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March 8, 1973

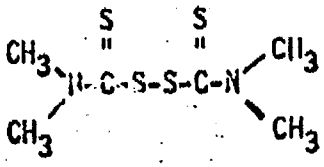
Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Registration No. : 352-EXP-X

Product Name : Textile Fungicide IB-81

Registrant : E.I. du Pont de Nemours & Co., Inc.
7056 Du Pont Building
Wilmington, Delaware 19898

Chemical Structure :



Quantity to be Shipped : 60 lbs.

Formulation : Textile Fungicide IB-81

43% Thiram

[redacted]

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Specific Gravity (active ingredient) (formulation)	:	1.29 (20°/4°C) 1.2
Use	:	Fabric fungicide
Application Rate	:	0.005 to 0.01 lbs per pound of fabric
Previous Petitions	:	9, 52, 91, 144, 170, 204, 278, 359, 9F0758, and 1E1123
Tolerance	:	7 ppm in or on apples, celery, peaches, strawberries, tomatoes 7 ppm in or on bananas (from preharvest and postharvest application) of which not more than 1 ppm shall be in the pulp after peel is removed and discarded. §180.132

Toxicity Data

Test Animal	Mode of Administration	Result	Reference
Rat	Oral	LD_{50} - 730 mg/kg Conf. limits 881 & 691 mg/kg	3
Rat	Oral	LD_{50} - 0.86 grams/kg	5
Rabbit	Oral	LD_{50} - 210 mg/kg	1
Man	Oral	No toxic effects seen in one man after an oral dose of 0.5 gr. "Arasan"	2
Rabbit	Intraperitoneal injection	4/6 survived 3 injections of 70 mg/kg/dose; 2/6 survived 4 injections of 70 mg/kg/dose	1

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Table continued

Rabbit	Skin absorption	ALD - 3400 mg/kg	3
Rabbit	Skin irritation	24 hr. contact gave moderate skin irritation	1
Rabbit	Inhalation	Lung tissue showed marked irritation on exposure to concentrations ranging from 0.00127 mg/L. 24 hrs/day for 30 days to 0.0019 mg/L 7 hrs/day for 5 weeks.	1
Guinea pig	Skin irritation and sensitization	20% aqueous paste moderately irritating to intact skin and 42% aqueous paste strongly irritating. Allergic skin sensitization.	3
Man	Skin patch test	"The application of the dry powder to the skin of men produced very slight erythema in 9% of the men examined. The same percentage of very slightly positive reactions was observed in the sensitization test."	1
Man	Skin patch test	Soap containing 1% tetramethyl thiuram disulfide proved irritating to 8 out of 309 and developed allergic sensitization in 1 out of 214 cases.	4

Man - No toxic effects were seen in one man after an oral dose of 0.5 gms "Arasan".

REFERENCES

1. Brieger and Hodes, Proceedings Ninth International Congress of Industrial Medicine, Page 598, 1948.

2. Domingo, A. F., Rev. Med. Vet. y Parasitol, 11, 335-48 (1952); C.A. 48, 10282 g (1954).

3. Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours & Co., uppublished data.

4. Baer and Rosenthal, "The Germicidal Action on Human Skin of Soap Containing Tetramethyl Thiuram Disulfide", Journal of Investigative Dermatology, 23, 193 (1954).

5. Vos, Bert J., Testimony at 1950 Residue Tolerance Hearings, FDC-57.

Subacute Toxicity

Five-Month Rat Feeding - Dr. H. C. Hodge

Ten rats of each sex were tested per level of 0.125 and 0.25%.

Observations and tests for effects included mortality, body weights, food consumption, neurological alterations, organ weights (individual organs not listed) and histopathological examination of the brain.

Results

The 0.25% level produced total mortality within one month; the 0.125% level produced eleven deaths during the study.

The neurological effect (a peculiar grasping of the hind legs when the rats are picked up by the tail) was evident at one month among the 0.125% level animals.

All organ weights were comparable.

Pathology revealed no brain lesions.

No-effect level is less than 0.125%.

26-Week Rat Feeding - Dr. Bert J. Vos - 1950

Five Osborne-Mendel rats of each sex were used per level of 0, 1,000, and 2,000 ppm of a 50 percent active formulation.

Observations and tests for effects included body weight, mortality, and a microscopic examination of an unspecified number of tissues.

Results

Body weight gain was inhibited among both test levels. Mortality was zero for the controls, 50% for the 1,000 ppm, and 70% for the 2,000 ppm level. Microscopic examination revealed only minor and inconsistent changes.

65-Week Rat Feeding - Dr. Bort J. Vos - 1950

Six Wistar rats of each sex were used per level of 0, 250, and 500 ppm.

Observations and tests for effects included body weights, mortality, and microscopic examination of an unspecified number of tissues.

Results

The body weight gain inhibition noted during the first 21 weeks was neutralized by the termination of the study. Increased mortality was noted at both test levels; 4/12 for control, 7/12 for 250 ppm and 8/12 for 500 ppm.

Microscopic examination revealed one case of interstitial fibrosis and tubular atrophy of the kidneys at the 250 ppm level.

— No-effect level is less than 250 ppm.

12-Day Rabbit Oral - Brieger and Hodes

Nine rabbits were given 0.1 to 0.13 grams/kg on alternate days.

Observations and tests for effects included mortality, body weight and histological examination of liver and kidneys.

Results

Three deaths occurred by the third dose and eight by the sixth dose. Histological examination of the liver revealed degenerative changes with occasional necrotic areas. The kidneys showed degenerative changes of the convoluted tubules, with swelling and congestion of the glomeruli.

✓ 24-Day Rabbit Oral - Brieger and Hodes

Six rabbits were given 0.05 gms/kg of thiram on alternate days.

Results

One death occurred after the first dose, one after the sixth dose and one after the twelfth dose. Blood counts showed a tendency to lymphocytesis. Histological examination of the liver revealed degenerative changes with occasional necrotic areas. The kidneys showed degenerative changes of the convoluted tubules, with swelling and congestion of the glomeruli.

Nopeffect level is less than 0.05 gms/kg.

8-Day Rabbit Intraperitoneally - Brieger and Hodes

Six rabbits received 0.007 gms/kg intraperitoneally on alternate days.

Results

Two died after three injections and two more died after four injections. Peritonitis with a hemorrhagic exudate resulted.

One-Year Dog Feeding - Haskell Lab. - April 24, 1957

The material tested was Lot 1459-25 (99.5% pure).

Three dogs were used per level of 0, 10, 50, and 200 ppm (approx 0, 0.25, 1.25 and 5.0 mg/kg).

Observations and tests for effects included weekly food consumption and body weights, rectal temperature three times a week, pulse rate taken three times a week beginning at six months, clinical condition; RBC, WBC, differential count, hemoglobin, cell size, hematocrit at twice a month for the first six months and monthly thereafter; BSP at monthly intervals; urine analysis twice a month for the first six months and monthly thereafter; monthly neurological examination beginning at the fifth month; gross and microscopic examination of all organs and major tissues; organ weights; residue analysis in the brain, kidney, liver, fat and muscle.

Results

No signfficant alterations were recorded in the body weight gains, food consumption, clinical condition, neurological examinations, tissue pathology, organ weights, and clinical laboratory studies. No significant residues were recorded in the tissues examined.

— No-effect level is greater than 200 ppm (5.0 mg/kg).

✓ Two-Year Rat Feeding - Div. of Pharmacology, FDA

Twenty-four rats were used per level of 0, 100, 300, 1000, and 2500 ppm thiram.

Observations and tests for effects included body weights, mortality, clinical signs, neurological examination, and microscopic examination of tissues (not listed).

Results

Twenty rats on the 2500 ppm level died within 17 weeks. No mortality was observed at the other dosage levels. Growth retardation was evident at the 1000 and 2500 ppm levels. Weakness, ataxia and varying degrees of hind leg paralysis were noted at the 300, 1000, and 2500 ppm levels. Tissue alterations (rounded calcified masses in the basal ganglia and in the cerebellum) in the brain were evident in the 300, 1000, and 2600 ppm levels.

— No-effect level is 100 ppm.

Conclusion

The toxicity provided for Thiram are sufficient to support the experimental status of this formulation. However, before consideration of final registration, information must be provided regarding use of the treated fabric. If such use involves chronic human contact, then toxicity information relating to safety of use will be required.

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Toxicology Branch
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cc:
EEB
DB
HPB
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PCCritchlow
GEWhitmore
Division Reading File
Branch Reading File

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