March 10, 2000

MEMORANDUM

EPA File Symbol: 100-OAA STRATEGO™ FUNGICIDE
DP Barcode: D263041
Case No: 068107
PC Code: 129112 Trifoxystrobin
122101 Propiconazole

From: Byron T. Backus, Ph.D., Toxicologist **/s/ JCR**
Technical Review Branch
Registration Division (7505C)

To: Janet Whitehurst/Cynthia Giles-Parker, PM 22
Fungicide Branch
Registration Division (7505C)

Registrant: NOVARTIS CROP PROTECTION, INC.

ACTION REQUESTED: According to the beansheet: "Attached please find the six pack for the combined formulation of trifloxystrobin and propiconazole..."

BACKGROUND: This package, as received by this reviewer, contains the following 6 acute toxicity studies, acute oral LD_{50} in rats (MRID 45025405), rabbit dermal LD_{50} (MRID 45025406); rat acute inhalation LC_{50} (MRID 45025407); rabbit eye irritation (MRID 45025408); rabbit dermal irritation (MRID 45025409); guinea pig sensitization (MRID 45025410). These studies were all conducted at Stillmeadow.

The proposed product is a fungicide, "for control of certain diseases in peanuts." The label declaration of ingredients is the following:

Active Ingredients:
Propiconazole (CAS No. 60207-90-1).....11.4%
Trifloxystrobin (CAS No. 141517-21-7).....11.4%
Other Ingredients:.....77.2%

COMMENTS AND RECOMMENDATIONS:

All six acute toxicity studies have been reviewed and classified as acceptable.

The following is the acute toxicity profile for this product, based on the submitted studies which have been reviewed:

Acute Oral LD50	III	Acceptable
Acute Dermal LD50	IV	Acceptable
Acute Inhalation LC50	IV	Acceptable
Primary Eye Irritation	II	Acceptable
Primary Dermal Irritation	IV	Acceptable
Dermal Sensitization	Negative	Acceptable

The following is the appropriate precautionary labeling for this product, based on the toxicity profile above, as obtained from the label review system:

Date: 03/10/00 LABEL REVIEW SYSTEM

ID #: 000100-00966 Stratego

AGRICULTURAL USE REQUIREMENTS:

DIRECTIONS FOR USE:

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, wear: coveralls over long-sleeved shirt and long pants, socks and chemical resistant footwear, Wear goggles or face shield, and waterproof gloves.

SIGNAL WORD: WARNING AVISO

PRECAUTIONARY STATEMENTS:

Causes substantial but temprary eye injury. Harmful if swallowed. Do not get in eyes or on clothing. Wear long-sleeved shirt and long pants, socks and shoes. and goggles or face shield.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

The following "Note to Physician" statement is required for the subject product:

NOTE TO PHYSICIAN; Probable mucosal damage may contraindicate the use of gastric lavage.

The following statements should appear under the heading USER SAFETY RECOMMENDATIONS:

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove contaminated clothing and wash clothing before reuse.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100, formerly §81-1)

Product Manager: 22
MRID No.: 45025405
Lab Study No.: 4977-99

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: July 22, 1999
Sponsor Study No.: 757-99

Testing Facility: Stillmeadow Inc., Sugar Land, TX 77478
Author: Kuhn, J.O.

Quality Assurance (40 CFR §160.12): Included (p. 5)

Test Material: CGA-64250/CGA-279202 250 EC FL-990185 A9525E, with active ingredients CGA-279202 (11.5%) and CGA-64250 (11.6%); described as a dark brown liquid with a density of 1.0832 g/mL.
Species: Rat: albino: HSD: Sprague-Dawley
Age: probably (based on body weight data) 8 -13 weeks of age
Fasted weight: Males: 208-321 g; Females: 160-214 g
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: = 4757 mg/kg; 95% C.L. of 2156-10497 mg/kg
   Females: = 4830 mg/kg; 95% C.L. of 4373-5334 mg/kg
   Combined: = 4805 mg/kg; 95% C.L. of 2956-7812 mg/kg
2. **Tox. Category:** III **Classification**: Acceptable

Procedure (including deviations from 870.1100): "The test substance was administered as received and was not diluted. An individual dose was calculated for each animal based on its fasted body weight and administered by gavage at a volume ranging from 1.85 mL/kg at the 2000 mg/kg level to 4.66 mL/kg at the 5050 mg/kg level. Each dose was administered using an appropriately sized syringe and stainless steel ball-tipped intubation needle..."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10
3500	1/5	0/5	1/10
4200	0/5	1/5	1/10
4750	1/5	1/5	2/10
5050	5/5	4/5	9/10

Observations: "Clinical signs included activity decrease, ataxia, diarrhea, loss of limb coordination, dark material on nose, piloerection, polyuria, ptosis, respiratory gurgle, and stains on fur and cage paper. Surviving animals were asymptomatic by Day 8. Gasping, moist rales, lateral recumbency, ocular/oral/nasal discharge, salivation and splayed legs were observed only in animals that died on test."

Body weight gain in survivors was not affected.

Mortalities occurred from 1 hr through day 4.

Gross Necropsy: "Gross necropsy in animals that died on test revealed matted, stained fur; discolored lungs, liver, spleen and thymus; gas in the stomach and discolored contents in the gastrointestinal tract. Gross necropsy in animals surviving to termination...revealed no observable abnormalities, except enlarged heart (not considered treatment related) in one female, and stained fur in another female."

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200, previously §81-2)

Product Manager: 22
MRID No.: 45025406
Lab Study No.: 4978-99

Reviewer: Byron T. Backus, Ph.D.
Report Date: May 21, 1999
Sponsor Study No.: 758-99

Testing Facility: Stillmeadow, Inc., Sugar Land, TX 77478
Author: Kuhn, J.O.

Quality Assurance (40 CFR §160.12): Included (p. 5)

Test Material: CGA-279202/CGA-64250 250 EC (FL-990185), with active ingredients CGA-279202 (11.5%) and CGA-64250 (11.6%); described as a dark brown liquid with a density of 1.0832 g/mL.

Species: Rabbit: albino, New Zealand White
Age: (when treated): 13-14 weeks
Weight: Males: 2.175-2.750 kg; Females: 2.250-2.750 kg
Source: Ray Nichols Rabbitry, Lumberton, TX

Dermal LD_{50} Testing:

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: > 5050 mg/kg (no mortalities); 95% C.L. not calculated
   Females: > 5050 mg/kg (no mortalities); 95% C.L. not calculated
   Combined: > 5050 mg/kg (no mortalities); 95% C.L. not calculated
2. **The estimated LD_{50} is** > 5050 mg/kg
3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (Including deviations from 870.1200): "Each animal was prepared on the day prior to treatment by clipping the dorsal surface of the trunk free of hair to expose not less than 10% of the total body surface area. Care was taken to avoid abrading the skin... All animals were treated with 5050 mg/kg (4.66 mL/kg) of undiluted test substance. An individual dose was calculated for each animal based on its Day 0 body weight just before exposure. The test substance was applied to each exposure area in a thin, uniform layer. The area of application was covered with an appropriately sized surgical gauze patch (8 x 4 in) and secured with non-irritating adhesive tape. The trunk of each animal was then wrapped with a semi-permeable dressing...which was secured in place with non-irritating adhesive tape to prevent possible ingestion of the test substance... After 24 hours, the wrappings were removed. The test sites were gently washed with room temperature tap water and a clean cloth to remove as much residual test substance as possible."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
5050	0/5	0/5	0/10

Observations: There were no deaths. "The only prominent in-life observation was soft feces in one female at 1 and 2 hours after dosing. The only sign of skin irritation was very slight to well-defined erythema on Day 1, and desquamation in one animal on Day 7." All animals had grade 1 or 2 erythema on Day 1, with no edema (score of 0). On day 4 all dermal irritation scores were zero. All

animals gained weight over the 2-week post-exposure period.

Necropsy: "No macroscopic abnormalities were observed..."

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (870.1300, formerly §81-3)

Product Manager: 22
MRID No.: 45025407
Lab Study No.: 4979-99

Reviewer: Byron T. Backus, Ph.D.
Report Date: May 26, 1999
Sponsor Study No.: 759-99

Testing Facility: Stillmeadow Inc., Sugar Land, TX
Author: Leeper, L.

Quality Assurance (40 CFR §160.12): Included (p. 5)

Test Material: CGA-279202/CGA-64250 250 EC (FL-990185), with active ingredients CGA-279202 (11.5%) and CGA-64250 (11.6%); described as a dark brown liquid.

Species: Rat: HSD: Sprague-Dawley
Age: Approximately 9 weeks
Weight: Males: 256-273 g; Females: 187-223 g
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN

Conclusion:

1. **LC_{50} (mg/L):**
   Males: >2.16 mg/L (no mortalities from exposure to this concentration)
   Females: >2.16 mg/L (no mortalities from exposure to this concentration)
   Combined: >2.16 mg/L (no mortalities from exposure at this concentration)
2. **The estimated LC_{50} is** > 2.16 mg/L (no 95% C.L. were calculated)
3. **Tox. Category:** IV **Classification**: Acceptable

Procedure (including deviations from 870.1300): Exposure was nose-only. "The animals were exposed to an aerosol generated from the undiluted liquid test substance for a period of 4 hours. When 99% concentration (t-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a...nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were returned to their stock laboratory cages."

"The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour and nominally at the end of the exposure. The analytical determination was made using a Beckman DU-65 UV Spectrophotometer..."

Exposure Concentration ± S.D. (Analytically Determined)	**Number of Deaths/Number Tested**		
mg/L	Males	Females	Combined
2.16 ± 0.09	0/5	0/5	0/10

Clinical Observations: "Prominent in-life observations included respiratory gurgle or chirp in males only, and activity decrease and piloerection in both sexes. Animals were asymptomatic by Day 4."
Gross Necropsy Findings: "The gross necropsy conducted on each animal at termination of the study revealed no observable abnormalities."

Chamber Atmosphere		
Analytical Concentration (mg/L)	**MMAD[a] (μm)**	**GSD[a]**
2.16	1.3, 1.5	2.2, 1.9

[a]Measurements at 1.75 and 3.75 hours respectively.

Other Information: The nominal concentration was 3.45 mg/L. 84% of the particles were $\leq$ 2.8 μm.

Chamber Environment	
Chamber Volume	500 L
Airflow	153 LPM
Temperature	69-71°F
Relative Humidity	55-57%

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400, previously §81-4))

Product Manager: 22
MRID No.: 45025408
Lab Study No.: 4571-98

Reviewer: Byron T. Backus, Ph.D.
Report Date: January 25, 1999
Sponsor Study No.: 674-98

Testing Facility: Stillmeadow, Inc., Sugar Land, TX 77478
Authors: Kuhn, J.O.
Quality Assurance (40 CFR §160.12): Included (p. 5)
Test Material: CGA-64250/CGA-279202 250 EC FL-981956, with active ingredients CGA-279202 (11.3%) and CGA-64250 (11.4%); described as an amber liquid with a pH of 8.06

Dosage: 0.1 mL
Species: Rabbits; Albino, New Zealand White
Age: 12-13 weeks
Weight: 2.0 -2.6 kg
Source: Ray Nichols Rabbitry, Lumberton, TX
Conclusion:

1. **Toxicity Category:** II
2. **Classification**: Acceptable

Procedure (including deviations from 870.2400): "On Day 0, a dose of 0.1 mL of the undiluted test substance was placed into the conjunctival sac of the right eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test substance was dropped. The lids were gently held together for one second to prevent loss of material. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. The untreated left eyes served as comparative controls."

Results:

Observations	Number "positive"/number tested									
	Hours				Days					
	1	24	48	72	4	7	10	14	17	21
	Unwashed eyes									
Corneal Opacity	0/6	6/6	4/6	1/6	1/6	1/6	2/6	0/6	0/6	0/6
Iritis	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae:										
Redness[a]	6/6	6/6	5/6	4/6	1/6	1/6	0/6	0/6	0/6	0/6
Chemosis[a]	6/	6/	4/	3/	1/	1/	0/	0/	0/	0/

	6	6	6	6	6	6	6	6	6	6
Discharge[a]	6 / 6	6 / 6	5 / 6	3 / 6	1 / 6	1 / 6	2 / 6	0 / 6	0 / 6	0 / 6

[a]Score of 2 or greater considered a positive response.

Observations	Number "positive"/number tested									
	Hours				Days					
	1	24	48	72	4	7	10	14	17	21
	Washed eyes									
Corneal Opacity	0/3	3/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae:										
Redness[a]	3/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3
Chemosis[a]	1/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3
Discharge[a]	3/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3

[a]Score of 2 or greater considered a positive response.

"The corneas of all treated eyes were examined immediately after the 24-hour observation with a fluorescein sodium ophthalmic solution. Any of the corneas which exhibited fluorscein staining at the 24-hour observation were re-examined with the fluorscein sodium ophthalmic solution at each consecutive observation until fluroescein staining of the cornea no longer occurred."

Summary: Nonwashed eyes: The maximum average irritation score was 34.3, obtained at 24 hours after treatment. Fluorescein staining was observed in 6/6 eyes at 24 hours after treatment and was not observed in any eye on Day 14.

Washed eyes: The maximum average irritation score was 30.3, obtained at 24 hours after treatment. Fluorescein staining was observed in 3/3 eyes at 24 hours after treatment and was not observed in any eye at 72 hours after treatment.

DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500, formerly §81-5)

Product Manager: 22
MRID No.: 45025409
Lab Study No.: 4572-98

Reviewer: Byron T. Backus, Ph.D.
Report Date: November 4, 1998
Sponsor Study No.: 675-98

Testing Facility: Stillmeadow, Inc., Sugar Land, TX 77478
Author: Kuhn, J.O.

Quality Assurance (40 CFR §160.12): Included (p. 5)

Test Material: CGA-64250/CGA-279202 250 EC FL-981956, with active ingredients CGA-279202 (11.3%) and CGA-64250 (11.4%); described as an amber liquid with a pH of 8.06

Dosage: 0.5 mL of the undiluted test substance
Species: Rabbit; Albino, New Zealand White
Age: 12-13 weeks old
Weight: 2.3-2.6 kg
Source: Ray Nichols Rabbitry, Lumberton, TX

Conclusion:

1. **Toxicity Category:** IV
2. **Classification**: Acceptable

Procedure (including deviations from 870.2500): "Each animal was prepared on the day prior to treatment by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm... A single intact exposure site was selected as the test site..."

"On Day 0, 0.5 mL of the undiluted test substance was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and four single layers thick. Each patch was secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing...and secured on both edges with strips of tape to retard evaporation of volatile substances and to prevent possible ingestion of the test substance."

Exposure was for 4 hrs, after which the wrappings were removed and the sites washed with tap water and a clean cloth was used to remove as much residual test substance as possible.

Results: 3/6 sites were scored "1" for erythema at 1 hour; the other 3 sites scored "0." All sites scored zero for erythema at 24 hours and subsequently. All sites scored zero for edema at 1 hour and subsequently.

The Primary Irritancy Index (PII) was 0.13/8.00..

Special Comments: None

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600, formerly §81-6)

Product Manager: 22
MRID No.: 45025410
Lab Study No.: 4980-99

Reviewer: Byron T. Backus, Ph.D.
Report Date: May 26, 1999
Sponsor Study No.: 761-99

Testing Facility: Stillmeadow, Inc., Sugar Land, TX 77478
Author: Kuhn, J.O.

Quality Assurance (40 CFR §160.12): Included (p. 5)
Test Material: CGA-279202/CGA-64250 250 EC (FL-990185), with active ingredients CGA-279202 (11.5%) and CGA-64250 (11.6%); described as a dark brown liquid

Positive Control Material: 2-Mercapto-benzothiazole
Species: Guinea pig; Albino, Hartley
Age: Not stated, presumably young adult (consistent with body weights)
Weight: Males: 431-497 g; Females: 381-461 g
Source: Charles River Laboratories, Wilmington, MA
Method: Buehler

Conclusions:

1. There is no indication that the test material is a dermal sensitizer
2. **Classification**: Acceptable

Procedure (including deviations from 870.2600): Based on the results of a preliminary irritation study, the test material was used undiluted at both induction and challenge.

"For each induction treatment...animals were treated by introducing the test substance beneath a 3.8 x 5 cm patch (a 1.6 x 2.8 cm gauze pad secured to a 3.8 x 5 cm piece of adhesive)... Each adhesive coverlet patch was placed laterally from the midline of the back on the left front quadrant of the exposure area with the edge of the gauze patch adjacent to, but not overlapping the midline of the back... The entire trunk of each animal was then wrapped with clear polyethylene film to secure the patch in place. Each animal was then placed in a restrainer for approximately six hours. At the end of the exposure period, the animals were removed from the restrainers, the wrappings and patches were removed, and the animals were returned to their cages... animals were treated once weekly for three weeks with 0.4 mL of undiluted test substance. Induction treatments were on Days 1, 8 and 15..." Ten males and 10 females were exposed to the test material during the induction period.

Challenge: After a two week rest period, the 10 males and 10 females which had previously received induction exposures, as well as a naive group of 5 males and 5 females, were each challenged with an application of 0.4 mL of undiluted test substance. The challenge treatment was on Day 29. The dose was applied in a manner identical to the induction treatments, except the test site was placed laterally on the right rear quadrant of the exposure area with the edge of the gauze pad adjacent to the midline of the back..."

Results: The test material produced no irritation following either induction or challenge treatments in any of the animals. All scores were zero.

Positive Control: The positive control study was conducted between January 7, 1999 (first induction treatment) and February 5, 1999 (challenge was on February 3, 1999, and the last readings were made 48 hours later). As the first induction treatment of the study with CGA-279202/CGA-64250 250EC (FL-990185) was made on March 31, 1999, and the challenge was made on April 28, 1999, the positive control study was conducted within six months of the definitive study. In the positive

control study, 8/10 previously induced animals had positive scores (0.5 or greater) at 48 hours following challenge, compared with 1/10 previously unexposed control animals.

Special comment: None

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D263041
2. **PC CODES:** 129112 [Trifoxystrobin]; 122101 [Propiconazole]
3. **CURRENT DATE:** March 10, 2000
4. **TEST MATERIAL:** CGA-64250/CGA-279202 250 EC FL-990185, with active ingredients CGA-279202 (11.5%) and CGA-64250 (11.6%); described as a brown liquid with a density of 1.0832 g/mL (used in the oral LD_{50} , dermal LD_{50}, inhalation LC_{50}, and dermal sensitization studies); CGA-64250/CGA-279202 250 EC FL-981956, with active ingredients CGA-279202 (11.3%) and CGA-64250 (11.4%); described as an amber liquid with a pH of 8.06, was used in the primary eye irritation and dermal irritation studies.

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Stillmeadow/4977-99/JULY-22-1999	45025405	LD_{50} (M) = 4757 mg/kg; 95% C.L. 2156-10497 mg/kg; LD_{50} (F) = 4830 mg/kg; 95% C.L. 4373-5334 mg/kg; LD_{50} (combined) = 4805 mg/kg; 95% C.L. of 2956-7812 mg/kg.	III	A
Acute dermal toxicity/rabbit/Stillmeadow/ 4978-99/ MAY-21-1999	45025406	LD_{50} > 5050 mg/kg (no mortalities following 24-hr exposure to this dose).	IV	A
Acute inhalation toxicity/rat/ Stillmeadow/ 4979-99/ MAY-26-1999	45025407	LC_{50}(female, male, combined) > 2.16 mg/L. No mortalities resulted from 4-hr exposure to this concentration.	IV	A
Primary eye irritation/rabbit/Stillmeadow/ 4571-98/JAN-25-1999	45025408	6/6 washed, 3/3 washed eyes had corneal opacity at 24 hrs. 1/6 unwashed eyes still had corneal opacity on day 7 (2/6 did on day 10) but all eyes had cleared (all scores zero) by day 14.	II	A
Primary dermal irritation/rabbit/ Stillmeadow/4572-98/NOV-04-1998	45025409	Mean Primary Dermal Irritation Index score = 0.13. 3/6 rabbits had grade 1 erythema at 1 hour following exposure; 3 other rabbits scored zero. All scores for edema were zero; all scores for erythema at 24 hrs and subsequently were zero.	IV	A
Dermal sensitization/guinea pig/ Stillmeadow/4980-99/MAY-26-1999	45025410	Buehler: Material applied undiluted for induction & challenge; all scores were zero. No evidence of dermal sensitization seen.	No	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self-Validated**