US EPA ARCHIVE DOCUMENT

10x

reviews +

00467?
004678
#75A

MEMORANDUM

DATE: November 14, 1980

SUBJECT: Benlate DF Fungicide
EPA File Symbol: 352-GOA

FROM: Sherell A. Sterling 11-18-80 E 11/19/80
FHB/TSS

TO: Henry Jacoby
Product Manager (21)

Applicant: E.I. duPont de Nemours and Co.
Legal Department
Wilmington, DE 19898
Attn: J.J. Trexel

Active Ingredient
Benomyl.....75%
Inert Ingredients.....25%

Background: This application for conditional registration was submitted under the "cite-all" method of support. Acute Oral, Acute Dermal, Eye and Skin Irritation studies were submitted. These studies were conducted at the Haskell Laboratories in Newark, Delaware. They may be located under Accession Number 243043. This product is a new formulation (flowable granule which dissolves rapidly in water) of an old active ingredient.

Recommendations:

1. The Acute Oral study is adequate and acceptable support for the conditional registration of this product.

2. The Acute Dermal study is adequate and acceptable support for the conditional registration of this product.

3. An Acute Inhalation study was not submitted for this product. This study may not be necessary according to §163.81-3 of the "Proposed Guidelines for Human Hazard Evaluation." This information should be included with the other data submitted. If the applicant determines that this study is not necessary according to §163.81-3, please submit a statement to this effec in writing
STS 11-1
4. The Eye Irritation study is adequate and acceptable support for the conditional registration of this product.

5. The Skin Irritation study is considered adequate and acceptable for conditional registration purposes.

6. FHB/TSS has no objection to the conditional registration of this product under the "cite-all" method of support.

ij 53

Labeling Recommendations:

1. Add the words "and Domestic Animals" to "Hazards to Humans."

2. The appropriate signal word is WARNING based on the Eye Irritation study. Consequently, the "Hazards to Humans and Domestic Animals" must be revised to the following (or similar) statements:

   "WARNING. Causes eye irritation. Do not get in eyes, on skin, or on clothing. Avoid breathing dust or spray mist."

3. The heading "Statement of Practical Treatment" is preferred to "First Aid." Also, we suggest that the eye wash instructions read "for 15 minutes with clean water" rather than "with plenty of water."

4. The statement "Keep out of lakes, streams or ponds" may be replaced with the statement "Do not apply directly to lakes, streams or ponds. The statement "Do not contaminate water by cleaning of equipment or disposal of wastes" must appear under the "Environmental Hazards" section.

5. The statement "Keep away from fire or sparks" should be placed under a section headed "Phy:ical or Chemical Hazards." This section should follow the "Environmental Hazards" section.

Review:

1. Oral LD_{50} Test in Rats; Haskell Rpt. No. 421-80; May 23, 1980; Acc. No. 243043

   Procedure: A group of 5M, 5F ChR-CD rats received oral application of the test substance by intubation. The substance used was "Benlate DF Fungicide" suspended in corn oil at a dosage rate of 5000 mg/kg. The animals were observed for 14 days. Survivors were sacrificed at the termination of the study; all animals were subjected to necropsies.

   Results: No mortalities. Symptoms included stained face, stained and wet perineal area, chromodacryorrhea and weight loss. Necropsies revealed testes slightly small to small, soft, grey with white subcapsular streaks and foci; livers - slightly heavy; lungs - pale red with grey foci throughout. LD_{50} is greater than 5000 mg/kg.

   Study Classification: Core Guideline Data.

   Toxicity Category: IV - CAUTION

2. Acute Skin Absorption LD_{50} Test on Rabbits; Haskell Rpt. #554-80; July 23, 1980; Acc. #243043

Procedure: 5M, 5F New Zealand white rabbits all with abraded skin were exposed dermally to "Benlate DF Fungicide". The test material was administered after being slightly moistened with physiological saline at a dosage rate of 2000 mg/kg. Exposure was for 24 hours under occlusive wrap. Animals were observed for 14 days. At termination of study, 2M and 2F were subjected to necropsies.

Results: No mortalities. Symptoms included sporadic weight loss and moderate to severe skin irritation. At necropsy, no compound related abnormalities observed. LD_{50} is greater than 2000 mg/kg.

Study Classification: Core Guideline Data.

Toxicity Category: III - CAUTION

3. Eye Irritation in Rabbits; Haskell Report #497-80; June 13, 1980; Acc. No. 243043

Procedure: "Benlate DF Fungicide" was applied into one eye of each of 9 albino rabbits. In each case, 0.1 ml of the test substance was applied. Three of the animals' eyes were irrigated with tap water for one minute, 20 seconds post-treatment.

Results: In the non-irrigated eyes at 24 hours, corneal opacity observed in 2/6=5, 1/6=10, 1/6=20, 2/6=40; iris irritation in 3/6=5; conjunctival redness in 5/6=1; chemosis in 5/6=1 and discharge in 3/6=1. By day 8, only irritation was slight corneal opacity (1/6=5, 1/6=10). All non-irrigated eyes were clear by day 11. Three animals showed injury when viewed with biomicroscope at 8 days. For the irrigated eyes at 24 hours, corneal opacity exhibited in 1/3=5, 2/3=10; conjunctival redness in 2/3=1. All irritation cleared by day 8.

Study Classification: Core Guideline Data.

Toxicity Category: II-WARNING. In this case 2/6 non-irrigated eyes exhibited corneal opacity, 3/6 animals showed corneal injury when viewed with biomicroscope all at day 8.

4. Skin Irritation Test on Rabbits; Haskell Report #367-80; May 12, 1980; Acc. No. 243043

Procedure: 6 New Zealand white rabbits were exposed to the "Benlate DF Fungicide" at 4 sites on each rabbit (2 abraded, 2 intact). The test substance was applied as a paste at 0.5g per site under occlusive wrap for 24 hours. Animals were observed at 24, 72 hours, 6 days.

Results: At 24 hours intact sites showed erythema in 6/12=1, 2/12=2; no edema. Abraded sites at 24 hours exhibited erythema in 9/12=1, 2/12=2; edema in 6/12=1, 1/12=2. By 72 hours, only 1/12 showed very slight erythema at abraded sites; no irritation at intact sites. All scores were 0 by day 6.

Study Classification: Core Guideline Data.

Toxicity Category: IV - CAUTION

004678

DUPONT

BENLATE® DF

FUNGICIDE

DRY FLOWABLE

Product Labeling

DIRECTIONS FOR USE

ACTIVE INGREDIENT

Benomyl [Methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate] 75%

INERT INGREDIENTS 25%

U.S. Pats. 3,541,213 & 3,631,176 EPA Reg. No. 352

Keep out of reach of children

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION! MAY IRRITATE EYES, NOSE, THROAT, AND SKIN. MAY BE HARMFUL IF INHALED OR SWALLOWED.

Avoid breathing dust or spray mist. Avoid contact with skin, eyes, and clothing. Keep away from fire or sparks.

First Aid: In case of contact, flush skin or eyes with plenty of water; for eyes, get medical attention.

ENVIRONMENTAL HAZARDS

This product is toxic to fish. Keep out of lakes, streams or ponds. Do not apply where runoff is likely to occur. Do not apply when weather conditions favor drift from areas treated.

IMPORTANT—Never allow "Benlate" DF to become wet during storage. This may lead to certain chemical changes which will reduce the effectiveness of "Benlate" DF as a fungicide. Keep container closed when not in use.

NOTICE OF WARRANTY

Du Pont warrants that this product conforms to the chemical description on the label thereof and is reasonably fit for purposes stated on such label only when used in accordance with the directions under normal use conditions. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as weather conditions, presence of other materials, or the manner of use or application, all of which are beyond the control of Du Pont. In no case shall Du Pont be liable for consequential, special or indirect damages resulting from the use or handling of this product. All such risks shall be assumed by the Buyer. DU PONT MAKES NO WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Du Pont "Benlate" DF Fungicide should be used only in accordance with recommendations on this label, or in separate published Du Pont recommendations available through local dealers.

Du Pont will not be responsible for losses or damages resulting from use of this product in any manner not specifically recommended by Du Pont. User assumes all risks associated with such nonrecommended use.

"Benlate" DF is a systemic fungicide recommended for the control of many important plant diseases. If treatment is not effective following use of "Benlate" DF as recommended, a tolerant strain of fungi may be present (contact your Du Pont representative); consideration should be given to prompt use of other suitable fungicides.

Apply as a spray with ground equipment (except as otherwise directed), using sufficient water to obtain thorough coverage of the plants. Under severe disease conditions use the higher rate and shorter interval specified for each crop; also, for tree crops, use the higher rate for large mature trees. For aerial application (listed crops only) use following gals. per acre: Almonds, 10 to 20; Avocados, 10 to 20; Beans, 10 to 20; Cabbage (seed crop), 5 to 10; Celery, 5 to 10; Cucurbits, 5 to 10; Grapes, 15 to 20; Peanuts, 5 to 10; Pecans, 10 to 20; Rice, 3 to 10; Stone Fruits, 10 to 20; Strawberries, 10 to 20; Soybeans, 3 to 10; Sugar Beets, 5 to 10. Roses, Flowers, Ornamentals, Shade Trees, 20.

Add required amount of "Benlate" DF to necessary volume of water in spray tank agitated by hydraulic or mechanical means; continuous agitation is required to keep the material in suspension. Do not tank mix "Benlate" DF with lime or alkaline pesticides such as Bordeaux mixture or lime sulfur.

Where use of spray oil is recommended (apples, peanuts, pecans, stone fruits), use a nonphytotoxic superior-type (60 to 70 second viscosity) spray oil; add as last ingredient to spray tank. Before applying other pesticides in conjunction with spray oil or immediately before or after oil application, consult product labels. Observe all cautions and limitations on labeling of all products used in mixtures.

BEST AVAILABLE COPY

#75A

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Mr. Cobe

2

SUBJECT: Registration No. 538-RGE

DATE: MAY 13 1975

FROM: TB

TO: PM

0 04678

Registration No: 538-RGE

Product Name: Pro Turf DSB Fungicide

Registrant: O.M. Scott + Sons Co.

Action Requested: Registration

Recommendation: No adverse comment

Formulation: Active Ingredient
1.10% Benomyl

[redacted]

Use: Herbicide on Turfgrasses only

Application Rate: 60 lbs of formulation per 11,000 to 22,000 sq.ft.

Related Background Information

Toxicity Data

Acute Oral-Rat (50% WP)	LD_{50} >10,000 mg/kg
Acute Oral-Rat (Tech)	LD_{50} >10,000 mg/kg
Acute Oral-Pat	LD_{50} >9590 mg/kg
Acute Oral-Rabbit (50% WP)	ALD >3,400 mg/kg
Acute Dermal-Rabbit (50% WP)	LD_{50} >10,000 mg/kg
Acute Inhalation-Rat (50% WP)	LC_{50} >2.0 mg/L
Acute Inhalation-Rat	LC_{50} >1.37 mg/L
Acute Inhalation-Rat (50% AI)	LC_{50} >4.01 mg/L Testicular alterations noted at all levels tested (0.27, 1.39, and 4.01 mg/L)

Primary Skin Irritation-Guinea Pig (50% WP) mild irritation.

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

BEST AVAILABLE COPY

EPA Form 1320-6 (Rev. 6-72)

6

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

004678

Sensitization-Guinea Pig (50% WP) mild sensitization noted.

Eye Irritation-Rabbit (53%) Mild Irritation-not an eye irritant as per FHSA.

14 Day Intubation-Rat (Unformulated)-NEL 200 mg/kg/day.

21 Day Inhalation-Rat (53.5% [redacted]-NEL >0.2 mg/L.

*90-day feeding study-Rat	Systemic NEL 500 ppm
**90-day feeding study-Dog	Systemic NEL 500 ppm
***2-year feeding study-Rat	Systemic NEL 2500 ppm
***2-year feeding study-Dog	Systemic NEL 500 ppm
***3-generation reproduction-Rat	Systemic NEL 100 ppm
Teratology-Rat	Negative at 5000 ppm
Teratology-Rabbit	Negative at 500 ppm
****Acute oral-Rat (metabolite)	LD_{50} >17 g/kg
****90-day feeding study-Rat (metabolite)	Systemic NEL 2500
****3-generation reproduction-Rat (metabolite)	Systemic NEL 2500

[redacted]

***both sample (* and **) were used
Since only adverse effect in rat reproduction is borderline, consisting of somewhat lower weanling weights in "500" and "2500 ppm" puns of the last 4 (of 7) litters, we can assign "no-effect level" for the dog, 12.5 mg/kg/day as that for the most sensitive species. This also applies to the metabolite.
**** Major plant metabolite, methyl 2-benzimidazolecarbamate.

BEST AVAILABLE COPY

7

Related Petitions: 0F0906, 0G0936, 0F1000, 0F1010, 1G1033, 1F1145, 2F1192, 2G1197, 2F1212, 2F1218, 2H5004, 2H5009, 2F1234, 2E1239, 2F1240, 2F1289, 2F1290, 2F1291, 3F1410, 3H5033, 4F1421, 4F1427, 5H5062, 4F1452, 4F1466, 4F1479

Existing Tolerances:

§ 180.294 Benomyl; tolerances for residues.

Tolerances are established for combined residues of the fungicide benomyl (methyl 1-(butylcarbamoyl) -2-benzimidazolecarbamate) and its metabolites containing the benzimidazole moiety (calculated as benomyl) in or on raw agricultural commodities as follows:

50 parts per million in or on bean vine forage.

35 parts per million in or on pineapples (from postharvest application).

15 parts per million in or on peanut forage, peanut hay, and sugar beet tops.

15 parts per million (from preharvest and/or postharvest application) in or on apricots, cherries, nectarines, peaches, and plums (including fresh prunes).

10 parts per million in or on citrus fruits (from preharvest and/or postharvest application), grapes, and mushrooms.

*7 parts per million in or on blackberries blueberries, boysenberries, dewberries, loganberries and raspberries.

7 parts per million (from preharvest and/or postharvest application) in or on apples and pears.

5 parts per million in or on strawberries and tomatoes.

3 parts per million in or on celery and mangoes.

2 parts per million in or on beans and peanut hulls.

1 part per million (from preharvest application) in or on bananas, of which not more than 0.2 part per million (negligible residue) shall be present in the pulp after the peel is removed and discarded.

1 part per million in or on almond hulls, avocados, cucumbers, melons, summer squash, and winter squash.

0.2 part per million in or on peanuts, soybeans, and sugar beet roots.

0.2 part per million (negligible residue) in or on nuts.

0.2 part per million in poultry liver.

0.1 part per million in eggs; milk; and the meat, fish and meat by products of cattle, goats, hogs, horses, poultry (except liver), and sheep.

§ 121.343

125 ppm in dried grape pomace and raisin waste when present therein as a result of application of the fungicide to growing grapes.

70 ppm in dried apple pomace when present therein as a result of application (preharvest and/or postharvest) of the fungicide to the raw agricultural commodity apples.

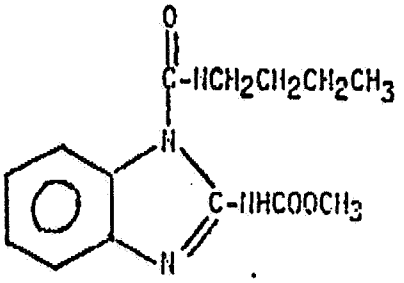
BEST AVAILABLE COPY

50 ppm in dried citrus pulp when present therein as a result of application (preharvest and/or postharvest) of the fungicide to the raw agricultural commodity citrus fruits.

§ 121.1254

A tolerance of 50 ppm in raisins when present therein as a result of the fungicide to growing grapes.

Structural Formula:



Molecular Weight: 290

Color and Form: White Crystalline

Vapor Pressure: Negligible

Melting Range: Decomposes without melting

Present Action

The following toxicity data were submitted to support registration.

Acute Rat Feeding LD_{50} (1.13% formulation) WARF 12/31/74

The test material was identified as Batch No. 4-352-IB DY containing 1.13% 1-(butylcarbamoyl)-2-benzimidazole carbamic acid methyl ester.

Six male Sprague-Dawley rats were tested at the level of 20 gms/kg.

BEST AVAILABLE COPY

Results-No mortality occurred. LD_{50}=greater than 20 gms/kg

Primary Skin Irritation (1.13% formulation) WARF-12/31/74

The test material was identified as Bath No 4-352-IB DY containing 1.13% 1-(butylcarbamyl)-2-benzimidazole carbamic acid methyl ester.

Approximately 0.5 gm of the undiluted test material was applied to two test sites on each of six rabbits. Half these test sites were abraded. Length of exposure was 24 hrs.

Results: no irritation was reported.

Acute Rabbit Dermal LD_{50}-(1.13% formulation) WARF-12/31/74

The test material was identified as Bath No 4-352-IB DY containing 1.13% 1-(butylcarbamoyl)-2-benzimidazole carbamic acid methyl ester.

Two rabbits were tested at 8 gm/kg. Length of exposure to the test material was 24 hours. Observetion time was 14 days.

Results: LD_{50}=greater than 8 gms/kg

Conclusion: The information obtained from the toxicity data submitted with the registration and also from the related toxicity data are judged sufficient to support the request for registration.

Robert D. Coberly, Biologist
Toxicology Branch
Registration Division

cc: Branch Reading File
RCoberly:ir: 5/6/75
Initial G.E. Whitmore
GEW 5/19/75

Mr. Coberly / Reviewer

ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D. C. 20460

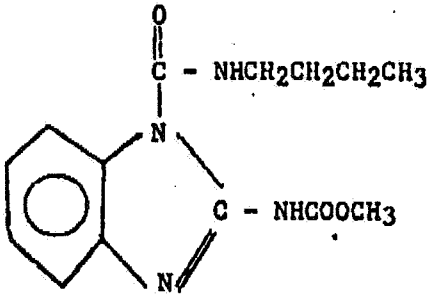
004678

Date: February 23, 1973

Reply to Attn of:

Subject:

To: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Registration No.	:	352-354
Product Name	:	Benlate Benomyl Fungicide
Registrant	:	E.I. du Pont de Nemours & Co. (Inc.) Wilmington, Delaware
Chemical Name	:	Methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate
Chemical Structure	:	
Use	:	Fungicide for control of certain diseases of peanuts, sugar beets, beans (snap), pineapple, sugarcane, roses, flowers, and ornamentals.
Application Method	:	Spray with ground equipment or dip.

BACKGROUND INFORMATION

Related Petitions	:	0F0906, 0G0936, 0F1000, 0F1010, 1G1033, 1F1038, 1F1145, 2F1192, 2G1197, 2F1218, 2H5004, 2H5009, 2F1234, 2E1239 and 2F1240.

INFORMATION WHICH MAY REVEAL A MANUFACTURING PROCESS OR AN INERT INGREDIENT IS NOT INCLUDED

Existing Tolerances: 40 CFR 180.294

15 ppm - apricots, cherries, nectarines, peaches, and plums
2 ppm - snap beans (succulent)
1 ppm - bananas - 0.2 ppm (negligible) on banana pulp after the peel is removed
1 ppm - cucumbers, melons, summer squash, and winter squash
0.2 ppm - peanuts and sugar beet roots

TOXICITY DATA

The following tests were reviewed in memos of Dr. M.L. Quaife dated March 25, 1970 (0F0906, 0G0936), May 3, 1971 (0F0906, 0F1000, 1F1010, 1F1033, 1F1045), and January 3, 1972 (1F1145, 2F1192, 2G1197):

Acute oral - Rat	LD_{50} > 9590 mg/kg
Acute dermal - Rabbit	LD_{50} >10000 mg/kg
Acute inhalation - Rat	LC_{50} >1.37 mg/liter air
*90-day feeding study - Rat	Systemic NEL 500 ppm
**90-day feeding study - Dog	Systemic NEL 500 ppm
***2-year feeding study - Rat	Systemic NEL 2500 ppm
***2-year feeding study - Dog	Systemic NEL 500 ppm
***3-generation reproduction - Rat	Systemic NEL 100 ppm
Teratology - Rat	Negative at 5000 ppm
Teratology - Rabbit	Negative at 500 ppm
Acute oral - Rat (metabolite*)	LD_{50} >17 g/kg
90-day feeding study - Rat (metabolite*)	Systemic NEL 2500 ppm
3-generation reproduction Rat (metabolite*)	Systemic NEL 2500 ppm

[redacted]

***both samples (* and **) were used

Other data contained in our files plus Pesticide Petition No. 0F0906 include the following:

BEST AVAILABLE COPY

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

004679

Acute Rat Oral LD_{50} (50% WP)	greater than 10,000 mg/kg
Acute Rat Oral LD_{50} (technical	greater than 10,000 mg/kg
Acute Rabbit Oral ALD (50% WP)	greater than 3,400 mg/kg
Acute Rabbit Dermal LD_{50} (50% WP)	greater than 10,000 mg/kg
Acute Rat Inhalation LC_{50} (50% WP)	greater than 2 mg/L

Primary Skin Irritation In Guinea Pig (50% WP) - Mild irritation

Rabbit Eye Irritation (50% WP) - Mild irritation

Sensitization In Guinea Pig (50% WP) - Mild sensitization noted

Acute Rat LC_{50} - Hazleton Lab October 18, 1968

The material tested was identified as fungicide 1991 - 50% active ingredient.

Six male rats were used per level of 0.27, 1.39 and 4.01 mg/L. Length of exposure was four hours.

Results

Two cases of slight aspermatogenesis and two cases of a moderate reduction in spermatogenic activity were observed at the 0.27 mg/L level. One case of slight to moderate aspermatogenesis and one case of reduction in spermatogenic activity were noted at the 1.39 mg/L level. Two cases of severe aspermatogenesis and one case of reduced spermatogenic activity were evident at 4.01 mg/L. The incidence and severity of inflammatory lesions in the lung and inflammatory cell infiltration into the submucosa of the trachea were increased at the 4.01 mg/L level.

21 Day Rat Inhalation - Haskell Lab - April 30, 1970

The material tested was identified as "commercial" formulation of 53.5% methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate [redacted]

Ten Charles River male rats were exposed per air concentration of 0.02 and 0.2 mg/L for four hours a day. Half the animals were sacrificed after the 15th exposure, the remainder at 14 day post treatment.

Observations and tests included gross and histopathologic examination of the lung, liver, spleen, kidney, testes, and bone marrow; clinical signs and body weight.

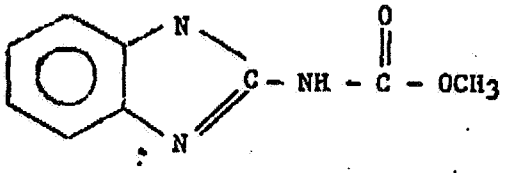
Results

No clinical or histopathologic effects attributable to Benlate were noted.

100-66 14 Day Rat Intubation (Unformulated chemical): 100-65

Adverse tissue alterations were observed at 3400 mg/kg/day in the stomach, liver and testes. No significant histological changes were noted at 200 mg/kg/day.

2-Benzimidazolecarbamic acid, Methyl Ester



99-66 Rat Oral ALD - Haskell Lab - July 15, 1966

The material tested was identified as 2-Benzimidazolecarbamic acid, methyl ester.

One male ChR-CD rat was used per level in a range of from 200-17,000 mg/kg. Material was administered as a 5-30% suspension in peanut oil.

Results

ALD is greater than 17,000 mg/kg. Levels of 1000 mg/kg and above exerted an adverse effect upon the testis.

99-65 Rat Oral ALD - Haskell Lab - August 20, 1965

The material tested was identified as 2-Benzimidazolecarbamic acid, methyl ester (INE-965).

ChR-CD male rats were tested in a dose range of from 670 to 11,000 mg/kg. Material was given as a 25% suspension in peanut oil.

Results

ALD is greater than 11,000 mg/kg. Levels of 1500 mg/kg or greater caused depression of spermatogenesis.

Fourteen Day Rat Intubation- Haskell Lab - July 15, 1966

The material tested was identified as 2-Benzimidazolecarbamic acid, methyl ester.

Six male ChR-CD rats were used per level of 200 and 3400 mg/kg. Material was administered as a suspension in peanut oil. A total of ten treatments were given. Half the animals were sacrificed four hours post treatment and the remainder at 14 days post treatment.

Observations and tests for effects included mortality, body weight, histological examination of the liver, kidney, spleen, bone marrow, thyroid, lung, GI tract, brain, thymus and pancreas from the control and 3400 mg/kg/day animals.

Results

Two deaths occurred at the 3400 mg/kg/day level due to the cumulative oral toxicity. Edema and focal necrosis of the duodenum, reduction in the blood-forming elements of the bone marrow and a decrease in the large globular-shaped vacuoles located centrolobularly in the liver were evident at the high level. Mild diarrhea and body weight loss were also noted at the high level.

Three of six animals at 200 mg/kg/day showed slight adverse changes in the testis.

3-5-65 Fourteen Day Rat Intubation - Haskell Lab - August 20, 1965

The material tested was identified as 2-Benzimidazolecarbamic acid, methyl ester (INE-965).

Six Charles River-Wistar male rats were used at the level of 5000 mg/kg/day. Material was administered as a 25% suspension in peanut oil for a total of ten doses. Half the rats were sacrificed at three hours post treatment, the remainder at 10 days post treatment.

Results

No mortality occurred. Toxic signs displayed were body weight loss, weakness, loss of hair and polyuria. Pathologic changes included small testes and abolished spermatogenesis.

PRESENT ACTION

P.C. Critchlow requested a review of the precautionary labeling for Benlate in reference to the new use patterns accepted in Petitions 1F1033, 1F1145, 1F1192, 2F1212, 2F1240, 2F1289 and 2F1290.

CONCLUSION

The aforelisted toxicity data support the judgement that the proposed usage pattern will not create an undue human health hazard.

Robert D. Coberly, Biologist
Toxicology Branch
Registration Division

cc:
Ecological Effects Branch
Division Reading File
PCCritchlow
GEWhitmore
Branch Reading File

RDCoberly/km 02-27-73

A

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

004678

Date: March 25, 1970

Reply to Attn of:

Ltr: PP# OFO 906

Subject: Benomyl ("Benlate;" methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate), requested tolerances: At 1 ppm on bananas, of which not more than 0.2 ppm shall be in pulp after peel is removed and discarded (PP No. OFO-906); temporary tolerances at 10 ppm in or on peaches, nectarines, apricots, cherries, prunes, plums, and grapes; at 2 ppm in or on beans; and at 0.2 ppm (negligible residue) in or on pecans, peanuts, and sugar beet roots (PP No. OGO-936).

PESTICIDE PETITION NO. OFO-906
PESTICIDE PETITION NO. OGO-936

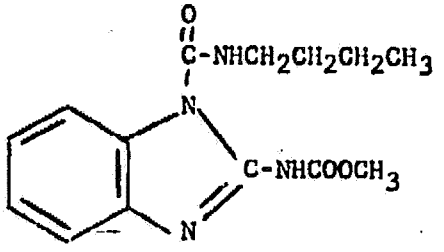
E. I. du Pont de Nemours & Co.
Wilmington, Delaware 19898
(AF 4-408)

TO: Mr. Drew Baker, DRPC (BF-320)

Petitioner wants tolerances for benomyl, a fungicide, as listed in title.

Formulated as a 50% wettable powder (Benlate), it is to be used at ½ to 1 lb per 100 gallons water (= 300 to 600 ppm) for single post-harvest treatment as dip or spray of bananas for control of crown rot and surface molds, (PP No. OFO-906). Recommended rates vary from 3/8 to 2 lbs per acre for nut crops and from 3/8 to 1 lb per 100 gallons of water for fruit and nut crops for control of certain diseases (PP No. OGO-936).

Benomyl is methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate.



Its formula is shown here.

A white crystalline solid, benomyl is decreasingly soluble in chloroform dimethylformamide, acetone, xylene, ethanol, heptane, and (negligibly soluble in) water.

APR 17 1970

18

INFORMATION WHICH MAY REVEAL A MANUFACTURING PROCESS OR AN INERT INGREDIENT IS NOT INCLUDED

[redacted]

Benomyl is formulated, as follows:

PP No. OFO-906. "Benlate," Benomyl, 50% wettable powder

[redacted]

Samples of benomyl used for toxicity studies were, as follows:

Haskell No.	Dates of Use	Sample	% Active Ingredients (Technical)
5043	3/22/67 - 5/17/67	INT-1991-30	72.2
5167-1	5/17/67 - 11/6/67	INT-1991-54	51.5
5167-2	11/6/67 - 1/3/68	INT-1991-75	51.5
5167-2	1/3/68 - 4/3/68	INT-1991-90	52.0
5167-5	4/3/68 - present	INT-1991	52.0

[redacted]

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

[redacted]

In diet preparation, formulations were used as if they consisted of 70% or 50% active ingredient, 1-butylcarbamoyl-2-benzimidazolecarbamic acid, methy ester.

No tolerances presently exist for this material (benomyl).

TOXICITY:*

A. Acute toxicity, oral.

Rat LD_{50} > 9,590 mg/kg

BEST AVAILABLE COPY

Acute toxicity, dermal.

Rabbit LD_{50} > 10,000 mg/kg; no deaths.**

Acute toxicity, inhalation.

Rat LC_{50} > 1.37 mg/liter; no deaths.***

Skin and Eye Tests

174-60

No skin irritation and moderate sensitization, seen in guinea pigs, and "mild transitory conjunctivitis, with minor corneal effects and slight iritic congestion," seen in rabbits.

B. Subacute toxicity studies

Rat, M, Crl:CD strain. Six rats each were intubated with peanut oil suspension of benomyl as unformulated chemical 5 times/wk for 2 weeks at 200 and 3,400 mg/kg body wt. Former caused no deaths, latter 4/6. Lethal dose caused weight loss, diarrhea, and histologic changes in stomach, liver, and, especially, the testis; effects in former two organs were erosion and thickening of squamous mucosa of the stomach

* All studies were done at Haskell Laboratory of E. I. du Pont de Nemours & Co. unless otherwise indicated.

** Except for dermal irritation, no signs of toxicity. Test involved 24-h exposure of intact and abraded abdominal skin (wrapped).

*** Four-hour exposure to atmospheric dust.

with submucosal inflammation and a decrease in the large globular-shaped vacuoles located centrolobularly in the liver. Low dose caused no clinical signs of toxicity and only very minor changes in testis of 2 of 6 rats, as seen on histological examination.

90-day feeding in rat (ChR-CD).

(Report says. INT-1991-9 Unsitell # 4715 formulation MPC 8/13/84)

No. of Animals. 16 M and 16 F/group.
Feeding Levels.* 0, 100, 500, and 2,500 ppm.
Duration. 90 days.
Mortality. One male at 100 ppm died after 39 days; death not related to feeding of benomyl, according to Petitioner.
Body Weight. No effect. (No effect, also, on food consumption or on food efficiency.)
Organ Weight. Livers of females at 2,500 ppm, significantly heavier ($p < 0.001$) than those of corresponding controls. Otherwise, no effect on weights of following: Brain, heart, lungs, liver, spleen, kidney, testis, stomach, thymus, adrenal, or pituitary.
Clinical Laboratory Tests. No effect on hematological values (on 6 male and 6 female rats, done pre-test and at 30, 60, and 90 days), including RBC, WBC (total and differential), hemoglobin, and hematocrit. No effect on alkaline phosphatase in 2,500-ppm rats, but increased serum glutamic-pyruvic transaminase (34 vs. 23 for controls) of males at 2,500 ppm. No effect on results of urinalysis, including determinations of volume and concentration; tests for protein, sugar, and ketone bodies; determinations of pH and color; test for presence of occult blood; or microscopic examination of sediment.
Histopathology. No significant effects on following tissues of control and of 2,500-ppm rats: Brain, heart, lung, liver, spleen, kidney, testis, stomach, thymus, adrenal, pituitary, ovary, epididymus, fallopian tube, prostate, uterus, urinary bladder, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eye, thoracic aorta, spinal cord, trachea, pancreas, thyroid, parathyroid, salivary gland, and exorbital lacrimal gland; mammary gland, not examined.
"No-Effect Level." 500 ppm.
("Effect-Level," 2,500 ppm, caused increased liver weight in female rats and slightly increased serum glutamic-pyruvic transaminase level (SGPT) in males.)

90-day feeding in dog (beagle).

No. of Animals. 4 M and 4F/group.
Feeding Levels. 0, 100, 500, and 2,500 ppm.**
Duration. 90 days.
Mortality. No deaths.
Body Weight. No effect. (Nor any on food consumption.)

*Test material was 70% wettable powder, formulated as given above (for INT-1991 30).
** Test material was INT-1991-54, formulated as described (above) for "other samples of INT-1991."

Organ Weight. No effect on weights of brain, heart, lungs, liver, spleen, pancreas, kidney, testis, prostate, stomach, thyroid, adrenal, or pituitary.

Clinical Laboratory Tests. No effect on hematological values (determined pre-test and at 1, 2, and 3 months), including RBC, WBC (total and differential), hemoglobin, and hematocrit. No effect on values for blood glucose and urea nitrogen (determined at 1, 2, and 3 months); however, 2,500-ppm dogs had slightly increased cholesterol, alkaline phosphatase, and glutamic-pyruvic transaminase; slightly decreased total protein; and consistently increased (about 40%) albumin-globulin ratio. No effect on results of urinalysis, including determinations of volume and concentration; tests for protein, sugar, urobilogen, presence of occult blood, acetone, and bilirubin; determination of pH; and microscopic examination of sediment.

Histopathology. No effect on brain, heart, lungs, liver, spleen, pancreas, kidney, testis, prostate, stomach, thyroid, adrenal, pituitary, epididymus, fallopian tube, uterus, ovary, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eye, thoraic aorta, mammary gland, esophagus, gall bladder, urinary bladder, trachea, thymus, salivary gland, and tonsil.

"No-Effect Level." 500 ppm.

"Effect Level " is 2,500 ppm, and effect consists of slightly increased cholesterol, alkaline phosphatase, and serum glutamic-pyruvic transaminase and significantly decreased A/G ratio.

C. Chronic toxicity studies

Rat, 2-year feeding.

No. of Animals. 36 M and 36 F/group.

Feeding Levels.* 0, 0 (second control group), 100, 500, and 2,500 ppm.

Duration. 2 years.

Mortality. No effect.

Body Weight. No significant effect. (None on food consumption or food efficiency, either.)

General Behavior. No effect. No clinical signs of toxicity attributed to effect of benomyl.

Organ Weight. No effect on weights (either absolute or relative to body weight) of brain, heart, lungs, liver, spleen, kidneys, testes, stomach, adrenals, and pituitary.

Clinical Laboratory Tests. No effect on alkaline phosphatase or serum glutamic-pyruvic transaminase determined in rats of both control

* Test substance was 70% or 50% wettable powder formulated as given, above, for either INT-1991-30 or INT-1991. Dietary levels based on active ingredient.

groups and those at 500 or 2,500 ppm at 0, 1, 3, 6, 9, 12, 18, and 24 months on test. No effect on hematologic values (same ones as determined in rat 90-day study at time intervals given in preceding sentence). No effect on results of urinalysis (also done at same time intervals): Volume; solute concentration; levels of sugar, protein, and ketone bodies; color; pH; presence of occult blood; and microscopic appearance of urinary sediment.

Histopathology. Tissues examined histologically, in addition to those listed under "organ weight," above, are: Ovary, epididymus, fallopian tube, prostate, uterus, urinary bladder, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eye, thoracic aorta, lumbar spinal cord, trachea, thymus, pancreas, thyroid, parathyroid, salivary gland, lymph node, and exorbital lacrimal gland. These tissues from control groups and from 2,500-ppm group examined at both 1 and 2 years. At 2 years, liver, kidney, and testis of 100- and 500-ppm groups also studied. No significant findings believed related to intake of test compound, benomyl, were made. Validity of this opinion is verified by K. Davis, DVM, Pathologist (told to M. Quaife on January 20, 1970). We note that only certain tissues of animals in one of the control groups were studied. In male rats of the other control group (IA), there was a very high incidence of pituitary tumors and chronic nephritis (> 85% each); such incidence of pituitary tumors is not matched in the 2,500-ppm male rats. Liver changes were of frequent occurrence but about equally spread between control and test groups. Likewise, for testicular degeneration in male rats.

Neoplasms. No effect.

"No-Effect Level," 2,500 ppm.

Dog, 1-year feeding.

A study with 4 M and 4 F dogs/group and with same feeding levels as used in the chronic rat study has been conducted for 1 year. Results are said to show no nutritional, clinical, hematologic, urinary, or pathologic evidence of toxicity due to benomyl except some aberrant biochemical values in 2,500-ppm dogs. The latter include decreased total serum proteins and albumin/globulin ratios and increased levels of cholesterol, plasma alkaline phosphatase, and serum glutamic-pyruvic transaminase.

E. Reproduction study

Rat, 3-generation, 7-litter.

No. of Animals. 6 M and 6 F/group, F_0 parents (animals left from 90-day study); 12 M and 12 F/group, F_{1b} parents; and 20 M and 20 F/group, F_{2b} parents.

Feeding Levels.* 0, 100, 500, and 2,500 ppm.
Duration. Time to produce 3 generations, 7 litters in all.
Mortality. No effect on numbers of stillborn or on survival to 4 days or to weaning.
Body Weight. Pups from parents at 500 and 2,500 ppm weighed less, at weaning, than control or "100-ppm" pups in the F_{2b}, F_{3a}, F_{3b}, and F_{3c} litters. (See Table, below.) However, the various groups of F_{3c} pups kept on test for 9 weeks post-weaning and for a further 6 weeks on control diets had growth curves of similar slope.
Histopathology. No effect on F_{3b} weanlings. Tissues studied were: Pituitary, thyroid, parathyroid, adrenal, skeletal muscle, sciatic nerve, brain, spinal cord, eye, exorbital lacrimal gland, mammary gland, bone marrow, spleen, thymus, lung, upper trachea, heart, stomach, duodenum, cecum, salivary gland, pancreas, liver, testis or ovary, epididymus or fallopian tube, uterus or prostate, urinary bladder, and kidney.
"No-Effect Level." Conservatively, 100 ppm; since average weanling weights in F_{2b}, F_{3a}, F_{3b}, and F_{3c} litters are low for "500-ppm" and "2,500-ppm" pups, as compared to corresponding control and "100-ppm" values.

* Test substance was 70% or 50% wettable powder prepared from technical grade benomyl and formulated as described in introduction to this memo for either INT-1991-30 or INT-1991. (However, in place of INT-1991-30, a sample numbered INT-1991-9 was used.) Dietary levels are of active ingredient.

Parameters in this reproduction study are tabulated:

ppm Benomyl	Average Litter Size	Average No. Born Alive	F.I. (%)	G.I. (%)	V.I. (%)	L.I. (%)	Average Weanling Weight (g)
			F_{1a} Litter				
0	11.7	11.2	100	100	94	98	48
100	11.2	11.2	67	100	100	100	54
500	10.2	10.0	83	100	98	98	59
2,500	13.0	12.8	100	100	97	93	57
			F_{1b} Litter				
0	12.5	10.8	100	100	87	98	57
100	13.6	13.2	83	100	97	100	58
500	11.6	10.6	83	100	91	93	62
2,500	13.2	12.1	100	100	91	100	54
			F_{2a} Litter				
0	10.8	10.4	83	100	95	96	51
100	11.8	11.6	92	100	97	95	56
500	10.6	10.5	83	100	98	97	52
2,500	11.3	11.2	91	100	96	98	48
			F_{2b} Litter				
0	10.8	10.0	92	91	90	99	60
100	13.6	13.6	92	100	100	100	59
500	11.1	10.6	67	100	89	97	52
2,500	12.9	12.6	91	90	96	100	51
			F_{3a} Litter				
0	9.5	8.9	85	100	93	99	56
100	11.3	10.7	75	93	90	98	57
500	9.6	9.5	70	100	98	100	52
2,500	11.9	11.7	80	100	98	99	51
			F_{3b} Litter				
0	13.1	12.6	80	100	95	99	58
100	13.5	13.3	68	92	97	100	59
500	11.1	10.7	70	100	94	99	52
2,500	11.9	10.4	85	100	84	98	54
			F_{3c} Litter				
0	11.6	10.0	65	92	87	100	60
100	11.9	10.5	67	100	87	100	62
500	9.5	8.5	55	100	88	93	52
2,500	13.0	10.6	75	93	79	96	51

D. Biochemical studies

"Isolation and Identification of a Metabolite of Methyl 1-(Butylcarbamoyl)-2-benzimidazolecarbamate in Rat Urine." J. A. Gardiner, R. K. Brantley, and H. Sherman, J. Ag. Food Chem. 16, 1050 (1968).

Methyl 5-hydroxy-2-benzimidazolecarbamate was the major metabolite of benomyl isolated from rat urine. Rats had received 2,500 ppm benomyl in the diet for 6 months. The metabolite occurred in urine as 40 ppm free and 1,200 ppm conjugated (as sulfate and/or glucosuronide benomyl.

"Metabolism of Methyl 1-(Butylcarbamoyl)-2-C^{14}-benzimidazolecarbamate in the Rat." J. A. Gardiner, H. Sherman, and R. W. Reiser.

This study is summarized in DOP/PEB memo of February 19, 1970, PP No. OGO-936, p. 4. Again, methyl 5-hydroxy-2-benzimidazolecarbamate was virtually the only urinary metabolite of benomyl, and no parent compound appeared in urine.

"Studies with 2-C^{14}-Labeled Methyl 1-(Butylcarbamoyl)-2-benzimidazolecarbamate (Benomyl) in Rats." I. J. Belasco, J.J. Kirkland, H.L. Pease and H. Sherman.

Residues of benomyl (I) and/or methyl 2-benzimidazolecarbamate (II), methyl 5-hydroxy-2-benzimidazolecarbamate (III), and methyl 4-hydroxy-2-benzimidazolecarbamate (IV) were simultaneously determined in rat blood and testis. Acid hydrolysis of sample converted I to II and freed metabolites from conjugates. An organic solvent extract of hydrolyzed sample was cleaned up by solvent-solvent partition and subjected to a single scan by cation exchange liquid chromatography.

After rats took 1,000 mg/kg benomyl by mouth, once, C^{14}-residues (calculated as benomyl) were 3 to 13 ppm in blood and 2 to 4 ppm in testis. The metabolite, III, appeared in both tissues within an hour after dosage. Concentration of I and/or II decreased with time, and that of III increased, in both tissues. No (< 0.1 ppm) IV occurred in either tissue.

At 1 hour after taking last of 10 repeat doses of 200 mg/kg/day of benomyl by mouth, rats showed no (< 0.1 ppm) I/II or IV and only low levels of III (1.5 ppm in blood and 0.3 ppm in testis). At 24 hours, no (< 0.1 ppm) I/II, III, or IV was found. (Only very minor histopathologic changes in testis occurred in these treated rats.)

No I/II or IV occurred in blood or testis of rats on 2,500 ppm benomyl for 1 year. Only 0.2 ppm III was found in blood and none (< 0.1 ppm) in testis.

F. "Toxicity-to-wildlife" studies

Species	Time	LC_{50} (ppm)
goldfish	96 hrs	4.2*
bluegill sunfish	96 hrs	2.6*
duckling	8 days	> 10,000 **
quail	8 days	> 10,000 **

DISCUSSION:

Benomyl, methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate, a fungicide, seems to be relatively non-toxic; acute toxicity values (oral and dermal) are in excess of 10 g/kg body wt/day. Lethal doses affect principally the testis but, also, the liver and stomach.

We consider Petitioner is remiss in not supplying enough details of acute toxic effects. In particular, does benomyl, a carbamate, produce cholinergic effects?

Further, no data on its effects, if any, on blood and/or brain cholinesterase are included: although such data is routinely requested for a carbamate.

Petitioner states that 2,500 ppm benomyl in the diet caused no overt effect in long-term feeding of rats and dogs (2 years and 1 year, respectively). Neither weight nor histologic appearance of the testis was affected in either species. Liver may have been affected adversely in dogs, as shown by decreases in total protein and in A/G ratio and by increase in blood values for GPT, alkaline phosphatase, and cholesterol. Livers of female rats were significantly heavier than those of controls.

In rat reproduction, the only adverse effect noted was lower weanling weights of pups on 500 or 2,500 ppm benomyl; these occurred in F_{2b}, F_{3a}, F_{3b}, and F_{3c} litters.

These results recall the lower growth rates in 2-year rat study and lower weanling weights in mouse reproduction study with Thiabendazole which, like benomyl, is also a benzimidazole derivative.

---

* Determined at Woodard Research Corporation.
** Determined at Hazleton Laboratories.

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

Plant metabolites consist of, primarily, methyl 2-benzimidazolecarbamate and, also, 2-aminobenzimidazole, the former having comprised 40% or more of total residue in a study on apples and oranges, according to DOP/PEB (memo of February 19, 1970, PP No. OGO-936). The compounds were not found as mammalian metabolites. No toxicity studies on either of them are included in either petition.

Various inert ingredients of the benomyl formulation are not of concern toxicologically; they are exempt under various sections except for the [redacted] (DOP memo cited in preceding paragraph).

EVALUATION:

Tentative "no-effect levels" of benomyl are listed:

Rat, 2-year feeding	2,500 ppm	250 mg/kg body wt
Dog, 1-year (interim)	500 ppm	12.5 mg/kg body wt
Rat reproduction	100 ppm*	10 mg/kg body wt*
Rat, 90-day	500 ppm	50 mg/kg body wt
Dog, 90-day	500 ppm	12.5 mg/kg body wt

*Since the only adverse effect in rat reproduction is borderline, consisting of somewhat lower weanling weights in "500-" and "2,500-ppm" pups of the last 4 (of 7) litters, we can assign the tentative "no-effect level" for the dog, 12.5 mg/kg body wt, as that of the most sensitive species.

The latter is equivalent to 500 ppm in the human diet. A corresponding ADI would be 5 ppm with 100-fold safety factor, but this applies to parent compound, only.

We lack information on possible cholinergic effects, including effects on blood and/or brain cholinesterase of benomyl and of its plant metabolite methyl 2-benzimidazolecarbamate. We, also, lack toxicity data (acute or subacute) on either of the plant metabolites, methyl 2-benzimidazolecarbamate and 2-aminobenzimidazole.

Although we conclude there is an ample margin of safety if the requested "negligible residue" and temporary tolerances of PP Nos. OFO-906 and OGO-936 (listed in title of this memo) are granted, before we can evaluate safety of any permanent, finite tolerances for benomyl, we will need information (as given below) in "Conclusions."

CONCLUSIONS:

1) Requested "negligible residues" tolerance for benomyl on bananas is safe (PP No. OFO-906; see title of this memo).

2) Requested temporary tolerances of PP No. OGO-936 are safe (see title of this memo).

3) To evaluate safety of any finite, permanent tolerances for benomyl which may be requested in the future, we are asking Petitioner to supply information on:

   a) Any information relative to possible cholinergic effects which benomyl may have and

   b) Subacute (90-day) toxicity data on at least one animal species for the principal plant metabolite of benomyl, methyl 2-benzimidazole-carbamate.

M. Quaife 3/25/70

Dr. M. Quaife
Division of Toxicology
Petitions Review Branch (BF-148)

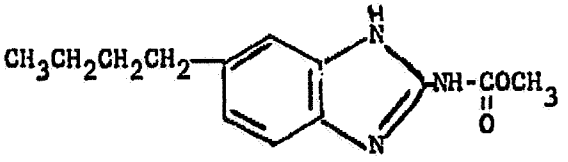
INIT:HBlumenthal

cc: BF-148
BF-140
SC-330
SC-310
VM-100
PP Nos. OFO-906 & OGO-936

MQuaife:dps 3-25-70

ADDENDUM to DT memo of March 25, 1970, Pesticide Petition Nos. OFO-906 and OGO-936.

Privileged data on a compound (which is related to benomyl), 2-carbomethoxyamino-5-n-butylbenzimidazole (structure shown), tell us



it is a teratogen in both sheep and rats (Cf. VID 221 or NDA No. D40-167V in our files.)

This being so, we will require studies to determine whether benomyl is a teratogen in at least two animal species before we can establish safety of any tolerances other than temporary, negligible ones.

NEW CONCLUSIONS:

1) Of requested tolerances for benomyl in PP Nos. OFO-906 and OGO-936 (Cf. title of memo for list), we judge only those temporary ones at 0.2 ppm (negligible residue) in or on pecans, peanuts, and sugar beet roots are safe.

2) To establish safety of any finite or permanent tolerance for benomyl will require satisfactory findings in studies for teratogenicity in at least two animal species in addition to studies listed under conclusions, 3a and b", in our memo (of March 25, 1970).

M. Quaife, Ph.D.

MQuaife:dps 4-7-70

004678

Benomyl (methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate), a fungicide, -- requests for tolerances, as follows: PP No. 0F0906, 1 ppm on bananas, of which no more than 0.2 ppm will be in pulp; PP No. 0F1000, 15 ppm in or on plums, peaches, nectarines, apricots, cherries, and prunes; PP No. 1F1014, 15 ppm in bean forage and hay, peanut hulls, forage, and hay, and sugarbeet tops; 2 ppm in beans; 0.2 ppm in peanuts and sugarbeets (roots), and 0.05 ppm in milk and meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep; PP No. 1F1033, 7 ppm in or on apples, crabapples, and pears; and PP No. 1F1045, 1 ppm on cucumbers, melons pumpkins, summer squash, and winter squash. (Toxicity data are from the Haskell Laboratory, Wilmington, Delaware or the Hazleton Laboratory, Falls Church, Virginia.)

Re: PP# 0F0906

TO: Mr. Drew Baker
Pesticides Tolerances Division

Pesticide Petition Nos. 0F0906, 0F1000, 1F1014, 1F1033, and 1F1045

E. I. DuPont De Nemours & Co.
Wilmington, Delaware

Petitioner requests tolerances for benomyl, methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate, on commodities listed in title of this memo.

TB (SW) So far, DT has approved tolerances for benomyl, as follows: temporary, negligible ones at 0.2 ppm on pecans, peanuts, and sugarbeet roots (PP No. 0F0936) and temporary ones at 15 ppm in or on peaches, nectarines, apricots, cherries, prunes, and plums; at 10 ppm on grapes; and at 7 ppm in or on apples, pears, crabapples, and quinces (PP No. 1E1038)--Cf. DT memo of March 1, 1971, in latter petition and that of March 25, 1970, in PP No. 0F0936.

TOXICITY:

Petitioner herewith submits report of completed chronic dog study and new material in response to DT's request (in earlier memo, above) for satisfactory teratologic findings in two animal species (including the rat), subacute data in one animal species for the chief plant metabolite of benomyl, methyl 2-benzimidazolecarbamate; and information on whether benomyl, a carbamate, exerts cholinergic effects.

One chronic feeding-study on benomyl, final report (Haskell Laboratory Report No. 48-70), dated March 17, 1970, submitted with PP No. 0F1000.

(For our review of interim report, Cf. earlier DT memo, above.)

No. of Animals. 4M and 4F/group.

Feeding Levels.* 0, 100, 500, and 2,500 ppm.

Duration. 2 years.

* See next page for footnote.

BEST AVAILABLE COPY

FF [illegible], DFI[illegible], FF1.1[illegible], FF1.23, and FF1.[illegible].

Mortality. No deaths, but one male dog at 2,500 ppm was killed at 47 weeks after showing weight loss, passage of black stools, and ascites.

A replacement dog was put on test for one year. One male and one female each from control and 2,500-ppm groups were killed at 1 year for histopathologic study.

Body Weight and Food Consumption. Both decreased at intervals in 2 males and one female at 2,500 ppm. When dogs were temporarily put back on control diet, they gained weight but lost it again on resuming test regimen.

General Behavior. Toxic effects, as noted above, in the male dog at 2,500 ppm which was killed at 47 weeks.

Clinical Laboratory Tests. Apparent elevated blood glutamic-pyruvic transaminase, cholesterol, and alkaline phosphatase and apparent decreased blood total protein and albumin-globulin (A/G) ratio in male dogs at 2,500 ppm. In females at 2,500 ppm, apparent increase in blood cholesterol level and decrease in both total protein and A/G ratio. No effect on hematological or urinary values.*2 No effect on blood glucose or urea nitrogen values.

Organ Weight and Histopathology.*3 In the male 2,500-ppm dog, killed at 47 weeks, severe liver damage (cirrhosis) plus mild arrest of spermatogenesis and reduced testis weight (said by Petitioner, probably due to failure of damaged liver to inactivate estrogen).

---

* Test material, an approximately 50% wettable powder, was of composition given in previous DI memo (March 25, 1970, PP No. 0F0900, p. 2), starting with Haskell No. 5167-B, 11/20/68 - 3/23/69, INT-1991, 51.5% active and Haskell No. 5167-C, 3/23/69 - End, INT-1991-190, 53.0% active ingredient.

*2 RBC, WBC (total and differential), hemoglobin level, and hematocrit. Urinary volume, concentration, protein, pH, sugar, urobilogen, acetone, bilirubin, occult blood, and sediment, microscopic appearance.

*3 Organs weighed: Brain, heart, lung, liver, spleen, kidney, testis, stomach, thyroid, adrenal, and pituitary. These and following, examined microscopically: Pancreas, prostate, urinary bladder, epididymis, fallopian tube, uterus, ovary, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eye, thoracic aorta, mammary gland, esophagus, gall bladder, spinal cord, trachea, thymus, salivary gland, and tonsil.

BEST AVAILABLE COPY

No effect in male or female killed at 1 year. In dogs on 2,500 ppm for 2 years, liver cirrhosis in 3 (of 6)--a female and 2 male; in 3rd male, marked diffuse testicular degeneration with reduced testis weight, absence of spermatozoa, and partial loss of primary spermatocytes. In 3 (of 4) male 500-ppm dogs (only), chronic orchitis; in one or two males at all test levels (not in controls), focal testicular degeneration--each of these conditions called "spontaneous" by Petitioner.

"No-Effect Level." 500 ppm, says Petitioner; Cf. "Addendum," below.

"Effect Level." 2,500 ppm, "effects" being liver damage (cirrhosis) and apparent adverse effect on testis, says Petitioner. Cf. "Addendum."

Addendum to evaluation of chronic dog study (above).

"No-Effect Level." Above estimation of this is based on Petitioner's account of the study; however, for confirmation, our pathologists checked slides from Petitioner's study (Cf. report of K. Davis, DVM, dated April 30, 1970). Based on his findings that "testicular lesions....are of little significance and do not appear to be attributable to benomyl ingestion," and that liver pathology in dogs at 2,500 ppm is considerably less severe than reported by Petitioner, we estimate "no-effect level" for this study to be at least as high as 100 ppm. To establish whether it is higher, e.g., 500 ppm or more, we will need the further histopathological examination of dog tissues recommended by Dr. Davis in the report.

Acute oral toxicity study of methyl 2-benzimidazolecarbamate, Haskell Laboratory Report No. 99-66, dated July 15, 1966, submitted with PP No. 1F1013.

Test material was given by stomach tube (as a 5-to-30% suspension of methyl 2-benzimidazolecarbamate (sample of Code No. DHL-965-27) in peanut oil to young adult Charles River-CD male rats in single doses. Survivors were killed after 14 days; testis and epididymis were studied grossly and microscopically.

The acute lethal dose is greater than 17 g/kg body weight.

One g/kg body weight and above causes adverse effect on testis, with reduction in, or absence of, sperm.

BEST AVAILABLE COPY

004678

Ten-day subacute oral toxicity of methyl 2-benzimidazolecarbamate, above report.

Details of study, as above, except five daily doses each per weal., at 0.2 and 3.4 g/kg/body weight/day, given during 2 weeks, and other tissues examined microscopically.*

Two (of 6) rats died after 7 or 10 doses on high level; survivors lost weight and had mild diarrhea. No toxic symptoms in low-level rats.

In high-level rats, severe testicular damage and absence of sperm plus edema and focal necrosis of duodenum; reduction of blood-forming elements in bone marrow; and decrease in large globular-shaped vacuoles located centrolobularly in the liver.

In low-dose animals, slight adverse effect on testis, only tissue checked histologically.

Acute oral and subacute oral toxicity of methyl 2-benzimidazolecarbamate, Haskell Laboratory Report No. 125-65, dated August 20, 1965, in PP No. 1F1010

Acute lethal dose of test substance to young adult Charles River rats of the Wistar strain is greater than 11 g/kg/body weight. Dose of 1 g/kg body weight, or higher, depresses spermatogenesis.

Rats (6/6) survived ten daily doses of 5 g/kg/body weight/day of methyl 2-benzimidazolecarbamate. They lost weight, showed weakness, hair loss, and polyuria. The testes were soft, small, and aspermatogenic both at 3 hours after, and at 10 days after, last dose.

Ninety-day rat feeding study on methyl 2-benzimidazolecarbamate, Haskell Laboratory Report No. 95-66, dated May 15, 1968, submitted with PP No. 1F1010.

No. of Animals. 16 M and 16 F/group.

Feeding Levels.** 0, 100, 500, and 2,500 ppm.

Duration. 90 days.

---

* In addition to testis--liver, kidney, spleen, bone marrow, thyroid, lung, G.I. tract, brain, thymus, and pancreas.

** Test substance: 70% wettable powder formulation of technical methyl 2-benzimidazolecarbamate, dietary levels being of active ingredient: for details of formulation, Cf. under reproduction portion of study (below).

BEST AVAILABLE COPY

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

Mortality. None.

Body Weight and Food Consumption. No effect.

General Behavior. No effect.

Clinical Laboratory Tests. No effect on routine hematologic or urinary test values except for hematuria in one male rat each at 500 and 2,500 ppm; no effect on plasma alkaline phosphatase or glutamicpyruvic transaminase (clinical laboratory tests, conducted at monthly intervals).

Organ Weight and Histopathology. No effect on various organ weights, including that of testis, or on tissues examined histopathologically.*

"No-Effect Level." 2,500 ppm (however, we note no higher "effect" level was tested).

Reproduction study portion of above report on methyl 2-benzimidazolecarbamate

No. of Animals. 6M and 6F/group.

Feeding Levels. 0, 100, 500, and 2,500 ppm.**

Duration. Time needed to produce one generation, two litters of offspring.

* Brain, heart, lungs, liver, spleen, kidney, testis, stomach, thymus, adrenal, pituitary, ovary, epididymus, fallopian tube, prostate, uterus, urinary bladder, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eye, thoracic aorta, spinal cord, trachea, pancreas, thyroid, parathyroid, salivary gland, and exorbital lacrimal gland from 2,500-ppm rats (and controls).

** [redacted] Dietary levels are of active ingredient, methyl 2-benzimidazolecarbamate.

BEST AVAILABLE COPY

Reproductive Performance. See table, below.

Feeding Level (ppm)	Av. No. of Pups/Litter (Born)	(Born Alive)	Indices* (%) F.I.	G.I.	Viab.	L.I.	Av. Weanling Wt. of Pups (g)
	---F_{1a} Litter---						
0	12.3	12.3	50	100	100	100	60
100	----	----	0	---	---	---	--
500	12.2	11.9	67	100	92	100	60
2,500	10.5	10.5	67	100	100	100	61
	---F_{1b} Litter---						
0	14.0	14.0	33	100	100	85	56
100	----	----	0	---	---	---	--
500	8.0	7.0	67	100	84	96	62
2,500	11.0	10.5	33	100	95	100	61

"No-Effect Level." 2,500 ppm (however, we note, a higher "effect" level was not tested).

Benomyl--*in vitro* test for effect on activity of cholinesterase, in PP #s. 1F1010.

Test was modified assay of Hobbiger *et al.* (J. Econ. Ent. 51, 324-9 (1958)) in which acetylcholine is added to test system after candidate inhibitor has been incubated with acetylcholinesterase of bovine erythrocytes for a specified period of time.

Test determines "acetylcholinesterase inhibition constant," K_I (concentration of inhibitor necessary to give 50% inhibition of enzyme).

$K_I = 4.5 \times 10^{-3}$ was found; whereas K_I's, determined by same procedure, for methomyl and carbaryl = 3.2×10^{-7} and 1.4×10^{-6}, respectively.

* Indices are, respectively: Fertility Index, per cent pregnancies of matings; Gestation Index, per cent live litters of pregnancies; Viability Index, per cent 4-day survivors of births; and Lactation Index, per cent 21-day survivors of 4-day survivors.

BEST AVAILABLE COPY

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

In vitro, then, benomyl inhibits cholinesterase very little. Compared to such standard carbamate-, cholinesterase-inhibiting pesticides as methomyl and carbaryl, it inhibits only 1/10,000th or 1/1,[illegible]th as much.

Teratological study on benomyl in rats, Haskell Laboratory Report No. [illegible], dated July 9, 1970. Submitted in PP No. [illegible], amended July 15, 1970.

No. of Animals. 26 to 28 (pregnant Charles River-CD) F rats/group.

Feeding Levels. 0, 100, 500, 2,500, and 5,000 ppm* in diet of rats from 6th through 15th days of gestation.

Duration. Twenty days of gestation. All rats killed then.

Body Weight and Food Consumption. No effect (on maternal rats) except for slightly lower food consumption in 5,000-ppm rats.

Clinical Signs. No effect (on maternal rats).

Gross Pathology. No effect (on maternal rats).

Teratologic Data. No effect on: number of implantation sites,*** number and location of live fetuses,**** dead fetuses,***** and resorption sites****** (in respective uterine horns); body weight, crown-rump length, and sex of fetuses; type or incidence of gross external, gross visceral,** or skeletal anomalies** in the fetuses.

"No-Effect Level." 5,000 ppm (but no higher level tested).

* [redacted]

** Studied, respectively by Wilson's method (fixation of fetuses in Bouin's fluid, followed by free-hand razor blade sectioning) and staining of skeleton with Alizarin, followed by clearing.

*** Implantation sites/pregnant female = 9.3, 9.[illegible], [illegible], [illegible], and 1[illegible], respectively in order of dosage = 0, 100, 500, and 2,500 ppm.

**** Live fetuses/litter= 8.8, 9.3, 9.0, 9.1, and 1[illegible], same order.

***** There were no dead fetuses.

****** Total resorption sites, % of implantation sites, = 5.1, 5.8, 2.7, 6.9, and 1.6, same order.

BEST AVAILABLE COPY

Teratologic study on benomyl in albino rabbits, Hazleton Laboratory Report, dated July 15, 1968, submitted with PP No. 1F1010.

We judge following summary to be a fair appraisal of results of study. We add selected values, below (in footnotes), to illustrate findings.

"The purpose of this study was to evaluate the potential of Fungicide 1991 (benomyl, Code No. IRT-1991-99, powder, approximately 50% active ingredient) for embryotoxic and/or teratogenic effects in (New Zealand White) albino rabbits. The test material was administered in the diet (Purina Rabbit Chow, available ad lib.) at dose levels of 0, 100, and 500 ppm (to 15 each artificially impregnated does/group on days 8-16, inclusive, of gestation).

"There were no maternal deaths during the study. One abortion occurred in the low level group. Tissue masses which were apparent fetuses and dead pups were found in the cage pans of one low-level doe and one high-level doe prior to initiation of the treatment period. Both of these animals were sacrificed on Day 6 and were excluded from the study. A total of 34 of 43 does used in this study (excluding the two does which were sacrificed) became pregnant (12 control, 13 low level, and nine high level).

"The appearance, behavior, body weight gain,* and food consumption of the test animals were, in general, comparable to the controls. No evidence of a compound-related effect was noted in the following criteria: Findings from gross necropsies performed on the does; the number and placement of implantation sites,** resorption sites,*** or live or dead fetuses**** from Caesarean deliveries; weight and length of fetuses, fetal external appearance, and gross visceral anatomy; the number of live and dead pups from full-term litters,***** pup weight and length, external appearance, and gross visceral anatomy. The development and structure of test fetal and pup skeletons (studied after alizarin staining and clearing) were comparable with the control animals and with accumulated control data.

"Dietary administration of Fungicide 1991 (benomyl) to female albino rabbits from Day 8 through Day 16 of gestation (at 100 or 500 ppm in the diet) had no discernible effect on fetal development."

---

* Mean weight gain during 3-week period for controls, 100-, and 500-ppm females is 413, 421, and 369 g, respectively.

** Implantation sites, 7.3, 7.3, and 8.0/maternal rabbit--control to high-level groups.

*** Resorption sites, 0.3, 0.9, and 0.2/maternal rabbit (0- to 500-ppm).

**** Live fetuses, 6.8, 6.0, and 6.6/maternal rabbit and dead fetuses, 0.2, 0.4, and 1.0/maternal rabbit--same progression.

***** Live pups, 6.8, 6.0, and 5.5/maternal rabbit and dead pups, 2.0, 0.6, and 0.3/maternal rabbit--same progression as above.

BEST AVAILABLE COPY

EVALUATION:

To our previous estimates of "no-effect levels" for benomyl and/or metabolites (in our memo of March 25, 1970, PP No. 0F0906, p. 11) can be added these new ones:

Study	"No-Effect Level"
Dog chronic, benomyl	At least 100 ppm (tentative)
Rat subacute, metabolite*	2,500 ppm**
Rat reproduction, 1-generation, 2-litter, metabolite*	2,500 ppm**
Rat teratologic, benomyl	5,000 ppm*
Rabbit teratologic benomyl	500 ppm**

* Metabolite is methyl 2-benzimidazolecarbamate.

** Value is highest level tested in study.

Also, acute lethal dose to rat of methyl 2-benzimidazolecarbamate exceeds 11 g/kg body wt. A 1-g/kg dose damages testis.

Regarding effect of benomyl on cholinesterase when tested in vitro, Petitioner has shown inhibition is very slight, e.g., 1/1,000th (or less) of that caused by carbaryl or methomyl--each a standard carbamate-, cholinesterase-inhibiting pesticide. (Nor are in vivo cholinergic effects of benomyl or metabolite noted anywhere in toxicity studies described in various benomyl petitions.)

Petitioner has now satisfactorily fulfilled requests we made for additional toxicity data on benomyl and metabolite, methyl 2-benzimidazolecarbamate (DI memo of March 25, 1970, PP No. 0F0906).

To date (May 3, 1971), dog chronic study shows lowest "no-effect level" for benomyl; it equals at least 100 ppm or 5.5 mg/kg body wt/day. (Since "no-effect levels" for methyl 2-benzimidazolecarbamate--in subacute rat or rat reproduction study--exceed this, on either ppm- or mg/kg/day-basis, the ADI, based on it applies to this metabolite as well.)

BEST AVAILABLE COPY

Based on dog "no-effect level," and on 100:1 safety factor, allowable daily intake (ADI) for humans is 0.025 mg/kg body wt/day (1 ppm in diet).

Maximum residues of benomyl to be expected in an average human daily diet, if all tolerances requested in petitions listed in title of this memo are granted (cf. accompanying table) total 0.5 ppm, whole-diet basis.

Since total residues to be expected in the average daily diet of a human in the U. S., should all presently requested tolerances for benomyl be granted, are less than the ADI calculated from available toxicity data, these tolerances will be safe.

For consideration of safety of any tolerances on benomyl which may be asked for in the future, however, we will need the studies asked for by Dr. Davis (report of April 30, 1971, PP No. 0F1000), i.e., "a detailed histopathology examination (and report) including fat stains on liver and iron stains on bone marrow....on the 500-ppm and 100-ppm dogs."

CONCLUSIONS:

1) Tolerances on benomyl asked for in PP's Nos. 0F0906, 0F1000, 1F1010, 1F1033, and 1F1045 (listed in title of this memo) are safe.

2) For consideration of safety of any tolerances on benomyl which may be asked for in the future, we require further studies on tissues from the dogs fed benomyl for 2 years. They are specified in Dr. K. J. Davis' memo of April 30, 1971, in PP No. 0F1000, viz. "a detailed histopathology examination (and report) including fat stains on liver and iron stains on bone marrow....on the 500- and 100-ppm dogs."

Mary L. Qualls, Ph.D.
Toxicology Branch
Pesticides Tolerances Division

cc:
OGFitzhugh
JCCummings
PSO/EPA
Perrine Br.
Atlanta Br. (Clewis)
PP Nos. 0F0906, 0F1000,
1F1010, 1F1033 & 1F1045

MLQualls/ccw
5/5/71
RD/Init: GEWhitmore
5/4/71

40
41

BEST AVAILABLE COPY

TABLE

Benomyl tolerances, calculations of diet coverage, to date*

Tolerance at	Commodity	Fraction in diet**	Whole-diet basis (ppm)
15 ppm	apricots	0.0012	
	bean forage & hay	------	
	cherries	0.0017	
	nectarines	0.0056	
	peaches	0.0105	
	peanut hulls, forage, & hay	------	
	plums)	0.0023	
	prunes)		
	sugarbeet tops	------	
		0.0161	0.2415
10 ppm	grapes ***	0.0032	
		0.0032	0.0320
7 ppm	apples	0.0181	
	crabapples	?	
	pears	0.0032	
	quinces***	?	
		0.0213	0.1492
2 ppm	beans	0.0124	
		0.0124	0.0248
1 ppm	cucumbers	0.0073	
	melons	0.0198	
	pumpkins, winter squash, and summer squash	0.0019	
		0.0290	0.0290
1 ppm (0.2 ppm in pulp)	bananas	0.0101	
		0.0101	0.0030
0.2 ppm	peanuts	0.0060	
	sugarbeets	?	
	pecans	?	
		0.0060	0.0012

(Table continued on next page)

* See next page for footnotes

BEST AVAILABLE COPY

004678

TABLE				
0.05 ppm	milk	0.2600		
	meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep	0.0902		
		0.3500	0.0175	
		TOTAL		0.4062

* These are tolerances requested in PP's nos. 506, 536, 1005, 1010, 1036, and 1045.

** Lehman's tables in Assoc. Fd & Drug Officials Quart. Bull. 26, 149 (1962).

*** Temporary tolerance only.

BEST AVAILABLE COPY

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

Mr. Cobarly
Reviewer

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D. C. 20460

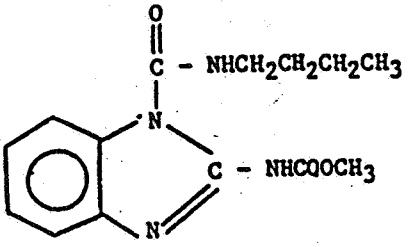
004678

Date: January 17, 1973

Reply to Attn of:

Subject:

To: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Registration No.	:	352-EXP-73G
Chemical Name	:	Methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate
Common Name	:	Benomyl
Action Requested	:	Experimental Permit
Registrant	:	E.I. DuPont De Nemours & Co. Wilmington, Delaware 19898
Structure	:	
Formulation	:	53% methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate, technical (95% min.)
		[redacted]
Use	:	Fungicide for preharvest and post harvest application site: crops (grapes, apples, pears, quinces, crabapples)

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

004678

TOXICITY DATA OF FORMULATION

Acute Rabbit Eye Irritation - Haskell Lab - June 22, 1972

A dose of 27 mg was placed in the right eye of six rabbits. The eye was examined with a hand-slit lamp at 24, 48 and 72 hours post treatment. Material tested contained 53% benomyl; [redacted]

Results

Corneal opacity was noted in 1/6, critis in 1/6, and diffuse crimson redness in 1/6.

Material is judged to be a mild eye irritant.

TOXICITY DATA OF BENOMYL

The following tests were reviewed in memos of Dr. M.L. Quaife dated March 25, 1970 (0F0906, 0G0936), May 3, 1971 (0F0906, 0F1000, 1F1010, 1F1033, 1F1045), and January 3, 1972 (1F1145, 2F1192, 2G1197); 2F1289, 2F1290, 2F1291.

Acute oral - Rat	LD_{50} > 9590 mg/kg
Acute dermal - Rabbit	LD_{50} >10,000 mg/kg
Acute inhalation - Rat	LC_{50} >1.37 mg/liter air
90-day feeding study - Rat (72% W.P.)	Systemic NEL 500 ppm
90-day feeding study - Dog (51.5% W.P.)	Systemic NEL 500 ppm
*2-year feeding study - Rat (72% and 52%)	Systemic NEL 2500 ppm
*2-year feeding study - Dog (72% and 52%)	Systemic NEL 500 ppm
*3-generation reproduction - Rat (72% and 52%)	Systemic NEL 100 ppm
Teratology - Rat (53.5%)	Negative at 5000 ppm
Teratology - Rabbit (INT-1991-99)	Negative at 500 ppm
Acute oral - Rat (metabolite*)	LD_{50} >17 g/kg
90-day feeding study - Rat (metabolite*)	Systemic NEL 2500 ppm
3-generation reproduction - Rat (metabolite*)	Systemic NEL 2500 ppm

* The different samples used in this study were varied in the active ingredient concentration. Some contained 72.2% and others 51.5%.

INFORMATION WHICH MAY REVEAL THE IDENTITY OF AN INERT INGREDIENT IS NOT INCLUDED

§ 180.294 Benomyl; tolerances for residues

Tolerances are established for residues of the fungicide benomyl (methyl 1-(butylcarbamoyl)-2-benaimidazolecarbamate) in or on raw agricultural commodities as follows:

15 parts per million (from postharvest and/or preharvest application) in or on apricots, cherries, nectarines, peaches, and plums (including fresh prunes).

2 parts per million in or on snap beans (succulent).

1 part per million in or on bananas, of which not more than 0.2 part per million (negligible residue) shall be present in the pulp after the peel is removed and discarded, from postharvest application.

0.2 part per million in or on peanuts and sugar beet roots.

SUMMARY

These data show extensive testing has been conducted on various formulations containing benomyl. These formulations are similar to but not identical to the formulation submitted for registration. Studies which were conducted with this formulation include an eye irritation (mild irritant) and a teratology study in rats (no effect at highest level tested, 5000 ppm).

An examination of the inert ingredients revealed the following:

[redacted]

004678

CONCLUSION

The aforelisted information is sufficient to support the experiment permit.

Robert D. Coberly, Biologist
Toxicology Branch
Registration Division

cc:
Ecological Effects Branch
PCCritchlow
Division Reading File
Branch Reading File
GEWhitmore

RDCoberly:km 01-18-73

LBDale:bjc
October 23, 1968

Methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate 004678

Acute Oral Toxicity (Rat) 100-66 1244-65 (Haskell labs)

Adult male Charles River-CD strain albino rats were divided into groups and given graded doses of technical methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate. The material was given as a single dose orally by intubation as a suspension in peanut oil. The animals were observed for 14 days for mortality and/or signs of toxicity.

The approximate lethal dose of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate in male albino rats was found to be greater than 9590 mg/KG. This was the maximum feasible dose.

Subacute Oral Toxicity (Rat) 100-66

12 adult male Charles River-CD strain rats were divided into 2 groups and administered 3400, or 200 mg/KG methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate orally 5 times a week for 2 weeks. The material was administered by intubation as a suspension in peanut oil. The animals were returned to their cages and observed for 14 days for mortality and/or signs of toxicity.

In the 3400 mg/KG dosage level 4/6 animals died. In the 200 mg/KG dosage level 0/6 animals died. Lethal doses produced weight loss and diarrhea. There were histologic changes in the stomach liver, and testis. At 200 mg/KG no clinical signs of toxicity or significant histologic changes were observed.

90 Day Feeding Study (Rat) 11-67

64 (32 male, 32 female) Charles River-CD strain rats were divided into 4

(Should be 16♂, 16♀/group)
MPC 8/12/64.

47

48

groups and received 0, 100, 500, and 2500 ppm methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate (as the 70% wettable powder) in their diets for 90 days. 00467.8

The animals were housed individually and observed for weight changes, pharmacologic signs of toxicity, behavioral changes, and mortality. Clinical studies including complete hematology, clinical blood chemistry and urinalysis were run on ~~all~~ 5♂/5♀ rats.

At the end of the 90 days all animals were sacrificed and complete gross and microscopic histologic studies were performed. Organ weights and organ to body weight ratios were recorded for all animals.

All controlled and test animals survived, except 1 male at 100 ppm. The latter death was unrelated to the feeding of the test compound.

The growth of all animals in the test groups were comparable to control.

The food consumption and efficiency of all test groups was comparable to control.

There were no medical signs of toxic effects.

The hematology which was determined at pre-test and at 30, 60, and 90 days revealed no changes attributable to the test material.

The urinalysis which was conducted at 30, 60, and 90 days revealed no changes attributable to the test material.

The plasma alkaline phosphatase and glutamic-pyruvic transaminase determined at 30, 60, and 90 days for control and 2500 ppm groups were within normal limits.

48

#MPE 5/13/64

All organ weight values were comparable to control except there were higher liver weights for females at the 2500 ppm level. The latter finding is not believed to be of biological significance as the heavier livers were histologically normal.

The histopathology revealed no changes that could be attributable to feeding of the test compound.

Acute Dermal Toxicity (Rabbit)

Adult albino rabbits were given dermal applications of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate as the 50% wettable powder to the intact and abraded abdominal skin at dosages ranging from 464-10,000 mg/KG. The sites of application were wrapped with rubber damming so as to hold the compound in contact with the skin for 24 hours.

The animals were housed individually and observed for 14 days for mortality, signs of toxicity, and irritation.

The LD_{50} was found to be >10,000 mg/KG. There were no deaths. Except for dermal irritation, there were no signs of toxicity.

Skin Irritation and Sensitization (Guinea Pig) 174-6C

For the primary irritation, 30 male guinea pigs were divided into 3 groups and received 0.05 gms of the test material as the technical chemical rubbed into the intact shaved skin as a 10, 25, and 40% paste in dimethyl phthalate.

For the sensitization tests, 5 animals received 9 applications of 40% paste on abraded skin during a 3 week period. 5 guinea pigs received intradermal injections of 0.1 ml of a 1% solution of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate in dimethyl phthalate. After a 2 week rest period a

challenge test was done on intact and abraded skin, which was repeated 2 and 5 weeks later.

004679

The test showed no skin irritation. Moderate sensitization was produced. There were stronger reactions in animals receiving the intradermal injections. The compound is not a dermatitis hazard.

Eye Irritation (Rabbit) 81-66 5/24/66

1 albino rabbit received 10 mgs of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate instilled into the conjunctival sac of both eyes. 1 rabbit received 10 mgs. of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate as a 10% solution in propylene glycol in both eyes. 1 eye of each rabbit was washed with water 20-25 seconds after treatment; the other eyes were not washed. The animals were returned to their cages and observed 2, 4, 8, 24 and 72 hours after treatment.

There was a mild transitory conjuncitivitis with minor corneal effects and slight iritic congestion. Prompt washing minimized the ocular reactions; all eyes were clinically normal 7 days after treatment.

Acute Inhalation Toxicity (Rats)

6 albino rats were placed in an inhalation chamber and exposed for 4 hours to an atmospheric dust of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate at a concentration of 1.37 mg/Liter. The animals were observed for behavioral reactions while in the chamber and for 14 days after removal.

The LC_{50} of methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate was found to be $>$1.37 mg/Liter. All of the animals survived without clinical signs of toxicity.

50

004678

CONCLUSIONS

Methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate is a fungicide used in the control of fungus diseases of ornamentals, fairways, athletic fields, etc.

The compound has a moderate oral inhalation and dermal toxicities. It is only a mild eye and skin irritant.

The product "Benlate" Fungicide is adequately labeled and should produce no undue human health hazard.

Oct 23, 1968

Methyl-1-(butylcarbamoyl)-2-benzimidazole carbamate

DATA SUMMARY

004678

174-65	Acute Oral Toxicity (Rat) Tech	:	Approximate lethal dose 9590 mg/KG (maximum feasible dose)
180-66	Subacute Oral Toxicity (Rat) Tech	:	14 days - no deaths at 200 mg/KG/day 4/6 at 3400 mg/KG/day
11-67	90 Day Feeding Study (Rat) (70% WP)	:	0,100, 500 and 2500 ppm. No toxic effects. "No-effect level" ≥2500 ppm.
Nazelton 201-214	Acute Dermal Toxicity (50% WP) (Rabbit)	:	LD_{50} ≥10,000 mg/KG. Slight dermal irritation.
174-66	Skin Irritation and Sensitization (Guinea Pig) Tech.	:	10, 25 and 40% paste in dimethyl phthalate. No skin irritation; moderate sensitization, no dermatitis hazard.
81-66	Eye Irritation (Rabbit) Tech	:	Mild transitory conjunctivitis; minor corneal effects and slight iritic congestion. Washing minimized ocular reactions.
	Acute Inhalation Toxicity (Rats) (50% WP)	:	LC_{50} ≥1.37 mg/l.

52