2/18/92

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

009267

FEB 18 1992

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Proposed Tolerance for Combined Residues of Iprodione, its isomers, and its Metabolites in or on Peppers

TO: Hoyt Jamerson PM 43
RD (H7505C)

FROM: K. E. Whitby, Ph.D. K E Whitby 1/30/92
Section, II
Toxicology Branch II/(HED) (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 1/30/92
Section Head
Toxicology Branch II/(HED) (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 2/4/92
Chief, Toxicology Branch II/(HED) (H7509C)

EPA MRID No. 419993-00
HED Project No. 1-2412
Caswell No. 470A

Action Requested

Two actions were requested for Iprodicne:

1) Review a dermal sensitization guinea pig study (§81-6) which evaluated Iprodione technical (MRID 405676-02). The DER for this study is attached.

2) IR-4 proposes a tolerance for combined residues of Iprodione, its isomer, and its metabolite in or on peppers at 6.0 ppm. Please evaluate and provide summary of available studies in support of the proposed tolerance.

Requested Use and Tolerance

Rovral 4F (EPA Reg No. 264-482) or Rovral 50% WP (EPA Reg No. 264-453) will be applied to the lower portion of the pepper plant and surrounding soil surface as 2.0 pints/acre with a minimum of 40

gallons of water/acre to control Rhizoctonia Root Rot (Rhizoctonia solani). In this manner of use the it may be applied by ground equipment after seedlings have become established, followed by a second application 10 days later; the last application may be made on the day of harvest.

Rovral 4F (EPA Reg No. 264-482) or Rovral 50% WP (EPA Reg No. 264-453) will be applied as a foliar spray using 3 nozzles/row on peppers as 1.0 to 2.0 pints per acre with a minimum of 40 gallons of water/acre to control Alternaria Fruit Rot (Alternaria spp.) or Botrytis Fruit Rot (Botrytis spp.). These diseases may be controlled by applying when conditions become favorable for disease development. Foliage may be subsequently sprayed on a 14 day schedule or prior to peak infection periods. The use of this agent for the control of these diseases permits a maximum of 4 sprays/crop (i.e. if 2 applications are made for root rot control, only 2 additional sprays may be made for fruit rot control).

1. TOXICOLOGY DATA AVAILABLE

GUIDELINE/TEST/CHEMICAL	REQUIRED	TOX CATEGORY/ PERFORMED	CLASSIFICATION
TECHNICAL			
§81-1 Acute Oral/Rat	Y	Y	minimum
§81-2 Acute Dermal Toxicity/Rabbit	Y	Y	minimum
§81-3 Acute Inhalation Toxicity/Rat	Y	Y	minimum
§81-4 Primary Eye Irritation/Rabbit	Y	Y	minimum
§81-5 Primary Dermal Irritation/Rabbit	Y	Y	minimum - Tox Cat 4
§81-6 Dermal Sensitization/Guinea Pig	Y	Y	supplementary
§81-7 Acute Delayed Neurotoxicity/Hen	N	N	
§82-1(a) 90-Day Feeding Study/Rodent	Y	Y	minimum
§82-1(b) 90-Day Feeding Study/Non-Rodent	Y	Y	minimum
§82-2 21-Day Dermal	Y	Y	under review
§82-3 90-Day Dermal	N	N	
§82-4 90-Day Inhalation/Rat	N	N	
§82-5 90-Day Neurotoxicity/Rat	N	N	
§83-1(a) Chronic Feeding/Rat	Y	Y	guideline
§83-1(b) Chronic Feeding/Non-Rodent	Y	Y	minimum
§83-2(a) Oncogenicity/Rat	Y	Y	guideline
§83-2(b) Oncogenicity/Mouse	Y	Y	guideline
§83-3(a) Developmental Toxicity/Rat	Y	Y	minimum
§83-3(b) Developmental Toxicity/Rabbit	Y	Y	minimum
§83-4 3-Generation Reproduction	Y	Y	minimum
§84-2(a) Mutagenicity - Ames	Y	Y	supplementary
§84-2(b) Mutagenicity - SCE	Y	Y	acceptable
§84-2(b) Mutagenicity - CHO cells chrom. aberr.	Y	Y	acceptable
§84-2(b) Mutagenicity - DNA damage/ repair B. subtilis	Y	Y	acceptable
§84-4 Mutagenicity - Dominant Lethal	Y	Y	minimum
§84-4 Mutagenicity - Forward Mutation	Y	Y	acceptable

GUIDELINE/TEST/CHEMICAL	REQUIRED	PERFORMED	CLASSIFICATION
§85-1 General Metabolism	Y	N	
§86-1 Domestic Animal Safety	N	N	
END USE PRODUCTS [Rovral 4F (Iprodione 41,6%)]			
§81-1 Acute Oral/Rat	Y	Y	guideline - Tox Cat 3
§81-2 Acute Dermal Toxicity/Rabbit	Y	Y	guideline - Tox Cat 3
§81-2 Acute Inhalation Toxicity/Rat	Y	Y	guideline - Tox Cat 3
§81-4 Primary Eye Irritation/Rabbit	Y	Y	guideline - Tox Cat 4
§81-5 Primary Dermal Irritation/Rabbit	Y	Y	guideline - Tox Cat 4
§81-6 Dermal Sensitization/Guinea Pig	Y	Y	guideline

Summary of Available Toxicology Data

In an acute oral LD_{50}, Rovral was classified in Toxicity Category 3; the LD_{50} for males was 1540 and for females was 1160 mg/kg. In a developmental toxicity study in rats the maternal NOEL was > 200 mg/kg (HDT). The developmental LEL was 200 mg/kg based on reduced fetal weight and delayed fetal development. In a rabbit developmental toxicity study with Iprodione the maternal NOEL was 20 mg/kg (LDT) the maternal LEL was 60 mg/kg based on reduced body weight gain and increased numbers of abortions at 200 mg/kg (HDT). The LEL for developmental toxicity was 200 mg/kg; the findings included skeletal variations such as 13th rib and malaligned sternebrae.

In a two year rat feeding/carcinogenicity study evaluating 125, 250, and 1000 ppm, the systemic NOEL was > 1000 ppm (HDT). The systemic NOEL in an 18 month feeding study in mice was > 1250 ppm (HDT); cancer was not induced in either study. The NOEL in a one year dog study was 100 ppm. The LEL was 600 ppm (hematopoietic changes- RBC, Hgb, and Hct counts were lower than in the controls). Increased and relative liver and adrenal weights, increased liver alkaline phosphatase, SGOT, SGPT, and LDH enzyme levels, and a slight increase in hypereflection in the eyes were observed in the 3600 ppm (HDT) group.

2. DATA GAPS

The Phase IV Review of List B chemicals revealed studies that can no longer be used to support the human safety of proposed tolerances for Iprodione for commonly consumed raw agricultural commodities. In addition, the registrant has agreed to perform a number of studies which have not yet been received.

<u>Previously Identified</u>

§81-1 Acute Oral[a]	Study due 5/24/92
§81-5 Primary Dermal[a]	Study due 5/24/91
§81-6 Dermal Sensitization/Guinea Pig	study (MRID 40567602) has been submitted and reviewed - coregrade supplementary
§82-1(a) 90-Day Feeding Rat	Previous study (Acc. No. 232702) is not acceptable; not required if new chronic study in rats is acceptable. Study due 5/24/92
§82-2 21-Day Dermal	Previous study (MRID 00157404) is not acceptable. The new study is currently under review (MRID 420232-01).
§83-1(a) Chronic Toxicity/Rat	Previous study (MRID 00071997) is not acceptable; registrant will submit a new study. Registrant may combine oncogenicity and chronic study.
§83-2(a) Oncogenicity/Rat	Study due 8/24/93

§83-2(b) Oncogenicity/Mouse Previous study (MRID 00070963) is not acceptable; registrant will submit a new study. Study due 8/24/93

Identified Under Phase IV Review of List B Chemicals

§81-3 Acute Inhalation	Study due 9/30/93
§81-6 Dermal Sensitization/Guinea Pig	Study due 9/30/92
§85-1 General Metabolism	Study due 9/30/93

a= The registrant offered to perform these studies in their phase IV response

3. REFERENCE DOSE (R_fD)

The R_fD for Iprodione is 0.04 mg/kg of body weight/day. This is based on a NOEL of 4.2 mg/kg/day (100.0 ppm) from a 1-year dog feeding study and a safety factor of 100. This value has been approved by HED (12/19/86) and was verified by the Agency reference dose committee (7/15/87). The total amount of the tolerance granted should not exceed the R_fD.

4. EFFECT OF TOLERANCE ON R_fD

A DRES analysis of the impact of the proposed tolerance on the R_fD should be performed.

5. REGULATORY ACTIONS PENDING

There currently are a number of pending regulatory actions for Iprodione.

a) 264-453 - (correspondence) rotational crop statement

b) 264-LEN - registration notice letter of rice to be written

c) 7F03545 - there is an action pending with the Tolerance Support Chemistry Branch for residue data on tomatoes.

d) 1G03998 - there are actions pending in the Tolerance Support Chemistry Branch and in Tox Branch II for a petition for temporary tolerance (EUP) for use on cotton seed.

e) 264-453 - (correspondence) label change.

f) 264-482 - (correspondence) label change.

g) 264-EUP-IO action pending in EFGB

6. PUBLISHED TOLERANCES

The established tolerances for residues of the fungicide iprodione

[3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolite 3-(3,5-dicholorphenyl)-2,4-dioxo-1-imidazolidine-carboxamide in numerous raw agricultural commodities are published under 40 CFR 180.399 and in food or animal feed additives under 21 CFR 193.251 and 21 CFR 561.263.

7. DISCUSSION

The toxicology data base for Iprodione is adequate for this regulatory action. Based on the currently acceptable data, as well as the NOELs in the unacceptable chronic studies, there does not appear to be a significant risk to human health. The impact of this request on the R_fD will be determined by a DRES analysis. Therefore, TB II does not object to the proposed tolerance at the present time.

009267

Primary Reviewer: K. E. Whitby, Ph.D. K. E. Whitby 1/23/92
Review Section II, Toxicology Branch II / HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 1/28/92
Section Head, Review Section II, Toxicology Branch II / HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization-Guinea Pigs (§81-6)

CASWELL NUMBER: 470A

MRID NUMBER: 405676-02

TEST MATERIAL: Iprodione Technical

SYNONYMS: MRD-87-098

STUDY NUMBER: 209821/MRD-87-098

SPONSOR: Rhone-Poulenc Inc.
Research Triangle Park, NC

TESTING FACILITY: EXXON Biomedical Sciences, Inc.
Toxicology Laboratory
Mettlers Road, CN 2350
East Millstone, New Jersey 08875-2350

TITLE OF REPORT: Iprodione Technical - Dermal Sensitization Test in the Guinea Pig Buehler Method

AUTHOR(S): G.W. Trimmer, B.A.

REPORT ISSUED: November 13, 1987

CONCLUSION:

TOXICITY CATEGORY non-sensitizer

CLASSIFICATION: Supplementary

This study does not satisfy the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

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I. MATERIALS

009267

1. Test Compound:
Description - small white pellets
Lot # - 85120-1
Purity - Report states that the Sponsor indicated the purity to be 95.8 %.
The report states that "determination of the stability, identity, strength, and composition or other characteristics which will apprcpriately identify the test substance is the responsibility of the Sponsor....No analysis for stability uniformity and concentration of Iprodione in the vehicle were performed by EBSI." Two archival samples of Iprodione technical were collected by the Compound Preparation Department and stored at room temperature.

Negative Control: Acetone

Positive Control: DNCB was tested concurrently using animals from the same shipment. The source was Kodak, Batch No. A11M. Ethanol (70%) was the vehicle during the induction phase. Prior to dilution with 80% ethanol, the DNCB was dissolved in 2 mL of acetone. Acetone was used as the vehicle during the challenge. There were 10 animals in this group.

Dosing was initiated September 30, 1987. The in vivo phase of the study was terminated November 13, 1987.

Iprodione was ground and diluted in acetone to form a 10% w/v solution for the induction and challenge phase, or to form a 5% w/v solution for the rechallenge phase.

2. Test Animals:

Species & Strain: Hartley Albino Guinea Pigs
Source: Charles River Breeding Laboratories
Kingston Facility
Stone Ridge, New York
Number: 15 ♀ (nulliparous and non-pregnant)
10 ♀ (additional) for positive control testing
5 ♀ (additional) for day 41 irritation control dosing (rechallenge)
Age: approx 5 weeks at beginning of dosing
Weight: 328 to 368 g
Quarantine and acclimation period: 15 days

More animals than required for this study were purchased and acclimated. All animals were examined by a Staff Veterinarian; those found to be unsuitable were excluded. The animals which were used for this investigation were selected from those examined by the veterinarian using a computer generated body weight sorting program.

0009

A signed statement that no claim of confidentiality was made for this study was included in this report.

A quality assurance statement was signed and dated March 16, 1988.

A statement of compliance with EPA Good Laboratory Practice Standards was signed and included in this report.

II. METHODS

The technique used in this study was reported to be similar to that described by E.V. Buehler in: "Delayed Contact Hypersensitivity in the Guinea Pig." Archives of Dermatology. Vol. 91: 171, 1965.

Experimental Design

Phase	Days Treated	Volume	Treated Group	Irritation Control Group
No. of Animals			10	5
Induction	0, 2, 5, 7, 9, 11, 14, 16, 19,	0.4 mL	10% w/v Iprodione in acetone	untreated
Challenge	33	0.4 mL	10% w/v Iprodione in acetone	10% w/v Iprodione in acetone
Rechallenge	41	0.4 mL	5% w/v Iprodione in acetone	5% w/v Iprodione in acetone*

* Five additional animals were dosed with 5% Iprodione in acetone for rechallenge dosing.

A. General: On two occasions the humidity (80 and 76%) was found to exceed the limit specified in the protocol (40 - 70%). This was not believed to have adversely affected the outcome of the study. Animals were checked for viability twice daily during the acclimation period and during the study (except for weekends when they were examined once daily). Clinical observations were made as to the nature, onset, severity, and duration of toxicological signs on days 0, 7, 14, 21, 28, and 35 and prior to terminal sacrifice. The treated animals were also examined on day 42.

Food (Purina Certified Guinea Pig Chow) and water were available ad libitum throughout the study. Body weights were recorded on days 0, 7, 14, 21, 28, 35 and at the end of the study (prior to terminal sacrifice). Body weights of treated animals were also recorded on day 42. Animals were housed individually during the study.

B. Induction: Concentrations for induction and challenge were determined in a range finding study (Primary Irritation Test). This study evaluated 0.4 ml of 10, 25, 50, and 100% w/v using acetone as the vehicle.

Iprodione was diluted in acetone (10% w/v). On the day prior to each topical induction of the test material, a 4 X 4 cm area on the dorsal surface of the animal was clipped with an Oster A-2 Small Animals Clipper with size 40 blades. The test material was applied beneath a 2 X 2 Webril cotton pad on a 37 X 40 mm Readi-Bandage (Parke-Davis) and firmly secured to the torso of the animals with elastic adhesive bandaging (Elastoplast) on days 0, 2, 5, 7, 9, 12, 14, 16, and 19. The irritation control group was untreated. The pads and bandaging were removed from treated animals after approximately 6 hours. The skin was then wiped of the test material. Dermal responses were observed 24 and 48 hours after each of the induction applications. Exposure was performed 3 times weekly for a total of 9 applications.

The positive control group was prepared, dosed, terminated and evaluated in the same manner as the Iprodione group. The positive control group was induced with 0.1% DNCB in 70% ethanol, on the same days as the Iprodione treated group except for the sixth dose which was administered on day 11 instead of day 12. The positive control group study was initiated on September 30, 1987 and terminated on November 12, 1987.

C. Challenge: Thirty-three days after the initial topical induction, all treated animals received the challenge by occlusive topical application. A comparison of the treated and irritation control group dermal responses was the basis of the evaluation of the sensitization potential.

The right flank in the abdominal region was clipped in an area of approximately 5 X 5 cm on the day prior to the challenge dose. Iprodione (10% w/v) in acetone was topically applied as 0.4 mL to the prepared area of all treated and irritation control group animals. The test material was applied 2 X 2 cm Webril cotton pad, covered by a 37 X 40 mm Readi-Bandage and secured by an elastic adhesive bandage. This was done in a manner to prevent adhesive coming into contact with the skin at the challenge site. The bandaging was removed after 6 hrs. Dermal responses were observed at approximately 24, 48, and 72 hours after removal of the challenge patch (days 34, 35, and 36 respectively), and 24, 48, and 72 hours after removal of the rechallenge patch (days 42, 43, and 44 respectively) according to the Draize method.

The positive control group was challenged on day 33 with 0.4 mL of 0.1% DNCB in acetone.

Iprodione treated animals were rechallenged on day 41 with 5.0% w/v Iprodione in acetone as previously challenged. Rechallenge was performed on day 41 as opposed to 40 as stated in the protocol due to a delay in contact with the Sponsor. The basis of the evaluation of sensitization was the comparison of the reaction of the treated animals with the control animals that received a single epidermal exposure to the test

material. Control responses were used to distinguish true sensitization from local irritation produced by the same concentration of test material.

On completion of the final dermal observations all animals were weighed and euthanized by CO_2 asphyxiation and discarded without further examination (day 43 for the irritation control group, and day 44 for the treated group).

III. RESULTS

There were no deaths in the treated or irritation control groups. One positive control animal was euthanized due to a broken leg on day 13. During the in life observations of the treated group, four of the ten animals were occasionally noted to have soft stools. Two of these animals were also found to be emaciated. Additional findings in these animals included unthrifty coat, and staining in the ano-genital area. The individual in life observations for the irritation control group revealed no observable abnormalities. The two emaciated animals were offered water in a bowl to attempt to replace fluids lost to soft stool and to stimulate an increase in food consumption. An increase in body weight was observed for all animals by termination of the study.

Desquamation was observed in four of the ten treated animals during induction. Eschar was observed in two treated animals during induction.

The tabulated incidence of challenge dermal scores for the irritation control and treated animals is attached. In addition, the positive control individual dermal scores and the tabulated incidence of challenge dermal scores are also attached.

IV. CONCLUSIONS

The erythema and desquamation noted in this investigation may have been caused by the acetone vehicle and or the test substance (primary dermal irritation). Iprodione, as tested in this investigation may be considered to be a non-sensitizing agent.

Toxicity Category - non-sensitizing agent

V. CLASSIFICATION: Supplementary

This study does <u>not</u> satisfy the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs. Analyses to determine the uniformity, concentration, or stability of the test material in the vehicle were not included in the report. The frequency of preparing the dosing solution was not stated. The pH of the test material was not provided. This study may be upgraded upon satisfactory review of the registrants response to the deficiencies listed below.

DERMAL SENSITIZATION TEST IN THE GUINEA PIG: 209821, MRD-87-098 009267

TABLE 2 - INCIDENCE OF CHALLENGE DERMAL SCORES

GROUP - TREATED

		DERMAL SCORES 0	1	2	3	4	
DAY 34	ERYTHEMA	3	6	1	0	0	N= 10
	EDEMA	10	0	0	0	0	N= 10
DAY 35	ERYTHEMA	4	6	0	0	[illegible]	N= 10
	EDEMA	10	0	0	0	0	N= 10
DAY 36	ERYTHEMA	7	3	0	0	0	N= 10
	EDEMA	10	0	0	0	0	N= 10
DAY 42	ERYTHEMA	6	4	0	0	0	N= 10
	EDEMA	10	0	0	0	0	N= 10
DAY 43	ERYTHEMA	8	2	0	0	0	N= 10
	EDEMA	10	0	0	0	0	N= 10
DAY 44	ERYTHEMA	9	1	0	0	0	N= 10
	EDEMA	10	0	0	0	0	N= 10

TABLE 2 - INCIDENCE OF CHALLENGE DERMAL SCORES CON'T

GROUP - IRRITATION CONTROL

		DERMAL SCORES 0	1	2	3	4	
DAY 34	ERYTHEMA	1	4	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5
DAY 35	ERYTHEMA	3	2	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5
DAY 36	ERYTHEMA	4	1	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5
DAY 42	ERYTHEMA	4	1	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5
DAY 43	ERYTHEMA	4	1	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5
DAY 44	ERYTHEMA	5	0	0	0	0	N= 5
	EDEMA	5	0	0	0	0	N= 5

DERMAL SENSITIZATION TEST IN THE GUINEA PIG: 209821, MRD-87-098

009267

APPENDIX F - POSITIVE CONTROL DATA (CONTINUED)

INDIVIDUAL DERMAL SCORES - CHALLENGE PHASE

		TIME=	DAY 3 4	DAY 3 5	DAY 3 6
JDG800F	ERYTHEMA		2	2	2
	EDEMA		1	1	1
JDG789F	ERYTHEMA		3	2	2
	EDEMA		1	1	1
JDG793F	ERYTHEMA		3	3	3A
	EDEMA		1	2	2
JDG816F	ERYTHEMA		X	X	X
	EDEMA		X	X	X
JDG818F	ERYTHEMA		3	3	2
	EDEMA		1	2	1
JDG803F	ERYTHEMA		3	3	2
	EDEMA		1	2	1
JDG786F	ERYTHEMA		3A	3	2
	EDEMA		2	2	1
JDG814F	ERYTHEMA		2	2	2A
	EDEMA		0	1	1
JDG794F	ERYTHEMA		4E	4E	4E
	EDEMA		3	3	2
JDG802F	ERYTHEMA		3	3	2
	EDEMA		1	1	1

NOTE: A - ATONIA
E - ESCHAR
X - ANIMAL DEAD

APPENDIX F - POSITIVE CONTROL DATA (CONTINUED) 009267

INCIDENCE OF CHALLENGE SCORES

		DERMAL SCORES 0	1	2	3	4	
DAY 34	ERYTHEMA	0	0	2	6	1	N= 9
	EDEMA	2	6	1	1	0	N= 9
DAY 35	ERYTHEMA	0	0	3	5	1	N= 9
	EDEMA	0	4	4	1	0	N= 9
DAY 36	ERYTHEMA	0	0	7	1	1	N= 9
	EDEMA	0	7	2	0	0	N= 9

VI. STUDY DEFICIENCIES

1. Determination of the stability, identity, strength, and composition or other characteristics which appropriately identify the test substance were not included in this report. The pH of the test material was not provided. No analysis for stability, uniformity and concentration of Iprodione in the vehicle were performed by EBSI.