4.0 mg protein/ml of S9Mix ; 500µl of S9Mix/plate

Formulation of the test item and final concentration: Purity: considered as being 100%

a) Without metabolic activation (-S9Mix):
Formulations: 0.050, 0.10, 0.20, 0.40, 0.79, 1.57, 3.13, 6.25, 12.5, 25 and 50 mg/ml.
Final concentrations: 5.0, 10, 20, 40, 79, 157, 313, 625, 1250, 2500 and 5000 µg/plate.

b) With metabolic activation (+S9Mix):
Formulations: 0.050, 0.10, 0.20, 0.40, 0.79, 1.57, 3.13, 6.25, 12.5, 25 and 50 mg/ml.
Final concentrations: 5.0, 10, 20, 40, 79, 157, 313, 625, 1250, 2500 and 5000 µg/plate.

Solvent and final concentration: dimethylsulfoxide (DMSO), volume of incorporation: 100 µl/plate

Formulation of the positive controls:

- a) Without metabolic activation (-S9Mix):
- Strain TA98: 2-Nitrofluorene (2-NF) at 0.1 mg/ml in DMSO.
 - Strains TA100 and TA1535: Sodium azide (NaA) at 0.2 mg/ml in DMSO.
 - Strain TA1537: 9-Aminoacridine (9-AA) at 1 mg/ml in DMSO.
 - Strain TA102: *t*-Butyl hydroperoxide (t-BHP) at 2 mg/ml in water for injection.

b) With metabolic activation (+S9Mix):
All the strains: 2-Aminoanthracene (2-A) at 0.1 mg/ml in DMSO.

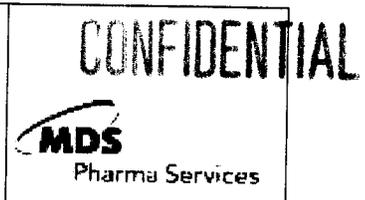
Number of independent experiments: **Number of replicate cultures:**

a) Without metabolic activation (-S9Mix): 1 a) Without metabolic activation (-S9Mix): 1

b) With metabolic activation (-S9Mix): 1 b) With metabolic activation (+S9Mix): 1

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

Tabulated Summary
Report
Page / Number
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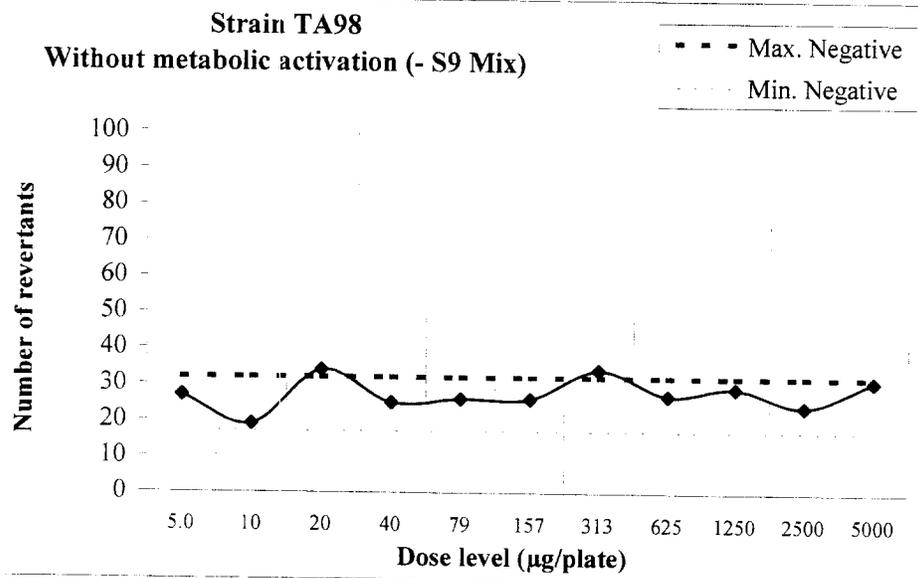
MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Results and Conclusion:

a) Without metabolic activation (-S9Mix):

Number of revertants	Dose levels (µg/plate) without metabolic activation											Positive control 2-NF. 5 µg/plate
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA98	27	19	34	25	26	26	34	27	29	24	31	482
Min. Negative	17	17	17	17	17	17	17	17	17	17	17	Conclusion: No mutagenic effect
Max. Negative	32	32	32	32	32	32	32	32	32	32	32	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	



Abbreviations (when applicable):
- (None); S (slightly) < F (fairly) < T (toxic).
ne: not evaluated, the precipitate prevented the evaluation of the bacterial background lawn.
P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

**Tabulated Summary
Report**
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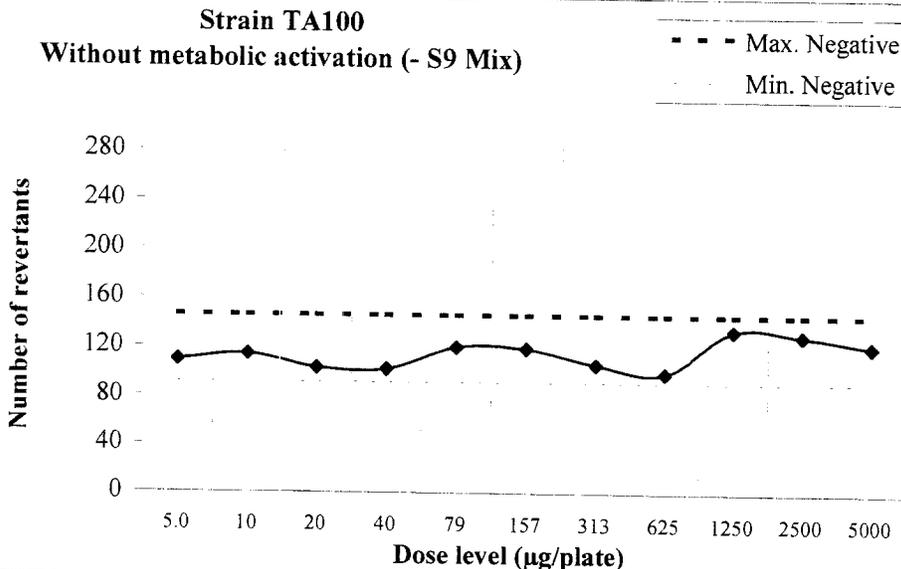


MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) without metabolic activation											Positive control NaA, 10 µg/plate
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA100	109	114	103	102	120	119	106	99	134	130	121	2475
Min. Negative	91	91	91	91	91	91	91	91	91	91	91	
Max. Negative	146	146	146	146	146	146	146	146	146	146	146	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect



Abbreviations (when applicable):
- (None); S (slightly) < F (fairly) < T (toxic).
ne: not evaluated, the precipitate prevented the evaluation of the bacterial background lawn.
P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

**Tabulated Summary
Report**

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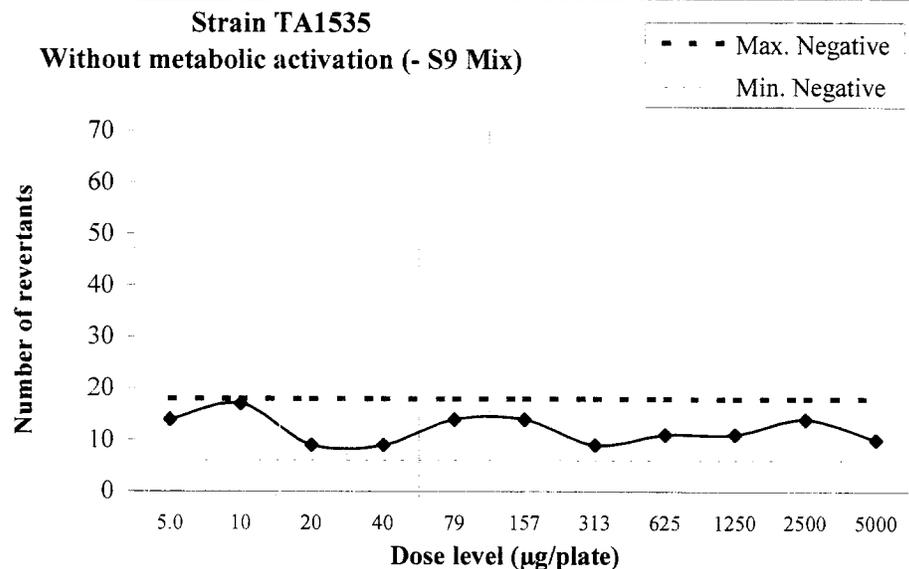


MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) without metabolic activation											Positive control NaA, 10 µg/plate
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA1535	14	17	9	9	14	14	9	11	11	14	10	2526
Min. Negative	6	6	6	6	6	6	6	6	6	6	6	
Max. Negative	18	18	18	18	18	18	18	18	18	18	18	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect



Abbreviations (when applicable):

- (None); S (slightly) < F (fairly) < T (toxic).
ne: not evaluated, the precipitate prevented the evaluation of the bacterial background lawn.
P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

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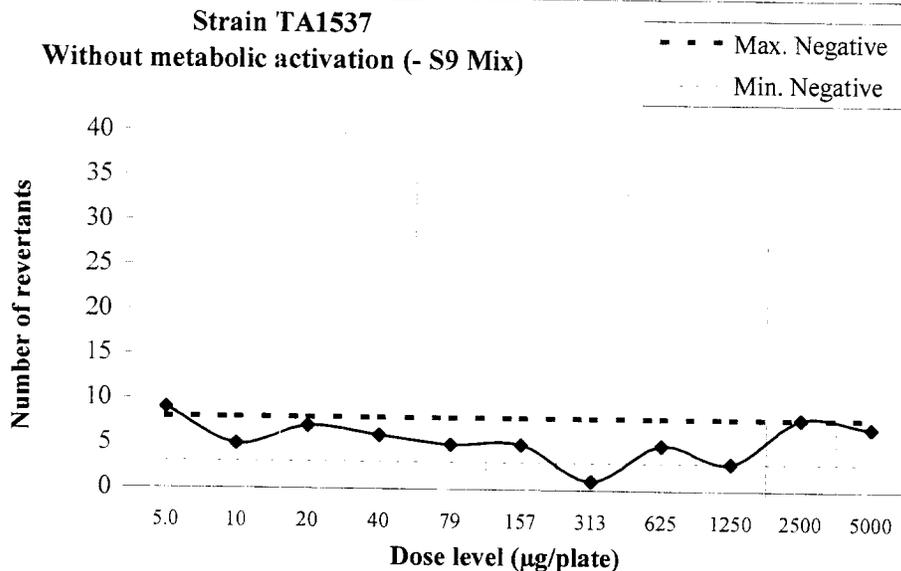
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MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) without metabolic activation											Positive control 9-AA, 50 µg/plate 353
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA1537	9	5	7	6	5	5	1	5	3	8	7	Conclusion: No mutagenic effect
Min. Negative	3	3	3	3	3	3	3	3	3	3	3	
Max. Negative	8	8	8	8	8	8	8	8	8	8	8	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	



Abbreviations (when applicable):

- (None); S (slightly) < F (fairly) < T (toxic).

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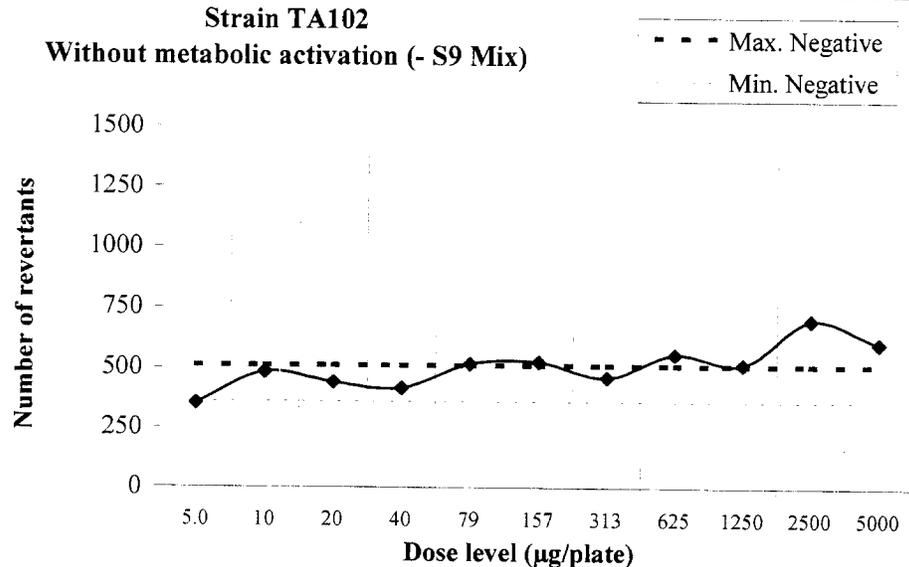
Name of Company: Efficas, Inc. Company Project number: Not applicable. Name of Active Substance(s): EFF-1001.C KiwiBerry, Extract (Batch: FD001)	Tabulated Summary Report Page / Number 6 / 12	CONFIDENTIAL 

MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening (5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) without metabolic activation											Positive control t-BHP, 100 µg/plate
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA102	352	485	440	417	518	526	462	559	517	699	604	1109
Min. Negative	359	359	359	359	359	359	359	359	359	359	359	
Max. Negative	511	511	511	511	511	511	511	511	511	511	511	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect



Abbreviations (when applicable):
 - (None); S (slightly) < F (fairly) < T (toxic).
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 P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:

Efficas, Inc.

Company Project number:

Not applicable.

Name of Active Substance(s):EFF-1001.C KiwiBerry, Extract
(Batch: FD001)**Tabulated Summary
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CONFIDENTIAL**MUTAGENIC POTENTIAL *In vitro***Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)**MDS Number:**

AA23553

Experimental period (Start - End):

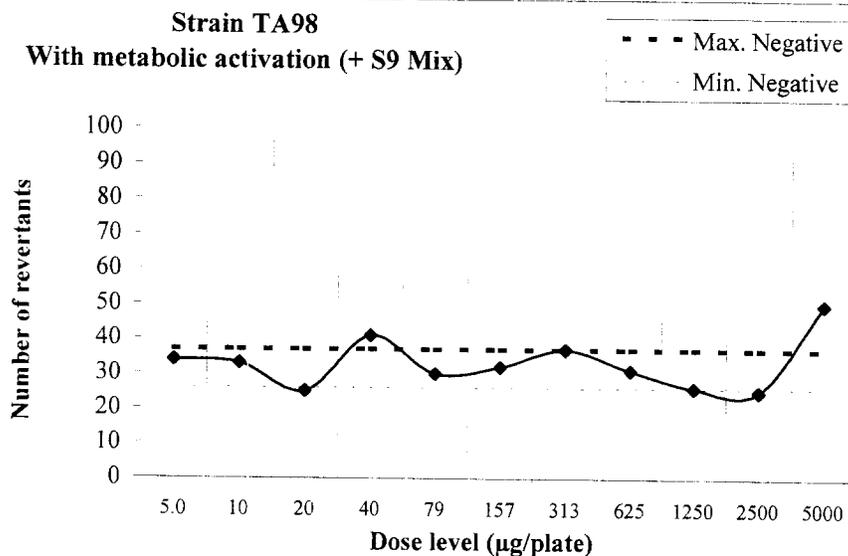
09 November 2004 – 15 November 2004

Report date:

15 November 2004

b) With metabolic activation (+S9Mix):

Number of revertants	Dose levels (µg/plate) with metabolic activation											Positive control 2-A, 5 µg/plate 1803
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA98	34	33	25	41	30	32	37	31	26	25	50	Conclusion: No mutagenic effect
Min. Negative	26	26	26	26	26	26	26	26	26	26	26	
Max. Negative	37	37	37	37	37	37	37	37	37	37	37	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

**Abbreviations (when applicable):**

- (None); S (slightly) < F (fairly) < T (toxic).

ne: not evaluated, the precipitate prevented the evaluation of the bacterial background lawn.

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Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

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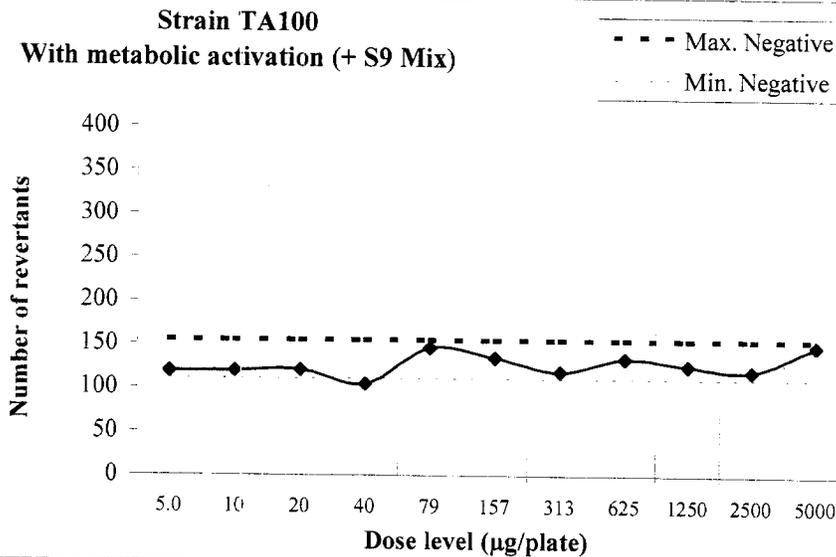


MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) with metabolic activation											Positive control 2-A, 5 µg/plate 1792
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA100	119	120	121	105	146	135	119	134	126	120	149	
Min. Negative	111	111	111	111	111	111	111	111	111	111	111	
Max. Negative	155	155	155	155	155	155	155	155	155	155	155	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect

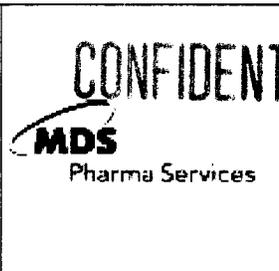


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Name of Company:
Efficas, Inc.
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Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

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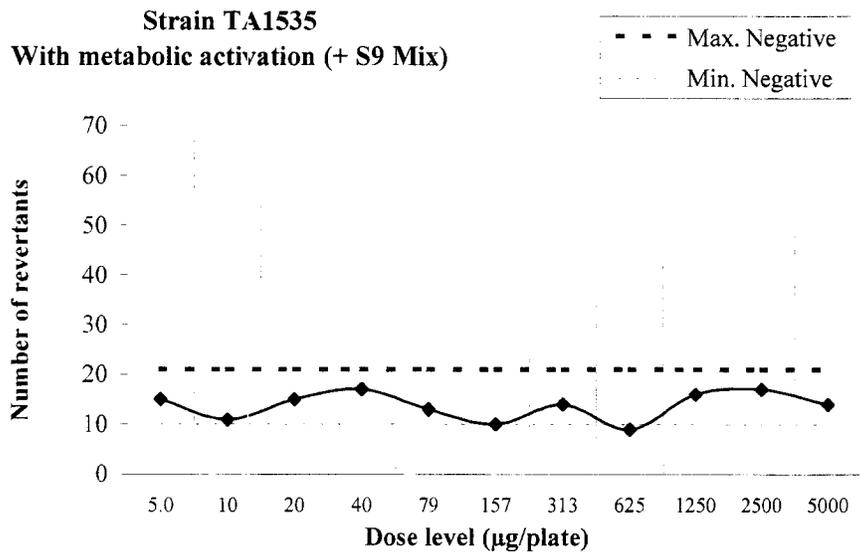


MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) with metabolic activation											Positive control 2-A, 5 µg/plate 242
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA1535	15	11	15	17	13	10	14	9	16	17	14	
Min. Negative	10	10	10	10	10	10	10	10	10	10	10	
Max. Negative	21	21	21	21	21	21	21	21	21	21	21	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect



Abbreviations (when applicable):
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 ne: not evaluated, the precipitate prevented the evaluation of the bacterial background lawn.
 P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

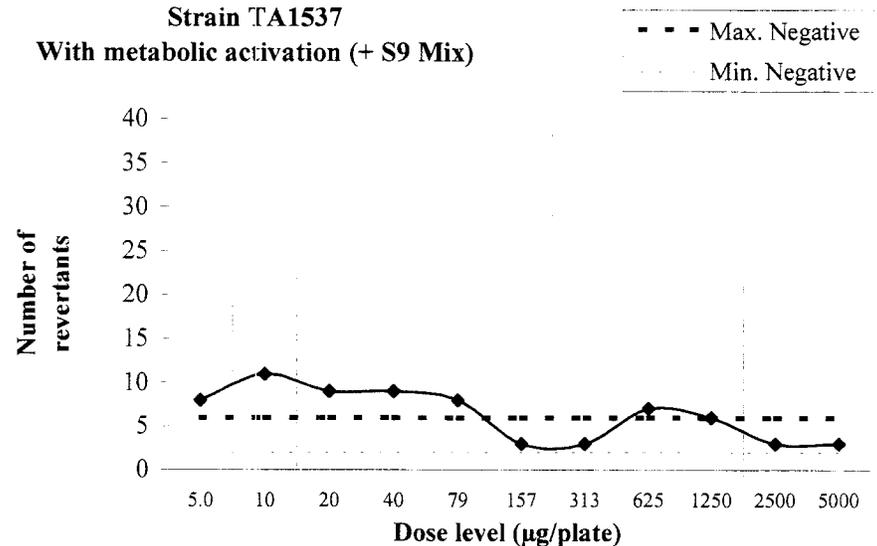
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MDS
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MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening (5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) with metabolic activation											Positive control 2-A, 5 µg/plate
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA1537	8	11	9	9	8	3	3	7	6	3	3	338
Min. Negative	2	2	2	2	2	2	2	2	2	2	2	
Max. Negative	6	6	6	6	6	6	6	6	6	6	6	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	Conclusion: No mutagenic effect
Precipitate	-	-	-	-	-	-	-	-	-	-	-	



Abbreviations (when applicable):
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 P: Precipitating dose level, NP: Not plated due to a technical problem.

Name of Company:
Efficas, Inc.
Company Project number:
Not applicable.
Name of Active Substance(s):
EFF-1001.C KiwiBerry, Extract
(Batch: FD001)

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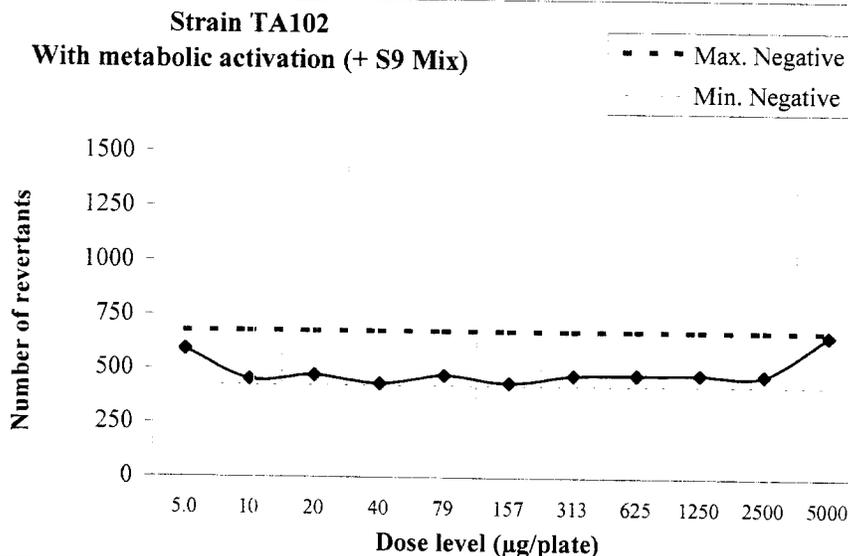
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MDS
Pharma Services

MUTAGENIC POTENTIAL *In vitro* Bacterial reverse mutation Ames test screening
(5 strains, Pre-incubation method)

MDS Number: AA23553 **Experimental period (Start - End):** 09 November 2004 – 15 November 2004 **Report date:** 15 November 2004

Number of revertants	Dose levels (µg/plate) with metabolic activation											Positive control 2-A, 25 µg/plate 2719
	5.0	10	20	40	79	157	313	625	1250	2500	5000	
TA102	591	453	472	434	472	438	473	476	479	476	659	
Min. Negative	425	425	425	425	425	425	425	425	425	425	425	
Max. Negative	676	676	676	676	676	676	676	676	676	676	676	
Cytotoxicity signs	-	-	-	-	-	-	-	-	-	-	-	
Precipitate	-	-	-	-	-	-	-	-	-	-	-	

Conclusion:
No mutagenic effect



Abbreviations (when applicable):

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P: Precipitating dose level, NP: Not plated due to a technical problem.



AB-4
FDA

November 3, 2005

Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

ATTN: Dr. Linda Pellicore

Re: Premarket Notification of New Dietary Ingredient, Kiwiberry Extract
Change in basis of safety determination.

Dear Dr. Pellicore,

Please find enclosed three copies of supplemental information for the Premarket Notification of a New Dietary Ingredient, KiwiBerry Extract. The supplemental information includes a revised statement of the basis for a determination of safety, and detailed results from a toxicology study with juvenile rats (Annex 6).

Given that detailed data are available from the juvenile rat study, Efficas respectfully requests that this evidence be changed from a supportive role to a primary basis of safety determination.

Please do not hesitate to contact me if you require additional information.

Sincerely,

Julianne Lindemann, Ph.D.
Consultant to Efficas
Tel: (925) 998-1658
FAX: (510) 669-9951

2005-6364
AIMS

Statement of the Basis for a Determination of Safety

Efficas has determined that KiwiBerry extract is safe for consumption under the suggested conditions of use based the following information:

1. The compositional equivalence of KiwiBerry fruit (*Actinidia arguta*), KiwiBerry extract and kiwifruit (*A. deliciosa*).
2. Documented acceptance of the KiwiBerry fruit as food in the United States.
3. Published evidence of a history of use of KiwiBerry fruit as food in fresh, dried, cooked, fermented and decocted (water extracted) forms.
4. Data from an Ames test demonstrating no mutagenic effect of the KiwiBerry extract.
5. Data from a juvenile oral toxicity study in rats fed KiwiBerry extract demonstrating a No Observed Effect Level > 2,000 mg/kg.

All other data are viewed as supplemental, rather than primary, evidence of safety.

Annex 6.

A Juvenile Oral Toxicity Study of KiwiBerry Extract in Rats

**REDACTED IN ITS
ENTIRETY
CONTAINS
TRADE SECRET
CONFIDENTIAL
COMMERICAL
INFORMATION**