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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MAR - 1 1995

MEMORANDUM

SUBJECT: Gibberellic Acid Registration: A List D Chemical (No. 043801); Case No. 4110. Bridging Toxicological Data From ProCone® to ProVide®. Submission No. S464095; MRID No. 430451-01 and 430451-02, PD Barcode D202518 and D210544

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FROM: Freshteh Toghrol, Ph.D., Chemist F. Toghrol
Biopesticide & Pollution Prevention Division

THRU: Roy Sjoblad, Ph.D., BPPD Senior Scientist
Biopesticide & Pollution Prevention Division R Sjoblad

TO: Phillip Hutton, Team Leader
Biopesticide & Pollution Prevention Division

INERT INGREDIENT INFORMATION IS NOT INCLUDED

ACTION

Abbott requests that EPA bridge the toxicological data from ProCone® (containing 4% Gibberellins as an active ingredient) to Provide® (EPA Reg. No. 275-02; containing 2% Gibberellins GA_4A_7). Both end-use products use the same inert in their formulations [redacted] which is exempt from the tolerance requirements when used as an inert). Registrant is currently applying for registration in the state of California, where a review of ProVide® by the California Med Tox Branch required, the registrant to initiate new studies for dermal irritation and eye irritation.

To support its request to BPPD, Abbott has submitted a revised label and a Confidential Statement of Formula for Provide® (previously known as Pro-Gibb®). Abbott has also submitted the following toxicological studies for Procone®, to be bridged to ProVide®: a primary eye irritation study in rabbits (MRID No. 430451-01) and a primary dermal irritation study in albino rabbits (MRID No. 430451-02).

Additionally, the registrant has submitted a copy of a letter from

EPA Office of Pesticide Programs Registration Division regarding Pro-Gibb 47 Plant Growth Regulator (now known as ProVide®). This letter recommended that Abbott delete the following from its proposed label: **" Some materials that are chemical-resistant to this product are listed below. If you want more options, follow the instructions for category __ on an EPA chemical resistance category selection chart."** The letter also recommended that the second-to-last sentence in the first paragraph in the Agricultural Use Requirements box on the proposed label read as follows: **"It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), notification to workers and restricted-entry interval."**

BPPD Recommendations

BPPD accepts the bridging of these toxicological data (MRID 430451-01 and 430451-02) from ProCone® to ProVide®. BPPD has no objection to the amended label submitted for the registered ProVide®.

BPPD CONCLUSIONS

BPPD recently completed acute tox studies for ProCone® registration (which included the above MRID Nos.; see F.Toghrol memo dated 2/28/95) and concluded that these data were acceptable for the registration of ProCone®. BPPD concludes that bridging data from Procone which contains 4% Gibberellins, to ProVide which contains 2% Gibberellins is acceptable. Increasing the level of the inert by 2% (from 96% to 98%) and decreasing the ai (Gibberellins A_4A_7) from 4% to 2% will not effect the toxicity of the product, to the extent there will be lower toxicity categories.

For convenience, we recite our Procone® study summaries and the review of dermal irritation and eye irritation from our previous memo (F. Toghrol memo - PD Barcode D202413 and D210629).

STUDY SUMMARY (from ProCone® registration F.Toghrol memo dated 2/28/95)

152-13 Primary Eye Irritation Study in Rabbits (MRID 430451-01)

A single dose (106 mg/0.1 ml) of ProCone (ABG-3149) produced corneal or iridal effects in both washed and unwashed eye groups. Conjunctival redness, chemosis and discharge were observed by the one-hour interval in the rabbits in both groups. Minimal conjunctival redness persisted in two rabbits in the unwashed group through day 10, and minimal redness persisted in one rabbit in the washed group through day 14. No ocular effects were observed in any of the rabbits on day 21 of the study. Washing of the eyes with water following test material administration resulted in a very slight difference in the incidence and persistence of ocular effects in the washed group when compared to the unwashed group. For the unwashed group, the maximum mean total score calculated

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according to the Draize method for grading ocular effects, was 34.2, observed at the 72 hour interval. For the washed group, the maximum mean total score, calculated according to the Draize method for grading ocular effects was 27.3, observed on day 7 of the study.

Classification: Acceptable, Toxicity Category II.

152-14. Primary Dermal Irritation Study In Rabbits (MRID 430451-02)

A single dose (0.5 ml/1.06 g/l) of ProCone®(ABG-3149) produced well-defined erythema which was cleared by day 4. No edema or other dermal effects were observed in any of the rabbits during the study. The primary irritation index of ProCone®(ABG-3149) is 0.9.

Classification: Acceptable, Toxicity Category IV

DATA EVALUATION REPORT

Reviewed by: Freshteh Toghrol, Ph.D. BPPD SCR 2/15/95
Secondary Reviewer: Sheryl K. Reilly Ph.D. BPPD

Study Type: Guideline series 152-13; primary eye irritation in rabbits

LIST/Chemical No. List D/043801 Gibberellic Acid

Case No. 4110

Caswell No. 467

MRID NUMBER: 430451-01

Name;TEST MATERIAL: ProCone (ABG-3149) (Lot No. 78-087-BR)

SPONSOR: Abbott Laboratories North Chicago, IL

STUDY NUMBER: Ricerca Study No 93-0161

TESTING FACILITY: Ricerca, Inc. Department of Toxicology and Animal Metabolism

Painesville, OH

TITLE OF REPORT: Primary Eye Irritation Study In Albino Rabbits With Procone (ABG-3149)

AUTHOR: Steven K. Shults, B.A., Ann W. Brock, M.S., and James Laveglia, Ph.D.

DATE OF REPORT: November 15, 1993

QUALITY ASSURANCE: **The test was performed under Good Laboratory Practice Standards. A Compliance Statement, signed by all three authors 11/15/93, 11/23/93, and 11/23/93 was submitted.**

CONCLUSIONS: **ProCone (ABG-3149) produced corneal or iridal effects in both unwashed and washed eye groups. Conjunctival redness, chemosis and discharge were observed by the 1-hour interval in the rabbits in both groups. Minimal conjunctival redness persisted in two rabbits in the unwashed group through day 10 and, in one rabbit in the washed group through day 14. No ocular effects were observed in any of the rabbits on day 21 of the study. Washing of eyes with water following test material administration resulted in a very slight difference in the incidence and persistence of ocular effects in the**

washed group when compared to the unwashed group.

CORE CLASSIFICATION: Acceptable.

TOXICITY CATEGORY: Tox category II

A. MATERIALS

Test Compound

Test material: ProCone (ABG-3149)
Lot No.: 78-087-3149
Purity: 4.1% Gibberellins A_4A_7

Physical description: Clear colorless liquid
Storage conditions: Room temperature
Dose levels: 0.1 ml
Density: 1.06 g/ml

Controls

There were no control test materials or animals.

Test Animals

Species: Albino Rabbits
Strain: New Zealand White
Source: Mohican Valley Rabbitry, Loudonville, Ohio
Sex: Male and female
Age at receipt: Young adults
Weight (pre-fasted): Ranged from 2.250 to 2.569 Kg.
No. animals/ dose: Nine (unwashed eyes: 3 males, 3 females; washed eyes: 3 females)
Acclimation: 21 days
Housing: Individually housed
Food: Lab Rabbit Chow HF (Purina #5326), ad libitum
Water: Automatic watering system, ad libitum
Temperature: Room temperature, monitored and recorded twice daily.
Photoperiod: 12 hours dark/12 hours light
Identification: Cage cards and ear tags
Selection: Random

B. TEST PERFORMANCE

Dosing: A single dose of 0.1 ml undiluted ProCone was introduced

into the lower conjunctival sac of the right eye of each animal. The upper and lower lids were gently held together for a second to prevent loss of material. The left eye was used as the control.

Observation: Three days (approximately 1, 24, 48, and 72 hours after treatment and on days 4, 7, 10, 14, 21 of the study. An examination was performed utilizing an ultraviolet light source, of all treated eyes following staining with 2% sodium fluorescein solution to check for the presence of corneal ulceration. Just prior to the test application, the eyes were examined again, but without fluorescein. Animals showing preexisting conditions were not used.

C. RESULTS

Clinical observations

All animals survived the study period. All animals were killed at termination of the study by an intravenous injection of a euthanasic agent, Sleepaway®. Necropsies were not conducted.

Ocular Observation

All six animals exhibited irritation consisting primarily of conjunctival irritation, with scores of 1 or 2 for redness, chemosis or discharge. Three animals also had slight iridial changes.

Unwashed eyes:

Corneal opacity was observed in one rabbit at one hour interval, in three rabbits at 24-hours interval, and in six rabbits from the 48 hours interval through day 4. Corneal opacity persisted in one rabbit through day 7. No corneal opacity was observed in any of the rabbits after day 7 of the study. Corneal epithelial effects involving up to approximately 25% of the corneal surface persisted in one rabbit through day 7 of the study. Five of the six animals with unwashed eyes were free of all ocular irritation by 24 or 48 hours, with the remaining animal free of irritation by 72 hours (both the test and control eyes had a discharge score of one at 48 hours).

Washed Eyes:

Corneal opacity was noted in two rabbits on day 7 and persisted in these tqwo rabbits through day 10. No. corneal opacity was observed in any of the rbbits after day 10 of the study. Corneal vascularization also was observed in this group up to 25% was oberved in two rabbits on day 10 and up to 5% of the corneal vascularization persisted in one rabbit through day 14. Corneal epithelial effects involving up to approximately 25% of the corneal surface persisted in two rabbits through day 7 of the study. This effect was noted in two rabbits on day 7 and persisted in theser two rabbits through day 10 of the study.

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D. CONCLUSION

A single dose (106 mg/0.1 ml) of ProCone® (ABG-3149) produced a Conjunctival redness which persisted in two rabbits from the unwashed group through day 10 after dosing and in one rabbit in the washed group through day 14. No ocular effects were observed in any rabbits after day 21. For the unwashed group, the maximum mean total score, calculated according to the Draize method for grading ocular effects was 34.2, observed at the 72 hour interval. For the washed group, the maximum mean total score by the Draize method for grading ocular effects was 27.3, on day 7 of the study.

Classification: Acceptable, Toxicity Category II.

Reviewed by: Freshteh Toghrol, Ph.D. BPPD SKR 2/15/95
Secondary Reviewer: Sheryl K. Reilly Ph.D. BPPD

Study Type: Guideline No. 152-14; primary dermal irritation study in rabbits

Chemical No. List D/043801 Gibberellic acid

Case No. 4110

Caswell No. 467

MRID NUMBER: 430451-02

Name;TEST MATERIAL: ProCone® (ABG-3149) (Lot No. 78-087-BR)

SPONSOR: Abbott Laboratories
North Chicago, IL

STUDY NUMBER: Ricerca Study No. 93-0162

TESTING FACILITY: Ricerca, Inc. Department of Toxicology and Animal Metabolism
Painesville, OH

TITLE OF REPORT: Primary Dermal Irritation Study In Albino Rabbits With ProCone® (ABG-3149)

AUTHOR: Steven K. Shults, B.A., Ann W. Brock, M.S., and James Laveglia, Ph.D.

DATE OF REPORT: 12/2/93

QUALITY ASSURANCE: The test was performed under Good Laboratory Practice Standards. A Compliance Statement, signed by all three authors 12/7/93, 12/7/93, and 12/2/93, was submitted.

CONCLUSIONS: The primary skin irritation index in this study is 0.9 for ProCone® (ABG-3149) in rabbits. This is a mild or slight irritant or erythema.

CORE CLASSIFICATION: This study is acceptable.

TOXICITY CATEGORY: Tox category IV.

A. MATERIALS

Test Compound

Test material:	ProCone®(ABG-3149)
Lot No.:	78-087-BR
Purity:	4.1% Gibberellins A_4A_7
Physical description:	Clear colorless liquid
Storage conditions:	Room temperature
Stability:	Reported stable
Dose levels:	0.5 ml/site
Density	1.06 g/ml

Controls

There were no control test materials or animals.

Test Animals

Species:	Albino Rabbits
Strain:	New Zealand White
Source:	Mohican Valley Rabbitry, Loudonville, Ohio
Sex:	Male and female
Age at receipt:	Young adult
Weight (day-1)	2.533 to 2.794 kg
No. animals	6 (2 groups of 3/sex)
Acclimation:	16 days
Housing:	Individually housed
Food:	Lab Rabbit Chow HF (Purina #5326)
Water:	Automatic watering system, ad libitum
Temperature:	Room temperature, monitored and recorded twice daily.
Humidity:	Not given: monitored and recorded twice daily.
Photoperiod:	12 hours dark/12 hours light
Identification:	Ear tags
Selection:	Random

B. TEST PERFORMANCE

Preparation of Animal:	Approximately 24 hours before dosing, the hair of each rabbit was clipped from the trunk with an electric clipper. 0.5 ml (530 g) of ProCone®(ABG-3149) was applied directly onto the exposed skin, beneath layers of gauze patch, and was secured with non-irritating tape. The plastic restraining collar was placed around the rabbit's neck and the animal was returned to its cage.

Observation period: At 30 - 60 minutes, 24 hours, 48 hours, and 72 hours, and the 4th day of exposure, the test site was evaluated for erythema, eschar, and edema, according to the Draize system.

Body weight interval: 2.533 to 2.794 kg

C. RESULTS

Mortality

All animals (3 males and 3 females) survived throughout the study.

Body weight

Not reported.

Evaluation of Dermal Irritation:

At each interval all sites were evaluated for erythema and edema or other evidence of dermal irritation. Very slight to well-defined erythema was observed at the site of application in five of six animals from the 30 to 60 minute interval through the 24 hour interval. Very slight erythema was noted in three rabbits at the 48 hour interval and persisted in these three rabbits through the 72-hours interval. No erythema was noted in any of the rabbits on day 4. No edema or other dermal effects were observed in any of the rabbits during the study.

D. BPPD CONCLUSION

The test material, 0.5 ml (1.06 g/l) of ProCone®(ABG-3149), produced well defined erythema which was cleared by day 4. No edema or other dermal effects were observed in any of the rabbits during the study. The primary irritation index of ProCone®(ABG-3149) is 0.9.
Classification: Acceptable, Toxicity Category IV

Guideline No. 152-15; dermal sensitization study:

The registrant did not submit Guideline No. 152-15; dermal sensitization study.

BPPD Comments

BPPD waives the data requirement Guideline No. 152-15; dermal sensitization, since the acute dermal study was in toxicity category III and primary dermal irritation with a primary irritation index of 0.9 (mild or slight irritant) is in category IV.
cc: R. Sjoblad, F. Toghrol, BPPD Subject File.
F. Toghrol, F.T.CS#1: (703)308-7014: 1/31/95.