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

JUN 15 2000

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Scientific Review of Registration Application for **Fosphite Fungicide** (EPA Reg. Symbol 68573-E)

FROM: Carol E. Frazer, Ph.D., Toxicologist Carve
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Biopesticides and Pollution Prevention Division (7511C)

THROUGH: Roy D. Sjoblad, Ph.D., Biologist Roy D. Sjoblad
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Biopesticides and Pollution Prevention Division (7511C)

TO: Driss Benmhend, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511C)

Submission Contents

Product Chemistry, acute toxicity and ecotoxicity studies of 53.0% mono- and di-potassium salts of phosphorous acid, MRID Nos. 448735-01 through -13; (Chemical No. 076416; Case No. 066126; Submission S568958; DP Barcode D259767).

Action Requested:

JH Biotech, Inc. requests registration of **Fosphite Fungicide**, a biochemical fungicide. The registrant submitted product chemistry comprised of §§158.162, .167, .180, and .190. Acute oral (§81-1), dermal (§81-2) and inhalation (§81-3) toxicity studies, primary eye (§81-4) and dermal (§81-5) irritation studies and a dermal sensitization (§81-6) study were also provided. In addition, the package contains a bacterial reverse mutation assay (§84-2), avian oral (§850.2100) and avian dietary (850.2200) toxicity tests, acute toxicity effects on fish (§72-1[850.1075]), daphnids (§72-2[870.1010]) and honeybees (§141-1 [850.3020]).

The manufacturer provided all chemistry data for Fosphite Fungicide in MRID 448735-13. Acute toxicologic studies were conducted by MB Research Laboratories (MRIDs 448735-01 through -06). BioReliance performed the bacterial reverse mutation study (MRID 448735-07) and Bio-Life Associates, Ltd. conducted the avian studies (MRIDs 448735-08 and -09).

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PC 076416

Springborn Laboratories, Inc. performed the toxicity studies for the other non-target species (MRIDs 448735-10 through -12).

CONCLUSIONS:

1 The label is in error and must be corrected to include the appropriate precautionary labeling for the acute dermal toxicity rating of III "Harmful if absorbed through the skin." (See next page for label language.)

2. The following product chemistry requirements were incomplete or not submitted:

   a.) Guideline 880.1100 (§151B-11) is incomplete, 40 CFR 158.155(a)(2)(ii) and (v) were not submitted

   b.) No data submitted for Guideline 880.1700 (§151B-13)

   c.) The data submitted for Guideline 880.1750 is incomplete without the information from 880.1700. Justification for CSF figures required.

   d.) The requirements of 40 CFR 158.180, guideline §151B-16, 880.1800, have not been adequately completed.

   e.) Data not submitted for 830.6314, .6316 and .6319 and thus does not meet the requirements of 40 CFR 158.690.

3. Of the ecotoxicity studies submitted for this product, several were not required for an end-use product (EP), but one which was required, Non-target Plant Studies: 850.4025 (§154-10), was not submitted.

4. Several toxicity studies (84-2, 850.2200, 850.1075, 830.3020) are classified Supplemental because of unclear definitions of what was tested and the concentration of the AI. The misunderstandings need to be clarified.

This registration cannot be evaluated until missing data or justification for their lack are submitted.

TOXICITY PROFILE

Acute oral toxicity	IV	Acceptable	MRID 448735-01
Acute dermal toxicity	III	Acceptable	MRID 448735-02
Acute inhalation toxicity	IV	Acceptable	MRID 448735-05
Primary eye irritation	III	Acceptable	MRID 448735-04
Primary dermal irritation	IV	Acceptable	MRID 448735-03
Dermal sensitization	No	Acceptable	MRID 448735-06
Mutagenicity (Ames test)	No	Supplemental	MRID 448735-07

LABELING: The Signal word is Caution from the Toxicity Ratings of III for acute dermal toxicity and primary eye irritation. Precautionary labeling should include:

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 and waterproof gloves.

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Wear long-sleeved shirt and long pants, socks and shoes. and waterproof gloves. Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF ON SKIN OR CLOTHING: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

IF IN EYES: Hold eye open and rinse slowly and gently with water for15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

BPB's reviews of **FOSPHITE FUNGICIDE** data are summarized below.

Study Summaries:

PRODUCT CHEMISTRY OF **FOSPHITE FUNGICIDE**

Guideline §880.1100: Product identity and disclosure of ingredients

Fosphite Fungicide contains 53.0% mono- and di-potassium salts of phosphorous acid and 47% other ingredients. This product is to be used as a systemic fungicide on ornamental crops to suppress downey mildew, phytophthora and pythium in ornamentals and bedding plants, phytophthora in conifers and pythium in turf.

The following table summarizes information submitted by the registrant regarding the active ingredient (AI).

Chemical Names:	monopotassium salt of phosphorous acid dipotassium salt of phosphorous acid
CAS Registry Nos.:	13977-65-6 13492-26-7
Synonyms:	mono and dipotassium salts of phosphonic acid mono and dipotassium phosphites mono and dipotassium phosphonates
Molecular Formulae:	KH_2PO_3 K_2HPO_3
Chemical Family:	metallic salts
Source of Biochemical:	manufactured
Mode of Action:	fungicide

An acceptable confidential statement of formula was submitted by the registrant.

BPB's Comment Regarding §880.1100: Data submitted on the product identity of Fosphite Fungicide does not satisfy the requirements of 40 CFR 158.155, guideline §151B-10, 880.1100. 40 CFR 158.155(a)(2)(ii) and (v) were not submitted.

Guideline §880.1200: Manufacturing process (MRID 448735-13)

BPB's Comment Regarding §151B-11: Data submitted on the manufacturing process of Fosphite Fungicide satisfy the requirements of 40 CFR 158.160 and 40 CFR.165, guideline §151B-11, 880.1200. No additional data required.

Guideline §880.1400: Discussion on the formation of unintentional ingredients (MRID 448735-13)

BPB's Comment Regarding §880.1400: Data submitted on the formation of unintentional ingredients of Fosphite Fungicide satisfy the requirements of 40 CFR 158.167, guideline §151B-12, 880.1400. No additional data required.

Guideline §880.1700: Preliminary Analysis Not submitted.

BPB's Comment Regarding §880.1700: No data was submitted on the preliminary analysis of samples of Fosphite Fungicide, and thus the submission does not satisfy the requirements of 40 CFR 158.170, guideline §151B-13, 880.1700. These data must be submitted for every end-use product.

Guideline §880.1750: Certification of ingredient limits Confidential Statement of Formulation

BPB's Comment Regarding §880.1750: Data submitted on the certification of ingredient limits of Fosphite Fungicide satisfy the requirements of 40 CFR 158.175, guideline §151B-15, 880.1750. No additional data required.

Guideline §880.1800: Enforcement analytical methods (MRID 448735-13)

BPB's Comment Regarding 880.1800: Data submitted on the analytical methods for certified limits of Fosphite Fungicide do not satisfy the requirements of 40 CFR 158.180, guideline §151B-16, 880.1800. Additional data required on details of testing requirements.

Guideline §151B-17: Physical and Chemical Characteristics (MRID 448735-13)

The registrant submitted information on the physical and chemical characteristics of Fosphite Fungicide which are summarized below:

STUDY TYPE	CHARACTERISTIC	GUIDELINE NUMBER
Physical state	Liquid	830.6303
Oxidation/reduction, chemical incompatibility	Not provided	830.6314
Flammability/Flame extension	Not applicable (CSF)	830.6315
Explodability	Not provided	830.6316

Storage stability	The formulation is stable in all environmental conditions to which it is expected to be exposed. Extended stability test with Fosphite Fungicide is being presently carried out by the manufacturer and results will be presented to the Agency upon request.	830.6317
Miscibility	Not provided	830.6319
Corrosion characteristics	This product has been marketed as a fertilizer for several years in the same type of bottle as that used for this product, with no indication of corrosion or incompatibility with equipment or packaging.	830.6320
Dielectric breakdown voltage	Not applicable. Fosphite Fungicide is not intended to be used with electrical equipment or conduits.	830.6321
pH	6.3 +/- 0.2	830.7000
Viscosity	<100cps	830.7100
Specific gravity Pounds/gal or Bulk density	1.41 +/- 0.02 at 25° C 6.22 lb/gal (CSF)	830.7300
Odor	Odorless	830.6304
Solubility	Fosphite Fungicide is an aqueous solution and is infinitely soluble in water	63-8
Vapor pressure	This formulation is an aqueous solution and contains no volatile substances other than water	830.7950

. . . Dissociation constant	The mono- and di-potassium phosphites are essentially completely dissociated in aqueous solution	830.7370
Boiling point	100° C	830.7220
Freezing point	-15° C	Not applicable/no guideline
Color	Clear water white	830.6302

BPB's Comment: Information submitted on chemical and physical characteristics is incomplete. Data not submitted for 830.6314, .6316 and .6319 and thus does not meet the requirements of 40 CFR 158.690.

PRODUCT TOXICOLOGY FOR FOSPHITE FUNGICIDE

Guideline §81-1: Acute oral toxicity study in rats (MRID 448735-01)

The LD_{50} of Fosphite Fungicide in males is 7,170 mg/kg, 6,038 mg/kg in females. The average for both sexes was 6,226 mg/kg. Decedents in all dose groups (2,000, 3,500, 4,000, 5,000 mg/kg; 5/sex) exhibited piloerection, lethargy, ataxia, tremors, prostration, lacrimation and wetness of the anogenital area. Survivors also demonstrated piloerection, lethargy and ataxia. Weight gain normal in survivors. Necropsy findings in the survivors normal, but decedents had abnormalities of the lungs, liver, kidneys, spleen, gastrointestinal tract and localized aloepecia. Classification: Acceptable; Toxicity Category IV.

Guideline §81-2: Acute dermal toxicity study in rabbits (MRID 448735-02)

A single limit dose of Fosphite Fungicide was tested in male and female rabbits. The LD_{50} > 3,374 mg/kg (>2,000 mg/kg AI). No deaths or overt toxicity observed, but dermal irritation noted in all animals. Grade 1 erythema observed in all rabbits, with grade 1 edema in half the group. Weight gain and all animal necropsies normal. Classification: Acceptable; Toxicity Category III

.Guideline §81-3: Acute inhalation toxicity study in rats (MRID 448735-05)

No deaths observed at the maximum achievable LC_{50} of this product for rats (5/sex) of >4.1 mg/L, MMAD 1.42 µM, GSD of 2.07, and 44.9 % of particles below 1.1 µM.. Minor clinical signs in all animals cleared by day 5. Necropsy and weight gain in most animals normal. Classification: Acceptable; Toxicity Category IV

Guideline §81-4: Primary eye irritation study in rabbits (MRID 448735-04)

Single (0.1 ml) dose of Fosphite Fungicide applied to 6 male rabbits' eyes. This substance is a minor irritant to rabbit eyes, causing hyperemia, chemosis, discharge and iritis in all animals, and, in one rabbit, vocalization. All eyes clear by 48 hours. Classification: Acceptable; Toxicity Category III.

Guideline §81-5: Primary dermal irritation study in rabbits (MRID 448735-03)

Single (0.5 ml) dose of Fosphite Fungicide applied to skin of 6 male rabbits. This substance is not irritating, demonstrating no erythema or edema. Classification: Acceptable; Toxicity Category IV.

Guideline §81-6: Delayed contact hypersensitivity in Guinea Pigs (Buehler technique) (MRID 448735-06)

Ten male guinea pigs treated with Fosphite Fungicide (0.4 ml) to induce sensitization. Also, five naive control males tested for sensitization. An equal number of males tested with a positive control (DNCB). No response in the treated animals, but positive control yielded 70% response. Classification: Acceptable; Toxicity Category Non-sensitizer.

Guideline §84-2: Reverse mutation assay (MRID 448735-07)

Fosphite Fungicide does not produce bacterial mutation in a variety of *Salmonella typhimurium* or *Escherichia coli* cells up to 5,000 μg/cell either with or without exogenous activation. Classification: Supplemental because of unclear dose levels; Toxicity Category: non-mutagenic.

Guideline 850.2100: Avian acute oral toxicity using bobwhite quail (154-6) (MRID 448735-08)

Five birds/sex/dose at 0, 1,000, 2,000 mg/kg. LD_{50} > 2,000 mg/kg; NOAEL > 1,000 mg/kg with no deaths observed. Only clinical signs, chalky excreta in all birds at highest dose. No change in weight gain or food consumption or any anomalies seen in necropsy. Classification: Acceptable; Toxicity Category: practically non-toxic.

Guideline 850.2200: Avian acute dietary test in ducklings (154-7) (MRID 448735-09)

Ten ducklings/dose in seven dose levels from 0 through 5,000 mg/kg/day, with no mortalities observed at highest dose LC_{50} > 5,000 ppm AI, 5 days feeding. No problems with weight gain or food consumption, and the only necropsy anomalies noted were pale kidneys in one 3,000 mg/kg/day bird. Classification: Supplemental because of unclear test material; Toxicity Category; practically non-toxic.

Guideline 850.1075: Freshwater fish acute toxicity-LC_{50} (154-8) (MRID 448735-10)

An acute 96-hour toxicity test yielded an LC_{50} of Fosphite Fungicide in rainbow trout following a test incorporating 6 levels of Fosphite Fungicide from 0 through 1,100 mg/L was estimated as 790 mg AI/L. All fish died at 1,100 mg/L and 10% at 630 mg/L. The NOEC was established at 370 mg/L. One of the surviving fish at the 630 mg/L exhibited a complete loss of equilibrium by the 48 hour observation. No mortality or sublethal effects observed in remaining subjects. Classification: Supplemental because of unclear instructions on test material; Toxicity Category: practically non-toxic.

Guideline 870.1010: Aquatic invertebrate, acute toxicity, freshwater daphnia 154-9 (MRID 448735-11)

Twenty *Daphnia magna* were tested in a 48-hour acute toxicity test with Fosphite Fungicide. The EC_{50} is >1,200 mg/L, as is the NOEC. No immobilization or sublethal (e.g., lethargy)

effects observed in any organism at any time. Classification: Acceptable; Toxicity Category: practically non-toxic.

Guideline 850.3020: Non-target insect testing honey bee acute contact toxicity 154-11 (MRID 448735-12)

No mortality or sublethal effects (e.g., lethargy) observed among bees exposed to any of the treatment levels of Fosphite Fungicide or controls, yielding an estimated 48-hour $LD_{50} > 25$ μg AI/bee. The NOEC also determined to be the same. Classification: Supplemental because of unclear test material; Toxicity Category: practically non-toxic.

BPB's Comment: Data submitted on the product toxicity of **Fosphite Fungicide** does not satisfy the requirements of 40 CFR 158.690, but BPB will reconsider when the missing study (§154-6) is submitted and clarifications provided on unclear dose and test material information.

DATA EVALUATION REVIEW FOR ACUTE ORAL TOXICITY (§81-1)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-01 **Report Date:** November 17, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952-01
Author(s): Daniel R. Cerven, M.S., Study Director
Species: Wistar albino rat
Weight: males: 202-277 g; females: 200-256 g
Age: ~8 weeks
Sex: 20 males, 20 females
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, lot #806012; clear, colorless liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary of Product:

1. **LD_{50} (mg/kg)(males):** 7,170 (95% confidence limit: 5,696 - 9,026)
   (females): 6,038 (95% confidence limit: 4,904 - 7,434)

2. **Toxicity Category:** IV (EP), III (AI)

3. **Classification:** Acceptable

Procedure: Animals acclimated at least 1 week. Dosages of AI (mono and dipotassium phosphites) calculated before administration based on specific gravity of product (1.4) and weights of animals for calculation (53% of product). A dose of 5,000 mg/kg of AI in the product was given via gavage to rats (5M, 5F) fasted 16-20 hours. Because deaths were noted at this dose, additional dosages (4,000, 3,500 and 2,000 mg/kg of AIs) were given. Deaths and overt signs of toxicity recorded 1, 2 and 4 hours after dosing and, subsequently, once daily for 14 days. Rats weighed prior to treatment, weekly and at death. Rats necropsied.

Results: The LD_{50} of Fosphite Fungicide for males is 7,170, for females 6,038 and for all animals 6,226 mg/kg, and all deaths occurred on day 1.

DOSE (mg/kg) EP	DOSE (mg/kg) AI	DEATHS (M/F)
9,434	5,000	4/5
7,547	4,000	3/4
6,603	3,500	2/4
3,774	2,000	0/0

Decedents in all dose groups exhibited piloerection, lethargy, ataxia, tremors, prostration, lacrimation and wetness of the anogenital area. Survivors also demonstrated piloerection, lethargy, ataxia and, in addition, chromorhinorrhea, diarrhea, soiling of the anogenital area, red staining of the nose/mouth area and unkempt appearance. Body weight changes of the surviving rats were generally normal, although one female in the lowest dose range lost weight during the second week of the observation period.

Necropsy findings in the survivors were normal, but decedents exhibited abnormalities of the lungs, liver, kidneys, spleen, gastrointestinal tract and localized aloepecia.

BPB's Comment: BPB finds this material meets the requirement for acute oral toxicity testing §81-1.

DATA EVALUATION REVIEW FOR ACUTE DERMAL TOXICITY (§81-2)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-02 **Report Date:** November 17, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952.02
Author(s): Daniel R. Cerven, M.S., Study Director
Species: New Zealand White rabbit
Weight: males: 2.2-2.5 kg; females: 2.1-2.6 kg
Age: 10 to 14 weeks
Sex: 5 males, 5 females
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, lot #806012; clear colorless liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **LD_{50} (mg/kg):** >3,774 (EP), 2,000 (AI)
2. **Toxicity Category:** III (EP), III (AI)
3. **Classification:** Acceptable

Procedure: Animals acclimated at least 1 week. On day before treatment dorsal area of trunk of animals clipped free of hair to approximately 10% of body surface. Treatment dose was 2,000 mg/kg of the AI, equivalent to 3,774 mg/kg EP, and applied to the prepared site by syringe. Test substance applied on top of a 4-layered surgical gauze patch measuring 10 x 15 cm. Gentle pressure applied on top to aid in the distribution of the test substance over the prepared site and the torso then wrapped with plastic and secured with non-irritating tape for 24 hours.

Animals observed for signs of toxicity at 1, 2 and 4 hours after dosing and subsequently once daily for 14 days. After the 24 hour exposure period the bandage was carefully removed and the treated skin and surrounding hair gently washed with distilled water to remove residual test material. Animals observed for evidence of dermal irritation following removal of dressings and on days 7 and 14. Rabbits weighed prior to treatment, weekly and at termination. All animals necropsied.

Results: LD_{50} of **Fosphite Fungicide** >3,774 mg/kg, with no deaths. No overt signs or symptoms of clinical toxicity, and only slight dermal irritation. All animals showed grade 1 erythema after bandages removed, with 1M and 4F demonstrating grade 1 edema. Later observations were negative. Body weight gain and necropsy results normal.

BPB's Comment: BPB finds this material meets the requirement for acute dermal toxicity testing, §81-2.

DATA EVALUATION REVIEW FOR ACUTE INHALATION TOXICITY (§81-3)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-05 **Report Date:** November 17, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952.05
Author(s): Daniel R. Cerven, M.S., Study Director
Species: Wistar albino rat
Weight: males: 243-263 g, females: 208-246 g
Age: ~6-8 weeks
Sex: 5 males, 5 females
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, Lot #806012; clear colorless liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:
1. **LC_{50} (mg/L):** >4.1 (EP), 2.2 (AI)
2. **Toxicity Category:** IV (EP), IV (AI)
3. **Classification:** Acceptable

Procedure: Acclimation time for test animals at least 1 week. Animals observed for effects hourly during exposure period, 1 hour after exposure and once daily thereafter. Body weights taken prior to exposure, one week later and prior to necropsy. Necropsy performed on all animals.

Exposure conditions recorded every 30 minutes: chamber: temperature 25-26 °C; ambient: humidity 64-65 % RH

Exposure chamber: 57 L dynamic glass chamber under negative pressure designed to insure uniform spatial distribution of aerosols permitting continuous observation during exposure. Chamber partitioned internally with wire screening into 10 non-restraining cubicles.

Particle size analysis calculated through an 8-stage Andersen cascade impactor pre-test and once on test. A pretest MMAD of 4 microns or less was required to ensure the particles generated during exposure were respirable.

Samples taken from the breathing zone of animals were measured gravimetrically 6 times using preweighed filters

Aerosol metered from a calibrated Harvard Infusion Pump (2.29 ml/min) into an atomizing nozzle (Spraying Systems Model 1/8 JBC). The spray nozzle was powered by pre-filtered compressed air. Pressure gauge initially recorded (25 psi). Concentrated aerosol diluted with filtered air and drawn into exposure chamber after filtering into a rotameter and vacuum pump,

ensuring the aerosol was drawn over the animals breathing zone. Atmosphere exhausted through tube from bottom of chamber.

Airflow measured every 30 minutes = 35/25 Lpm, 10 to 15 air changes/hour to ensure adequate oxygen content of at least 20.0% of exposure atmosphere.

Results: No deaths observed at the maximum achievable concentration of **Fosphite Fungicide** at 4.1 mg/L with MMAD 1.42 µM and GSD of 2.07 (with 44.9 % of particles below 1.1 µM). No mention that animals were cleaned after exposure to the mixture. Systematic observations noted fur coated with the test article on all rats through day of exposure and on 4 rats until the second day afterward.

Clinical signs observed during the exposure included closed eyes, nose/mouth area wet or stained red. Diarrhea noted in one male on day of exposure. Chromodacryohhrea in one male on day two and chromorhinorrhea in the same male on days 3 and 4. All animals gained weight over the observation period with one female losing about 3% weight over the first week. Necropsy normal for all subjects.

BPB's Comment: The MMAD was measured twice, pre-test and during the test period. BPB would prefer at least two MMAD measurements during the procedure to help assure the study is continuously exposing the animals to the product. BPB will, however, accept the data as presented for this study §81-3.

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

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-04 **Report Date:** November 17, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952.04
Author(s): Daniel R. Cerven, M.S., Study Director
Species: New Zealand White rabbit
Weight: 2.1-2.4 kg
Age: ~7-9 weeks
Sex: 6 male
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, Lot #806012; clear colorless liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary: 1. **Toxicity Category:** III

2. **Classification** Acceptable

Procedure: Animals quarantined at least one week. Both eyes of each animal examined for any evidence of irritation or abnormalities according to the Draize technique. A MiniMaglite® equipped with a high intensity bulb used to aid in the examination. Rabbits treated with 0.1 ml test substance instilled into the conjunctival sac of one eye, holding the eyelids shut for about 1 second. Contralateral eyes served as control. Ocular responses recorded at 1, 24, 48, 72 hours post dose using the Mini-Maglite®. At 24 hours, eyes of all rabbits examined with sodium fluorescein. Scoring system used the Draize technique.

Results: This test substance is a minor irritatant to rabbit eyes. One rabbit vocalized after dosing, but, no further symptoms observed. No corneal effects seen at any time. All rabbits had grade 1 iritis at the first reading which dissipated by 24 hours. All animals had grade 2 redness, chemosis and discharge at the 1 hour reading, which decreased to 5/6 animals having grade 2 redness at 24 hours and non-significance in all areas by 48 hours.

BPB's Comment: BPB considers this study acceptable to meet §81.4.

DATA EVALUATION REVIEW FOR PRIMARY DERMAL IRRITATION (§81-5)

Product Manager: 90 **Reviewer**: Carol Frazer, Ph.D.
MRID No.: 448735-03 **Report Date**: November 17, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952.03
Author(s): Daniel R. Cerven, M.S., Study Director
Species: New Zealand White albino rabbit
Weight: 2.2-2.4 kg
Age: ~10-13 weeks
Sex: 6 males
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, Lot #806012; clear colorless liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **Toxicity Category**: IV

2. **Classification**: Acceptable

Procedure: Animals quarantined at least 1 week. Rabbits clipped on ~10 x 15 cm of dorsal area of trunk and skin examined for irritation on day prior to test. Test material (0.5 ml) applied to site and covered with a 2.5 x 2.5 cm 4-ply gauze patch with gentle pressure to aid in the distribution of test substance. Patch secured with a strip of non-irritating tape. Trunk of each rabbit wrapped with plastic in a semi-occlusive manner and again secured with non-irritating tape which completely covered the plastic. After 4 hours exposure, wrappings removed and test site gently washed with distilled water to clean off residual test substance. Observations for erythema and edema were made 30-60 minutes after removal of wrappings, and at 24, 48, and 72 hours. Draize grading scale used for scoring presented in study report.

Results: This product is not a dermal irritant. No erythema or edema observed in any rabbit at any reading.

BPB's Comment: Data is accepted for §81-5..

DATA EVALUATION REVIEW FOR DERMAL SENSITIZATION (§81-6)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-06 **Report Date:** November 18, 1998
Testing Laboratory: MB Research Laboratories
Report No.: MB 98-6952.06
Author(s): Theresa Hoff, Study Director
Species: Hartley albino guinea pig
Weight: 310-386 g
Age: born: week of 07/03/98, experimental start date: 08/04/98
Sex: 15 males
Source: Ace Animals, Boyertown, PA
Test Material: Fosphite Fungicide, Lot #806012; clear colorless liquid
Positive Control: Dinitrochlorobenzene - 0.2% in ethanol; challenge: 0.1% in acetone; study completed 04/23/98
Quality Assurance (40 CFR §160.12): Included, acceptable

Method: Buehler

Summary: 1. **Rating:** Non-sensitizer

2. **Classification:** Acceptable

Procedure: Acclimation period 5 days.

Treatment Group: The day prior to first induction application ~5 x 10 cm on left dorsal area of each animal in group clipped free of hair with electric clipper. Animals with skin irregularities or irritation eliminated from study Treated sites reclipped the day prior to each induction application. Ten animals in treatment group dosed with 0.4 ml of 100% test article on the left shoulder using a 25 mm Hilltop Chamber. Chamber then covered with a 8 x 8 cm piece of rubber dental dam and wrapped with non-irritating tape to provide occlusion for 6 hours. After removal any residual test material cleansed from the site with distilled water and dried with soft toweling. Procedure performed once/week on same day for a three week period.

Naive Control: Five animals clipped of hair as treated group but untreated for three week induction period.

Challenge: Thirteen days after last induction exposure, a site on each animal clipped free of hair on left hip. The following day animals in both groups were challenged using the same procedure as in the induction phase. Based on the results of the induction application, 100% chosen as the highest non-irritating concentration for the challenge.

Positive Control: Identical study performed with 0.2% dinitrochlorobenzene (DNCB) in ethanol as treatment and 0.1% DNCB in acetone as challenge.

Treated sites scored for erythema and edema incidence and severity 24 and 48 hours after each induction and 24, 48 and 72 hours after challenge. Animals observed once daily for duration of study for mortality, toxicity and pharmacological effects. Body weights recorded pretest, the day following last induction, and day following challenge.

Results: No dermal sensitization exhibited in this study on test animals or controls. All study animals gained weight and none exhibited toxic reactions. The positive control yielded 70% sensitization.

BPB's Comment: Data is accepted for §81-6..

DATA EVALUATION REVIEW FOR BACTERIAL REVERSE MUTATION ASSAY (§84-2)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-07 **Report Date:** December 15, 1998
Testing Laboratory: BioReliance
Report No.: G98AT88.502
Author(s): Valentine O. Wagner, III, M.S., Emily W. Walton, B.S.
Test Material: Fosphite Fungicide, Lot #806012; clear colorless liquid
Cell Source: *Salmonella* tester strains from Dr. Bruce Ames, University of California, Berkeley; *E. coli* from National Collection of Industrial and Marine Bacteria, Aberdeen, Scotland
Vehicle Used: sterile distilled water
Control Materials: Negative: vehicle; Positive: Nonactivation – 2-nitrofluorene, sodium azide, 9-aminoacridine, methyl methanesulfonate; Activation -- 2-aminoanthracene
Activation: S9 derived from Aroclor 1254 induced male Sprague-Dawley rat liver
Media: Overnight culture: 50 mL culture medium inoculated by subculture and incubated at 37±2°C in resting shaker/incubator at 125 rpm for ~12 hours. Plating: Top agar (0.8% agar (w/v) and 0.5% NaCl (w/v) melted and supplemented with L-histidine, D-biotin and L-tryptophan solution to a final concentration of 50 μM each. Top agar not used with S9 or Sham mix supplemented with 25 mL of water for each 100 mL minimal top agar. Bottom agar was Vogel-Bonner minimal medium E containing 1.5% (w/v) agar. Nutrient bottom agar: Vogel-Bonner minimal medium E containing 1.5% (w/v) agar and supplemented with 2.5% (w/v) Oxoid Nutrient Broth No. 2. Nutrient Broth was Vogel-Bonner salt solution supplemented with 2.5% Oxoid Nutrient Broth No. 2.
Strains: *Salmonella typhimurium*: TA 98, TA 100, TA 1535, TA 1537, *Escherichia coli* WP2 *uvr*A
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary: 1. **Rating:** Non-mutagenic

2. **Classification:** Supplementary

Procedure: Solubility test conducted to select vehicle (purified water, dimethyl sulfoxide, ethanol, acetone) and toxicity assay on single plates of ten doses (6.7 - 5,000 μg/plate) on TA98, TA100, TA1535, TA1537 and WP2 *uvr*A with and without activation.

Test article dilutions for assays prepared immediately before use: vehicle, 100, 333, 1,000, 3,333 and 5,000 μg/plate. Final test series doses (50 μL), with and without activation, were assayed in triplicate against each tester strain (100 μL) using direct plate incorporation. Plates incubated at 37°C for approximately 48-72 hours and revertant colonies counted either by

automated colony counters or manually. Positive controls were strain-specific, and the test decision criteria encompassed in the study was presented in the study report.

Results: None of the experiments using the test material or vehicle controls showed any significant increase in bacterial mutants. All positive controls, however, were strongly mutagenic.

BPB's Comment: Dose levels in this study are unclear. The product is liquid and dissolved in water, yet the doses are presented in μg/plate. There is mention on page 7 that "...dosing solutions were adjusted to compensate for the strength of the test article" but no further explanation is provided.

This study meets the requirements of §84-2 and indicates the test material does not produce bacterial mutation in a variety of *Salmonella typhimurium* or *Escherichia coli* cells either with or without exogenous activation. But the problem in dose interpretation needs to be clarified before the study may be accepted.

DATA EVALUATION REVIEW FOR AVIAN ACUTE ORAL TOXICITY TEST
IN BOBWHITE QUAIL WITH **FOSPHITE FUNGICIDE** (850.2100)

Product Manager: 90 **Reviewer**: Carol Frazer, Ph.D.
MRID No.: 448735-08 **Report Date**: January 19, 1999
Testing Laboratory: Bio-Life® Associates, Ltd.
Report No.: BLAL No. 165-002-03
Author(s): Bryan R. Helsten, B.S.
Species: Bobwhite Quail (*Colinus virginianus*)
Weight: males: 198.7-231.7 g; females: 195.4-219.9 g
Age: ~21 weeks old on experimental start date
Sex: 15 males, 15 females
Source: Wolf River Game Farm, Shiocton, WI
Test Material: Fosphite Fungicide, Lot No. 806012, 53% mono and di-potassium phosphite solution; clear liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **LD_{50} (mg/kg)**: >3,774 (EP), 2,000 (AI)
2. **NOAEL (mg/kg)**: >3,774 (EP), 2,000 (AI)
3. **Toxicity Category**: Minimally toxic
4. **Classification**: Acceptable

Procedure: Birds quarantined 30 days. Fed Wolf River Poultry Feed with 100 g of Penicillin G/ton at the supplier's facility, and switched to Purina® Custom Game Bird Layena® 28% containing 1 lb. bacitracin methylene disalicylate/100 lbs. throughout the quarantine period. Untreated feed offered throughout the definitive study.. Beginning the second day of the quarantine period, birds treated with Lincomycin-Spectinomycin at a rate of 3 g/1.5 gal for three days and amprolium at a rate of 2.8 g/1.5 gal for 5 days. On the 10th day of quarantine, birds were wormed with Safe-Guard® 6 cc/1.5 gal water. One female died on day 6 of quarantine and necropsy revealed a friable liver surrounded by red masses. All birds fasted for approximately 19 hours with water *ad libitum* before the start of dosing.

One-week range-finding study with 1M and 1F bird each dosed at 464, 681, 1,000, 1,470 and 2,150 mg/kg. Doses calculated based on the conversion from ml to mg using the specific density of 1.46g/ml for the EP. One female was lethargic shortly after dosing. No mortalities and remaining birds normal and active during observation period.

For the major study, concentrations of 0, 1,000 or 2,000 mg AI/kg body weight were administered. Appropriate dose for each individual bird volumetrically measured and dispensed

into one gelatin capsule, with control birds receiving an empty gelatin capsule. The capsule was administered by oral insertion into the esophagus followed by a hand massage down the esophagus towards the proventriculus.

Five birds per sex per dose group were housed indoors in approximate 51-cm (L) x 51-cm (W) x 25-cm (H) steel wire pens maintained over steel shelves.

Birds individually weighed just prior to dosing, and on test days 3, 7 and 14. Group feed consumption values were recorded on the same days. Inspections were made daily for mortalities, abundance of feed and water, and feed spillage. Each bird was closely observed at least once daily for clinical signs. Four birds (2M, 2F) per dose group were necropsied.

Results: LD_{50} of **Fosphite Fungicide** > 3,774 mg/kg; NOAEL > 3,774 mg/kg with no deaths observed.

Clinical signs observed were chalky excreta in all birds at the highest dose (2,000 mg/kg) approximately 20 hours following dosing, with complete remission noted on the second day. No clinical signs noted in the control or 1,000 mg/kg dose groups.

No significant differences in body weights between control and test groups observed. Food consumption values comparable in all groups over the observation period.

Bird necropsy normal.

BPB's Comment: Data is acceptable for 850.2100.

DATA EVALUATION REVIEW FOR AVIAN ACUTE DIETARY TOXICITY (LC_{50})
STUDY IN MALLARD DUCKLINGS WITH **FOSPHITE FUNGICIDE** (850.2200)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-09 **Report Date:** February 23, 1999
Testing Laboratory: Bio-Life® Associates, Ltd.
Report No.: BLAL No. 165-001-02
Author(s): Bryan R. Helsten, B.S.
Species: Mallard ducklings (*Anas platyrhynchos*)
Weight: 112.7-166.3 g
Age: 10 days old on experimental start date
Number: 70 ducklings
Source: Whistling Wings, Inc., Hanover, IL
Test Material: Fosphite Fungicide, Lot No. 806012, 53% mono and di-potassium phosphite solution; clear liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **LC_{50} (ppm):** >9,434 (EP), 5,000 (AI)
2. **NOAEL (ppm):** >9,434 (EP). 5,000 (AI)
3. **Toxicity Category:** Minimally toxic
4. **Classification:** Supplemental

Procedure: Ducklings (82) quarantined seven days. One death recorded during the first four days of the quarantine period, but all survivors normal and active. Prior to the treatment, all birds examined and found suitable for testing.

Pre-test diet mixes were prepared prior to the experimental start date so that homogeneity and brooder temperature stability testing could be performed. Stock diet ground in the Hobart H-600-DT mixer for 30 minutes prior to diet preparation. For each mix, the appropriate amounts of test material and stock diet were mixed in the Pulsematic Osterizer blender for three minutes to form a premix, which was them added to the appropriate amount of stock diet and mixed in the Hobart mixer for 5 minutes. Then an additional amount of stock diet added and the entire batch mixed for another 30 minutes. Control diets prepared in the same manner, but without adding any test substance.

Homogeneity measured by duplicate samples from the control and from the top, middle and bottom of each of the test mixes on the day after the diets were prepared. For brooder stability evaluation, test diets were placed in an empty mallard duckling brooder (= 95°F) on the day after

preparation. Duplicate samples from the control and each test level at the end of day one were collected and analyzed.

Diets prepared before the definitive experiment were employed throughout the five-day treatment period. For the major study, a.i. concentrations of 0 (2 groups), 648, 1,080, 3,000 and 5,000 ppm in the food were administered to groups of 10 ducklings/concentration for 5 days, and ducklings fed untreated food for three days.

Ten birds housed in brooders approximate 91-cm long x 71-cm wide x 28-cm high. A thermostatically-controlled, heated environment in the room offered temperatures averaging 26°C (78°F), with an average relative humidity of 43-44%. Brooder dry-bulb temperatures averaged 36°C (96°F).

Ducklings individually weighed during the quarantine period, and on test days 0, 5 and 8. Group feed consumption values were recorded during the last three days of the quarantine period, daily during the five-day test period and at the end of the three-day recovery period. Inspections were made daily for mortalities, abundance of feed and water, and feed spillage. Each bird was closely observed at least once daily for clinical signs. Four birds per group were necropsied, with inspections of the GI tract, heart, liver, kidneys and spleen made. Muscle and subcutaneous fat were examined for evidence of deterioration.

Results: No mortalities yielded an LC_{50} of **Fosphite Fungicide** > 9,434 or >5,000 ppm a.i.. No clinical effects were seen in the treatment or recovery phase of the study nor were there statistically significant differences in body weights or food consumption values. The only gross pathological anomaly was pale kidneys in one 3,000 ppm a.i. bird. For these reasons, the NOAEL is also considered to be > 9,434 EP or >5,000 ppm a.i.

BPB's Comment: This data is supplemental because the method of correction "...was made for the active ingredient content of the test material" and is not defined in the procedure. With this correction, the data may be acceptable for 850.2200.

DATA EVALUATION REVIEW FOR **FOSPHITE FUNGICIDE** ACUTE TOXICITY TO RAINBOW TROUT (*Oncorhynchus mykiss*) UNDER STATIC CONDITIONS (850.1075)

Product Manager: 90 **Reviewer**: Carol Frazer, Ph.D.
MRID No.: 448735-10 **Report Date**: 13 April 1999
Testing Laboratory: Springborn Laboratories, Inc. and Benchmark Analytics
Report No.: 13702.0998.6101.103
Author(s): Ronald C. Biever
Species: Rainbow trout (*Oncorhynchus mykiss*)
Weight: mean wet weight = 0.59 g (range 0.43-0.84 g)
Length: mean total length = 41 mm (range 38-45 mm)
Number: 30
Source: Mt. Lassen Trout Farms, Red Bluff, California
Test Material: Fosphite Fungicide, Lot No. 806012, 53% mono and di-potassium phosphite solution; clear liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **LC_{50} (mg/L)**: 1,490 (EP), 790 (95% confidence limits: 630 and 1100 mg/L) (AI)
2. **NOEC (mg/L)**: 698 (EP), 370 (AI)
3. **Toxicity Category**: Practically non-toxic
4. **Classification**: Supplemental

Procedure: Fish quarantined 14 days in 500 L fiberglass tank -- 16 hr light/8 hr dark -- and fed with dry commercial pelleted fish food. Well water total hardness/alkalinity ($CaCO_3$) of 33-38 mg/L /29-31 mg/L, conductivity 140-145 μmhos/cm, pH 6.9-7.3, dissolved O_2. 65-93% of saturation, flow rate of 7.2 to 12.5 tank volume replacements/day. Tank temperature 11-12 °C with no mortality during 48 hours prior to testing. Fish not fed during 24 hours prior to test initiation or during exposure period.

Nominal/measured test concentrations of 130/120, 220/230, 360/370, 600/630 and 1,000/1,100 mg a.i./L. Dilution water reconstituted from deionized water prepared from the same source as the water flowing into the fish holding tank. This soft reconstituted dilution water had a total hardness and a total alkalinity (as $CaCO_3$) of 46 and 29 mg/L respectively, a pH of 7.0 and a specific conductivity of 120 μmhos/cm. Representative samples of dilution water tested for presence of pesticides, PCBs and toxic metals, and monthly for total organic carbon (TOC) concentration. TOC concentration water source was 0.90 mg/L for the treatment month.

Test vessels,18.9-L glass aquaria, each aquarium contained 15 L of test solution. Test solution was 18.4 cm deep with a surface area of 760cm^2. These were placed in a temperature controlled

waterbath solution temperatures of12 ± 1 °C. One test aquarium was established for each treatment level and the control. Prior to test initiation, a 100 mg a.i./mL stock solution was diluted to a volume of 500 mL with dilution water, resulting in a clear solution. The control aquarium contained dilution water but no test material. Ten rainbow trout were selected (two at a time) from the holding tank and placed in each test aquarium following exposure solution preparation. All test vessels were covered with galvanized metal mesh covers.

All aquaria examined at test initiation and after 24, 48, 72 and 96 hours of exposure. Mortalities recorded, dead fish removed and observations of fish and physical characteristics of the test solutions recorded. Dissolved oxygen concentration, temperature, pH measured in all solutions at test initiation and at each subsequent 24 hour interval. In addition, continuous temperature monitoring was performed in the control solution throughout the exposure period. One water sample removed from each treatment level and the control at 0 and 96 hours of exposure for analysis of total phosphorous concentration by Inductively Coupled Plasma spectroscopy.

Results: The 96-hour LC_{50} of **Fosphite Fungicide**, with corresponding 95% confidence levels calculated by binomial probability, was estimated by nonlinear interpolation as 1,490 or 790 mg/L (630 - 1,100) for the AI. All fish died at 1,100 mg/L (7 found dead at 24 hours, and the remaining three at 48 hours), and 10% died at 630 mg/L (1 fish dead at 24 hours). The NOEC of the EP was established at 698 and the AI at 370 mg/L. One of the surviving fish at the 630 mg/L exhibited a complete loss of equilibrium by the 48 hour observation. No mortality or sublethal effects observed in remaining subjects.

BPB's Comment: This data is supplemental because of a discrepancy in the term of AI. On page 10 of the study report, the test substance is termed Fosphite. The next sentence says test concentrations were adjusted for the purity of the test substance and are reported as milligrams of Fosphite per liter of solution (mg a.i./L). Is the a.i. described here Fosphite or the potassium phosphites? From the material in previous studies, we have assumed the a.i. is the latter. When this is defined, the data may be acceptable for 850.1075

DATA EVALUATION REVIEW FOR **FOSPHITE FUNGICIDE** ACUTE TOXICITY TO DAPHNIDS (*Daphnia magna*) UNDER STATIC CONDITIONS (870.1010)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-11 **Report Date:** 13 April 1999
Testing Laboratory: Springborn Laboratories, Inc. and Benchmark Analytics
Report No.: 13702.0998.6102.110
Author(s): Ronald C. Biever
Species: water fleas (*Daphnia magna*)
Age: ≤24 hours
Number: 20
Source: Springborn Laboratories culture facility
Test Material: Fosphite Fungicide, Lot No. 806012, 53% mono and di-potassium phosphite solution; clear liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **EC_{50} (mg/L):** >2,264 (EP), >1,200 (AI)
2. **NOEC (mg/L):** >2,264 (EP), >1,200 (AI)
3. **Toxicity Category:** Practically non-toxic
4. **Classification:** Acceptable

Procedure: This test designed as a Limit Test at one dose level, 1,000 mg/L for 48 hours. Preliminary range-finding studies at 1, 10, 100, 500 and 1,000 mg/L indicated no effects at the highest dose tested; the definitive study only tested a single dose level.

Daphnids raised under regulated photoperiod of 16 hr light/8 hr dark in fortified well water with total hardness/alkalinity ($CaCO_3$) of 160-180 mg/L /110-130 mg/L, conductivity 400-600 μmhos/cm, pH 7.6-8.0, dissolved O_2. >60% of saturation, temperature 20 ± 2 °C and fed with unicellular green algae, at a rate of 2 mL per vessel per day.

In preliminary studies, nominal/measured test concentrations of 130/120, 220/230, 360/370, 600/630 and 1,000/1,100 mg a.i./L. Dilution water was from the same source as the culture water, and had a total hardness and alkalinity (as $CaCO_3$) of 180 and 120 mg/L respectively, a pH of 8.1 and a specific conductivity of 500 μmhos/cm. Representative samples of dilution water tested for presence of pesticides, PCBs and toxic metals, and monthly for total organic carbon (TOC) concentration. TOC concentration water source was 0.65 mg/L for the treatment month.

In the definitive study, test vessels,1 L glass beakers, each contained 500 mL of test solution. Test solution in each aquaria was 12.7 cm deep with a surface area of 79 cm^2. Three replicate

test vessels established for the treatment level and a dilution water control. These were placed in a temperature controlled waterbath designed to maintain solution temperatures at 20 ± 1 °C. Prior to test initiation, a 100 mg a.i./mL stock solution was prepared by dissolving Fosphite Fungicide and brought to volume with NANOpure® water, then further diluted with dilution water to the requisite concentration, resulting in a clear solution. The set of control beakers contained dilution water but no test material. Test initiated when 20 daphnids ≤24 hours old, were impartially selected and distributed to each beaker (replicates A, B, and C, ten daphnids per replicate). Daphnids not fed during exposure.

All beakers examined at test initiation and after 24 and 48 hours of exposure. Numbers of immobilized daphnids recorded, and biological observation of the physical characteristics of each test solution were also made and recorded. Dissolved oxygen concentration, temperature, pH measured in all solutions at test initiation and at each subsequent 24 hour interval. In addition, continuous temperature monitoring was performed in one of the control beakers throughout the exposure period. One water sample removed from each treatment level and the control at 0 and 48 hours of exposure for analysis of total phosphorous concentration by Inductively Coupled Plasma spectroscopy which gave the final real concentration.

Results: The 48-hour EC_{50}, is >2,264 (EP) or >1,200 mg/L (AI). No immobilization or sublethal (e.g., lethargy) effects observed in any organism at any time. The only unusual finding was a significant decrease in the pH of the test substance (6.4) as compared with the control (8.2). None of the other water quality parameters were affected by the Fosphite Fungicide. (Referral back to 850.1075 indicated a similar discrepancy between the control and treatment pH for those tests.)

BPB's Comment: Data is acceptable for 870.1010.

DATA EVALUATION REVIEW FOR **FOSPHITE FUNGICIDE** ACUTE CONTACT TOXICITY TEST WITH HONEY BEES (*Apis mellifera*) (850.3020)

Product Manager: 90 **Reviewer:** Carol Frazer, Ph.D.
MRID No.: 448735-12 **Report Date:** 13 April 1999
Testing Laboratory: Springborn Laboratories, Inc. and Benchmark Analytics
Report No.: 13702.0998.6100.266
Author(s): Ronald C. Biever
Species: honey bees (*Apis mellifera*)
Age: 5 to 10 days old
Number: 30/treatment level
Source: Apiary Services Inc., Wareham, Massachusetts
Test Material: Fosphite Fungicide, Lot No. 806012, 53% mono and di-potassium phosphite solution; clear liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Summary:

1. **LD_{50} (μg/L):** >47 (EP), >25 (AI)
2. **NOEC (μg/L):** >47 (EP), >25 (AI)
3. **Toxicity Category:** Practically non-toxic
4. **Classification:** Supplemental

Procedure: Bees harvested from brood frame in a mature hive on day of initiation and placed in individual test cages which were transported to the laboratory. Forceps were used to move bees throughout the procedure. During the 48-hour test the bees were supplied with 50% sucrose solution and distilled well water. Both the sucrose solution and water were replaced daily.

Test chambers measured 12.7 cm^3, with chamber frame constructed from sheet PVC and each chamber covered with a polyester mesh (~3.5 mm mesh size). The end of each individual chamber was made of glass and designed to slide open, with the glass door having a hole with a self-sealing rubber closure large enough to accommodate the glass tube used to add test organisms at the initiation of the test. Three replicates were maintained for each treatment and the controls, with each test chamber labeled to identify the treatment or control and the designated replicate. The 48-hour exposure was conducted in an incubator designed to maintain temperature and humidity at a constant value. An opaque black curtain covered the front of the incubator which maintained the test organisms in near total darkness to approximate natural hive conditions.

Preliminary testing indicated nominal concentrations of 1.6, 3.1, 6.2, 13 and 25 μg a.i./bee should be tested. Measured concentrations ranged from 1.6 to 19 μg a.i. per bee (109 to 115% of

the nominal fortified levels). Bond surfactant was added to the test material to maintain stickiness of the substance to the bee's thorax. Bees anaesthetized with CO_2 prior to dosing with either test material or control (Bond). Observations made daily and number of mortalities recorded, as well as any unusual behavior. Temperature and humidity in the incubator monitored using a Fisher brand alcohol thermometer (31-32 °C) and a Hanna Instruments Thermo Hygrometer (64-65%). Temperature was continuously monitored with a Fisher Scientific Min-Max thermometer. All analytical samples analyzed using Inductively Coupled Plasma spectroscopy.

Results: No mortality or sublethal effects (e.g., lethargy) observed among bees exposed to any of the treatment levels or controls, yielding an estimated 48-hour LD_{50} of **Fosphite Fungicide** > 47 μg or >25 μg a.i./bee. The NOEC also determined to be the same.

BPB's Comment: Again, the data as presented in the study report is unclear. On page 9, it states: "Test concentrations were adjusted for the purity of the test substance and are reported as micrograms of Fosphite per bee (ug a.i./bee)." How is the "purity" of the test substance adjusted, and what does this mean? Does this mean the potassium phosphites are the "real" a.i., and how should this be reconciled with the reported LD_{50}s? When this is clarified the data may be acceptable for 850.3020.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

CONFIDENTIAL APPENDIX

Guideline 880.1100: **Fosphite Fungicide** (068573-E) is composed of 53.0% mono- and di-potassium salts of phosphorous acid as active ingredients, and [redacted]

BPB's Comments on 880.1100: The submitted data do not satisfy guideline §151B-10, 880.1100. 40 CFR 158.155(a)(2)(ii) and (v) were not included.

Guideline 830.1620: Description of beginning materials and manufacturing process (MRID 448735-13)

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

MSDS's of manufacturing materials included in document.

[redacted]

[redacted]

BPB's Comment: Data submitted satisfy requirements of 40 CFR 158.162, 830.1620. No further information required.

Guideline 830.1670: Discussion of the formation of unintentional ingredients (MRID No. 448735-13)

[redacted]

BPB's Comment: The submitted data meet the requirements of 40 CFR 158.167, 830.1670, and no further information is needed.

Guideline 880.1700: Preliminary analysis

Not submitted.

BPB's Comment: As no information including the five batch analysis as required in 880.1700 was submitted, this application does not meet the requirements of 40 CFR 158.170, 880.1700.

Guideline 880.1750: Certification of ingredient limits Confidential Statement of Formulation

The confidential statement of formulation, dated 5/25/99, includes mono-and di-potassium salts of phosphorous acid at a concentration of 53.0%, as the active(s), and [redacted] The upper and lower limits of the active(s) are 54.59% and 51.41% respectively. However, without the Preliminary Analysis data, the validity of the upper and lower limits of the active are unknown.

BPB's comment: BPB does not agree that submitted data satisfies requirements of 40 CFR 158.175, 880.1750, and new justifications should be provided.

Guideline 830.1800: Enforcement analytical method (MRID 448735-13)

[redacted]

GPA No. 6853-2 Notice of Re. by Rohm

Page _____ is not included in this copy.

Pages 33 through 36 are not included in this copy.

The material not included contains the following type of information:
Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

__✓__ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s)

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

[redacted]

BPB's Comment: There may be some problems with the document describing the method proposed for §151B-16 as satisfying the requirements for 40 CFR 158.180, 830.1800. Details clarifying the below questions are required.

[redacted]