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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE: January 26, 1979

SUBJECT: Evershield RTU-1050 Seed Protectant. EPA Reg. # SLN KS 780020
Caswell No.: 165A, 856

FROM: William Dykstra, Ph.D. *WLD 1/30/79*
Toxicology Branch/IED TS-769

TO: Henry Jacoby (PM #21)
RD, TS-767

Action Type: Section 24 (c): Label Revision with Data

Recommendations:

1. In order to evaluate the human hazards from use of the formulated product, the registrant is required to submit a skin sensitization study of the formulated product.
2. The eye irritation study is considered supplementary data and does not support the registration. All products tested were described as thick, bright purple liquids. Results of the eye irritation study with Evershield RTU 1000 showed the conjunctiva and nictitating membranes were stained purple after the 60 second rinse. Similar results were not reported for Evershield RTU 1050 and Evershield RTU 1010. This absence of staining in those reports needs to be addressed. It is uncertain from the protocol and the results of the eye irritation reports whether the staining effect of these test materials interfered with the evaluation of corneal opacity or vision of the animals. A repeat of the eye irritation studies with sodium fluorescein examination is recommended. The registrant is requested to inquire from the laboratory whether a staining effect occurred with all test materials and to what extent was the eye stained. Was the entire eye stained purple after administration of the test material? How long did the staining effect last and did the effect interfere with evaluation of corneal opacity?
3. The registrant is requested to submit samples of the formulated products to EPA for evaluation of the eye irritation toxicity by EPA laboratories.
4. The present label cautions that "Care must be exercised in the handling of treated seeds." The registrant is requested to specifically explain the hazards for which "care must be exercised". Does this statement refer to the non-food use of the seeds?
5. The information on the product "notice" on the label states "Our recommendations for use of this product are based on tests believed to be reliable. The use of this product being beyond the control of the manufacturer, no guarantee, expressed or implied, is made as to the effects of such or the results to be obtained if not used in accordance with directions etc. . . . " The present toxicological information does not support such a "carte blanche" "notice" for the registrant of the product. It is expected that eyes exposed to the product and subsequently rinsed would be stained purple.

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The staining effect may prevent complete hazard evaluation of eye toxicity data unless sodium fluorescein examination is performed.

6. The acute oral, acute dermal and primary skin irritation studies are acceptable as core minimum data. The eye irritation studies are regarded as supplementary data.

Registrant: Cargill Incorporated
P.O. Box 9300
Minneapolis, Minn. 55440

Product: Evershield RTU 1050 seed protectant

<u>Ingredient</u>	<u>Percent Weight</u>
Thiram (98.5%)	10.15
Vitavax (97%)	5.16
Inerts	84.34

confidential statement of formulation was furnished. For distribution and use only within Kansas.

Use Directions: Apply 4.36 fluid ounces or 128.7 milliliters per 100 pound of seed (wheat, oats, barley) for control of seed and seedling diseases, smut and bunt.

Tolerances for Vitavax 40 CFR 180.301
Tolerances for Thiram 40 CFR 180.132

Review

1. Acute Toxicity and Irritation Studies of :

Evershield RTU 1000 - 10% Thiram
Evershield RTU 1050 - 10% Thiram + 5% Vitavax
Evershield RTU 1010 - 10% Thiram +10% Vitavax
(Hill Top Research, Ref. 78-427-21; June 29, 1978)

Test materials: Evershield RTU 1000-10% Thiram, Evershield RTU 1050-10% Thiram and 5% Vitavax, and Evershield RTU 1010 - 10% Thiram and 10% Vitavax.
All products are thick, bright purple liquids.

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a. Acute Oral Administration - Rats

For each sample, the test material was administered orally by stomach tube to five groups, each composed of five male and five Sprague-Dawley derived albino rats from Murphy Breeding Laboratories, Inc. The weight range for male rats was 172 to 266 grams and for the female rats was 161 to 258 grams. Each sample was administered undiluted at dosage levels of 0.464, 1.00, 2.15, 4.64 and 10.0 grams ($\pm 8\%$) per kg BW. The dose in milliliters was calculated on the basis of specific gravities of 1.14, 1.24 and 1.19 for Evershield RTU 1000, RTU 1050, and RTU 1010, respectively. Food was withheld from the rats for approximately 24 hours prior to dosage. Following dosage, food consisting of Purina Lab Chow and water were available ad libitum. The rats were housed in groups in stainless steel wire mesh cages suspended above the droppings. The animals were housed under a 12-hour light/12-hour dark cycle. All animals were observed closely for gross signs of systemic toxicity and mortality at frequent intervals during the day of dosage, and at least once daily thereafter for a total of 14 days. Gross necropsies were performed on the animals that died. At the end of the 14-day observation period the surviving rats were weighed, sacrificed by CO₂ inhalation and gross necropsies were performed.

Results - 1. Evershield RTU 1000-10% Thiram.

Three males and one female died at the 1.00 gm/kg level and one female died at the 10.0 gm/kg level. Because of the unusual dose-exposure relationship, the 1.00 gm/kg level dosage was repeated using 5 additional male rats. No males died on the repeat test.

LD₅₀ > 10.0 gm/kg (Both Sexes)

Toxic Signs: depression, emaciation

Body Weight: Survivors gained weight except females at 2.15 gm/kg which lost weight.

Necropsy: Diarrhea stains, congested lungs, kidneys and adrenals, dark livers, intestines distended with gas for rats which died. Gross necropsy of survivors revealed no gross pathological alterations.

Classification - Core-Minimum Data

Toxicity Category IV - CAUTION

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2. Evershield RTU 1050 - 10% Thiram + 5% Vitavax one female died at the 0.464 gm/kg level. No other mortalities occurred at any dosing level tested.

LD₅₀ > 10.0 gm/kg (Both Sexes)

Necropsy: Gas filled intestine in rat which died. Survivors revealed no gross pathology.

Toxic Signs: depression, alopecia

Body Weight: All rats gained weight

Classification: Core-Minimum Data

TOX Category IV: CAUTION

3. Evershield RTU 1010 - 10% Thiram + 10% Vitavax, one female died at 1.00 gm/kg level and one female at the 10.0 gm/kg level.

LD₅₀ > 10.0 gm/kg (Both Sexes)

Toxic Signs: piloerection, slight emaciation

Body Weight: Survivors gained weight except for males at 4.64 gm/kg level which showed no weight gain.

Necropsy: Dead rats showed clear fluid in lung and abdominal cavity, irritated intestine, dark livers. Survivors revealed no gross pathological alterations.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

b. Acute Dermal Toxicity - Rabbits.

For each sample, the test material was applied to the skin of ten New Zealand White Rabbits, 2004-2575 grams, at a dosage level of 21.5 gm/kg BW under an impervious cuff for 24 hours. One half of the animals were further abraded. At the end of the 24-hour exposure period the binder was removed and rabbits examined for gross signs of toxicity and dermal irritation. Observation for 14 days.

Results:

1. Evershield RTU 1000-10% Thiram, one mortality occurred during the study.

LD₅₀ > 21.5 gm/kg (Both Sexes)

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On completion of the exposure period, the binders and exposed areas were dry on eight rabbits and moist on two rabbits, indicating variable dermal absorption of the applied material.

Toxic Signs: nasal discharge, emaciation

Body Weight: Most survivors gained weight.

Necropsy: Dead rabbit revealed diarrhea, nasal discharge. Irritative effects included edema, desquamation, lumps on abdomen. Erythema would not be scored for 14 days in most rabbits due to sample staining.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

2. Evershield RTU 1050 - 10% Thiram and 5% Vitavax.

No mortalities occurred during the study.

LD₅₀ > 21.5 gm/kg (Both Sexes)

Toxic Signs: nasal discharge

Body Weight: All survivors gained weight.

Necropsy: No gross pathological alterations were noted. Irritative effects included edema, coriaceousness. Erythema could not be scored for 12-14 days in all rabbits due to sample staining.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

3. Evershield RTU 1010 - 10% Thiram + 10% Vitavax.

No mortalities occurred during the study.

LD₅₀ > 21.5 gm/kg (Both Sexes)

On completion of the exposure period, the binders and exposed areas were dry in all ten rabbits, indicating a generally good rate of dermal absorption of the applied material.

Toxic Signs: diarrhea, emaciation

Body Weight: Nine of ten animals gained weight.

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Necropsy: Depleted body fat & distended colon in one rabbit. Irritative effects included edema, desquamation, coriaceousness, alopecia of the chest. Erythema could not be scored for 3-14 days in all rabbits due to sample staining.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

c. Patch Test for Primary Skin Irritation and Corrosivity - Rabbits.

For each sample, 0.5 ml of test material undiluted was applied to intact and abraded skin sites on the skin of six NZW rabbits for 24 hours under occlusion. Scoring at 24 and 72 hours according to Draize.

1. Evershield RTU 1000 - 10% Thiram.

Erythema and Eschar formation could not be scored at the 24 hour reading due to sample staining. No edema was noted at the 24 hour reading. At the 72 hour reading, all sites were stained pink from sample. The results show no erythema or eschar formation at this time but staining effect may affect the results. No edema at 72 hours.

Conclusion: Although the staining effect precluded complete evaluation, the data show that the test material is not corrosive or a severe irritant.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

2. Evershield RTU 1050 - 10% Thiram + 5% Vitavax.

Erythema and Eschar formation could not be scored at the 24 hour reading due to sample staining. No edema was noted at the 24 hour reading. At the 72 hour reading, all sites were stained pink from sample. The results show no erythema or eschar formation at this time but staining effect may affect the results. No edema at 72 hours.

Conclusion: Although the staining effect precluded complete evaluation, the data show that the test material is not corrosive or a severe irritant.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

3. Evershield RTU 1010 - 10% Thiram + 10% Vitavax.

Erythema and Eschar formation could not be scored at the 24 hour reading due to sample staining. No edema was noted at the 24 hour reading. At the 72 hour reading, all sites were stained pink from sample. The results show no erythema or eschar at this time but staining effect may affect the results. No edema at 72 hours.

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Conclusion: Although the staining effect precluded complete evaluation, the data show that the test material is not corrosive or a severe irritant.

Classification: Core-Minimum Data

TOX Category IV: CAUTION

d. Acute Eye Irritation - Rabbits.

For each sample, 0.1 ml of the undiluted sample was applied to the right or left eye of each of nine NZW rabbits. The opposite eyes were untreated and served as controls. The eyes of six rabbits received no further treatment. The eyes of the three remaining rabbits were rinsed 30 seconds following application for 60 seconds with at least 200 ml of lukewarm tap water. Scoring at 24, 47, 72 hours and 4 and 7 days according to Draize.

Results:

1. Evershield RTU 1000 - 10% Thiram.

Acute eye irritative effects in rabbits whose eyes were not rinsed included slight conjunctival erythema in two rabbits, slight to moderate conjunctival swelling in one rabbit and slight discharge in three rabbits. All irritative effects subsided by the four-day reading. The conjunctiva and nictitating membranes were stained purple after the 60-second rinse. One rabbit showed slight conjunctival erythema at 24-hours after rinse.

Conclusion: It is uncertain from the report whether the staining effect of the test material interfered with the animals' vision or whether the staining effect interfered with complete evaluation of corneal opacity.

Classification: Supplementary Data

(a) The registrant is requested to inquire from the laboratory the extent of the staining effect of the test material in the rabbits eye. Was the entire eye stained purple after administration? How long did the staining effect last? Does the staining effect interfere with vision or the evaluation of corneal opacity?

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2. Evershield RTU 1050 - 10% Thiram + 5% Vitavax.

Acute eye irritative effects in rabbits whose eyes were not rinsed were confined to slight conjunctival erythema in one rabbit at the 24-hour rinse only. No irritative effects were noted in the rabbits whose eyes were rinsed.

Conclusion: It is uncertain from the report whether the staining effect of the test material interfered with the animals' vision or whether the staining effect interfered with complete evaluation of corneal opacity.

Classification: Supplementary Data

- (a) The report does not state whether washing of the treated eyes produced a purple stain in the conjunctiva and nictitating membrane as was observed with Evershield RTU 1000. The registrant is requested to inquire from the laboratory whether a staining effect of the treated eyes occurred and to what extent. Was the entire eye stained purple after administration of the test material? How long did the staining effect last?

Does the staining effect interfere with vision or the evaluation of corneal opacity?

3. Evershield RTU 1010 - 10% Thiram + 10% Vitavax.

Acute eye irritative effects in the rabbits whose eyes were not rinsed were confined to slight conjunctival erythema in one rabbit at the 24-hour reading only. No irritative effects were noted in the rabbits whose eyes were rinsed.

Conclusion: It is uncertain from the report whether the staining effect of the test material interfered with the animals' vision or whether the staining effect interfered with complete evaluation of corneal opacity.

Classification: Supplementary Data

- (a) The report does not state whether washing of the treated eyes produced a purple stain in the conjunctiva and nictitating membrane as was observed with Evershield RTU 1000. The registrant is requested to inquire from the laboratory whether a staining effect of the treated eyes occurred and to what extent. Was the entire eye stained purple after administration of the test material? How long did the staining effect last? Does the staining effect interfere with vision or the evaluation of corneal opacity?