

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
SABADILLA ALKALOIDS

Chemical Code # 000521, Tolerance # 52081  
SB 950 # 843  
Original date: 3/02/01

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file.
Subchronic, rat:	Data gap, unacceptable study, no adverse effect indicated <sup>1</sup>
Chronic toxicity, dog:	Data gap, no study on file.
Oncogenicity, rat:	Data gap, no study on file.
Oncogenicity, mouse:	Data gap, no study on file.
Reproduction, rat:	Data gap, no study on file.
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study on file.
Gene mutation:	No data gap, no adverse effect <sup>2</sup> .
Chromosome effects:	No data gap, possible adverse effect <sup>2</sup> .
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

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<sup>1</sup> An upgradeable, subchronic oral feeding study in the rat is on file.

<sup>2</sup> An acceptable mouse lymphoma assay, measuring both large and small colonies, and an *in vivo* micronucleus test are on file. Considering the data requirements under Addendum 9 of U. S. EPA, these two studies are part of the initial genotoxicity package. Because of the nature of the test material, a test with *Salmonella* (the third suggested assay of the initial battery) would be difficult to conduct and interpret.

“Sabadilla alkaloids” has been evaluated as a “biochemical”.

All record numbers through 159827 in 013 were examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T010302

Original by: J. Kishiyama and J. Gee, March 2, 2001

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### CHRONIC TOXICITY, RAT

No study submitted.

Subchronic:

012 159826 Kuhn, J. O. "90-Day Rat Oral Toxicity (Diet)". (Stillmeadow Incorporated, Laboratory Study Number 3220-96, December 5, 1997.) Sabadilla Seed, Technical (4.83% Total Alkaloids), was admixed with the feed for 90 days at nominal doses of 0, 250, 500 and 1000 mg/kg/day and evaluated for toxicity with 12 albino HSD:SD rats/sex/group. Doses overall were 230 mg/kg for males and females, respectively, in the low dose, 480 and 470 mg/kg for males and females in the mid dose, and 995 and 730 mg/kg, males and females, at the high dose. Sabadilla treatment effects had greater effect in females than males. Clinical signs in high dose females included emaciation. Food consumption and body weight were reduced for high-dose males and mid- and high dose females. AST, ALT and BUN levels were elevated and liver weight reduced for high dose females. There were no findings reported for hematology, gross pathology or histopathology. Although ophthalmology was stated to have been performed on day 83, no results were given. No adverse effects. NOEL = 250 mg/kg/day [230 mg/kg/day overall for males and females], based on body weight effects in females. UNACCEPTABLE. Upgradeable with submission of the details of the methodology for determination of the test material and ophthalmology data. No adverse effect identified. (Kishiyama and Gee, 2/27/01).

013 159827 Kuhn, J. O. "Range-Finding Study for a 90-Day Rat Oral Toxicity (Diet)". (Stillmeadow Incorporated, Laboratory Study Number 3218-96, April 23, 1997.) Sabadilla Seed, Technical (4.83% Total Alkaloids), was admixed with the feed for 14 days at concentrations of 0, 625, 1250, 2500, 5,000, 10,000 or 20,000 ppm and fed to 5 rats/sex/group. Food consumption for males and females progressively decreased with the increase in sabadilla dosage from 5000 to 20,000 ppm. Mortality was 40% for 20,000 ppm male and female groups. Body weight was reduced at 10,000 and 20,000 ppm for males and females with a greater effect on females. BUN and ALT levels were elevated for 20,000 ppm females. Clinical signs of Sabadilla toxicity were noted for the two highest dose female groups and consisted of piloerection, emaciation, polyuria, dark crust around the nose and decreased activity. SUPPLEMENTAL STUDY. (Kishiyama and Gee, 2/27/01).

### CHRONIC TOXICITY, DOG

No study submitted.

## ONCOGENICITY, RAT

No study submitted.

## ONCOGENICITY, MOUSE

No study submitted.

## REPRODUCTION, RAT

No study submitted.

## TERATOLOGY, RAT

\*\* 008, 010 150945, 151176 Denny, K. H., study director; M. B. Carlson, author. "Developmental Toxicity Study for Sabadilla Seeds in Rats". (MPI Research (formerly IRDC), Study ID 736-002, September 25, 1996.) Sabadilla seed brown powder (Veratran D, Technical, assumed 100%) was administered via oral gavage at doses of 0 (0.5% CMC), 50, 250, or 500 mg/kg/day to 30 mated CrI:CD<sup>®</sup> VAF/Plus<sup>®</sup> female rats/group during gestation days 6 through 17. Analyses of dosing solutions were reported in # 151176. The high dose group had reduced body weight change. Clinical signs of ataxia, decreased activity, abnormal gait, gasping, and labored breathing were seen at 500 mg/kg. At both 250 and 500 mg/kg, body surface staining, red area around eyes, material around eyes, and increased salivation were noted. Maternal NOEL = 50 mg/kg/day (clinical signs). Reduced mean fetal weight of approximately 10% was seen at the high dose. Developmental NOEL = 250 mg/kg/day (lower fetal weight, misaligned and unossified sternebrae at 500 mg/kg). ACCEPTABLE with no adverse developmental effects. (Kishiyama and Gee, 3/1/01).

007, 009 150944, 150943 Denny, K. H., study director; M. B. Carlson, author. "Range-Finding Developmental Toxicity Study for Sabadilla Seeds in Rats". (MPI Research (formerly IRDC), Study ID 736-001, January 25, 1996.) Sabadilla brown powder (Technical, assumed 100%) was administered via oral gavage at doses of 0 (0.5% CMC), 33, 100, 333, 1,000 and 3,333 mg/kg to 5 CrI:CD<sup>®</sup> VAF/Plus<sup>®</sup> female rats/group during gestation days 6 through 17. Record 150943 contained the analysis of dosing solutions. Sabadilla at 1000 mg/kg/day resulted in 3/5 deaths with 5/5 at 3333 mg/kg/day. There were clinical signs of body staining, decreased activity, material around the eye and nose at 333 mg/kg and higher. Increased salivation was noted at all treatment doses. Body weight gain was lower for days 6 to 9 of gestation at 333 mg/kg and higher. Based on this study, 500 mg/kg was selected as the high dose in the main test. SUPPLEMENTAL STUDY. No worksheet. (Kishiyama and Gee, 3/1/01).

## TERATOLOGY, RABBIT

No study submitted.

## GENE MUTATION/CHROMOSOME EFFECTS

\*\* **006 149005** San, R. H. and J. J. Clarke. "L5178Y/TK<sup>+/-</sup> Mouse Lymphoma Mutagenesis Assay". (Microbiological Associates Incorporated, Laboratory Study Number G95AX64.702, January 10, 1996.) Irradiated ground Sabadilla Seed, Technical Mixture, 4.83% alkaloids, was evaluated for mutagenic potential at concentrations of 0 (DMSO), 100, 200, 400, 500, 600, 700 800, and 1000 µg/ml, with and without rat liver metabolic activation using mouse lymphoma cells, duplicate cultures in a single trial. Osmolality was in an acceptable range. Ground Sabadilla seed treatment without activation did not increase the mutation frequency. All concentrations plated for mutation frequency (500 to 1000 µg/ml) with S9 Mix exhibited mutant frequencies approximately two-fold greater than the solvent control. There was, however, no concentration dependency. Total growth ranged from 25% to 59% without activation and 14% to 69% with activation over the concentrations assayed. There was an increase in small colonies compared with solvent controls, suggesting chromosomal aberrations on chromosome 11 as well as more localized damage. Positive controls were functional. Possible adverse effect. ACCEPTABLE. (Kishiyama and Gee, 2/28/01).

006 149005 "Characterization of dosing solutions." (Burton, S. D., Stillmeadow, Inc., Study no. 2375-95, 6/25/96) The study was conducted to characterize the dosing solutions used in the mouse lymphoma study, record 149005 above, prepared from ground Sabadilla seeds, lot # NP, at 10, 20, 40, 50, 60, 70, 80 and 100 mg/ml. The analytical standard was veratridine, Sigma Chemical, > 99%, and the standard was Veratran D technical, AN # 95-18. Methanol extracts were prepared from the samples of experimental solutions and the standard and analyzed by HPLC. Comparison of the actual weight of veratridine in the dosing solutions was quite close to the theoretical amount (page 11). No worksheet. (Gee, 3/1/01).

## DNA DAMAGE

\*\* 006 149004 Putman, D. L. and R. Gudi. "Micronucleus Cytogenetic Assay in Mice." (Microbiological Associates, Inc., Laboratory Study No. G95AX64.122, January 5, 1996.) Ground Sabadilla Seed, Technical Mixture, 4.83% alkaloids, dark brown powder, at doses of 0 (distilled water), 17.5, 35, and 70 mg/kg, was injected (single I.P.) into 5 ICR mice/sex/dose/sacrifice time (24, 48 and 72 hours post-dosing). It was evaluated for the ability to induce micronuclei in polychromatic erythrocytes in bone marrow cells. Clinical signs including lethargy were noted at 35 and 70 mg/kg and 2/20 deaths occurred in males at 70 mg/kg. There was no evidence of induction of micronuclei in polychromatic erythrocytes. ACCEPTABLE. (Kishiyama and Gee, 2/28/01).

006 149005 "Characterization of dosing solutions." (Burton, S. D., Stillmeadow, Inc., Study no. 2375-95, 6/25/96) The study was conducted to characterize the dosing solutions used in the micronucleus test, 149004, above. Amendment # 1 of the analytical study indicated that page 8 of 149005 incorrectly identified the dosing solutions as part of the mouse lymphoma study, rather than the

micronucleus study. The dosing material was ground Sabadilla seeds, lot/batch # NP, at 0, 0.875, 1.74 and 3.5 mg/ml (page 9). The standard was Veratran D technical, AN # 95-18 and the analytical standard was veratridine (Sigma Chemical), > 99% by thin layer chromatography. The standard curve was prepared from veratridine and analyzed by HPLC. The samples with Veratran D standard and GS seed experimental solutions were extracted several times with methanol and the extracts pooled. Duplicate aliquots were analyzed by HPLC. The results (page 11) indicated that the dosing solutions used in the micronucleus study were close in content of veratridine to the expected theoretical value. No worksheet. (Gee, 3/1/01).

## NEUROTOXICITY

Not required at this time.

## OTHER STUDIES

005 149003 "Hydrolysis of veratridine in aqueous solutions buffered at pH 5, 7 and 9." (Burton, S. D., Stillmeadow, Inc., Project 1877-95, 2/1/96) Veratridine [cevine-3,4,12,14,16,17,20-heptol, 4,9-epoxy-, 3-(3,4-dimethoxybenzoate), (3 $\beta$ ,4 $\alpha$ ,16 $\beta$ )], lot84H7831, Sigma, >99%, described as a white powder, was used. The reference standard was ground seed, AN # 95-18 (Veratran D technical), a light brown powder. Buffers were acetic acid-sodium acetate, 0.01M at pH 5, phosphate buffer at pH 7, and sodium borate- HCl at pH 9. The solubility in water over a 48 hour period was determined using HPLC. Extraction of veratridine from Veratran D technical was evaluated using methanol. For hydrolysis as a function of pH at 25 ° C, samples were taken over a 30-day period. RESULTS: The solubility of veratridine increased in water over time with an average of 127.6 ppm of a theoretical 175 ppm at 48 hours. The weight percent of veratridine in Veratran D technical was determined to be 1% with a recovery of 80% from spiked samples. The calculated half-lives were: pH 5, 407.65 days; pH 7, 315.0 days; and pH 9, 13.83 days. The two major degradates were cevine and veratric acid (3,4-dimethoxybenzoic acid). SUPPLEMENTAL STUDY. No worksheet. (Gee, 2/28/01)