4-8-82 RCB

Perfetti

Fulepetetan

Toxicology Branch/HED Review

To: *Henry Jacoby P M 21*

Registration No(s).: *359-685* *CFR 180-539*

Pesticide Petition No(s).: *2F 2596* *Acc. No 070441 070443*

Caswell No(s).: *470 A*

Chemical(s): *Iprodione (Rovral)*

RAC(s) - tolerance(s): *Request for tolerances of 10 ppm in appricots , nectarines, peaches , plums imc. prunes and cherries.*

Inert(s) cleared 180.1001: *(e) Yes*

% of ADI occupied: Existing: *0.03* Resulting: *2.58*

Resulting % increase in TMRC: *From 0.0045 to 0.3876*

Attached (?): ADI printout: YES/~~NO~~; TOX "one-liner": YES/~~NO~~; DER: ~~YES~~/NO

Existing regulatory actions against registration: *None*

RPAR status: *Is not in the R P A R list*

New Data: *None Submited / Data required on behalf of this action (next page)*

Data considered in setting the ADI: *Rat reproduction , 3 generations , study .NOEL= 500ppm*

Data gaps: *The three following study has been classified as supplementary data ; Acute dermal toxicity, second teratology study and mutagenicity other test. The studies classified as supplementary data must be upgraded.*

Recommendation: *Granting this request will not present a hazard since the ADI is not exceeded*

Comments: *A one year dog feeding study has been initiated and the report will be submitted within a year.* (Info obtained by phone by The PM) *The study 3 generation reproduction -rat has been used to find the ADI instead of the 3 month dog feeding study. It will lead to a better appriasal of the toxicity potential of the product*

Reviewer: *Alex Aasse* Date: *3-31-82*

Section Head: *William M Butler* APR 8 1982

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Data required

		Classification
Acute oral -rat	*3,700 mg/kg*	*m*
Acute dermal -rabbit	*30,000mg/kg male -5,000 mg/kg female*	*s*
Acute inhalation-rat	*3.29mg/l/4h*	*m*
Primary eye-skin-rabbit	*Not an irritant*	*m*
90 day feeding -dog	*NOEL 2,400 ppm - LEL 7,200 ppm*	*m*
Teratology - rat	*NOEL 400 mg/kg /day*	*m*
Teratogenicity - rabbit	*NOEL 400 mg/kg/day*	*s*
Chronic oncogenicity -rat 24 month feeding	*NOEL 1,000 ppm*	*m*
18 months oncogenicity -mouse	*NOEL 1,250 ppm*	*m*
Mutagenicity , dominant lethal - mouse -	*No evidence of mutagenicity at 1,500 or at 6,000 ppm*	*m*
Three generations reproduction study -rat	*NOEL 500 ppm*	*m*

Justification for using the 3 generation reproduction study -rat instead of the 3 month dog feeding study, to find the A D I

The NOEL in the 3 months feeding study -(dog)was found at the 2,400 ppm dose level. The LEL was 7,200 ppm and the symptom observed was muscular atony , no other signs of toxicity were reported

The three generation reproduction study (rat) with a NOEL of 500 ppm and with no toxic signs observed in the parent animals, will give a better indication of the potential toxicity of the material . The only adverse effect observed during the 3 generations study was the post natal pupgrowth for group 1V that was reduced in a minor percent as compared with group 1.

File last updated 4/1/82

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
25.000	500.00	100	0.2500	15.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Kiwi Fruit(204)	10.000	0.03	0.00450

MPI	TMRC	% ADI
15.0000 mg/day(60kg)	0.0045 mg/day(1.5kg)	0.03

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Unpublished,Tox Approved PP# 6G2087,0G2402

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Almonds(1)	0.050	0.03	0.00002
Apricots(3)	10.000	0.11	0.01686
Cherries(30)	10.000	0.10	0.01533
Nectarines(100)	10.000	0.03	0.00450
Peaches(114)	10.000	0.90	0.13490
Plums,inc prunes(125)	10.000	0.13	0.01993

MPI	TMRC	% ADI
15.0000 mg/day(60kg)	0.1960 mg/day(1.5kg)	1.31

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Current Action PP# 2F2596

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Apricots(3)	10.000	0.11	0.01686
Cherries(30)	10.000	0.10	0.01533
Nectarines(100)	10.000	0.03	0.00450
Peaches(114)	10.000	0.90	0.13490
Plums,inc prunes(125)	10.000	0.13	0.01993

MPI	TMRC	% ADI
15.0000 mg/day(60kg)	0.3876 mg/day(1.5kg)	2.58

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Tox Chem No.. 470A Iprodione (Rovral) File Last Updated 2-3-81 Current Date 7-11-81

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50}, mice	TECH	232701	LD_{50} = 3050 mg/kg (2630-3540)	III	Minimum
Acute oral LD_{50}, mice	TECH	232701	LD_{50} = 4.0 (3.3-4.8) g/kg - M 4.4 (3.3-5.9) g/kg - F	III	Minimum
Acute oral LD_{50}, rat	TECH	232701	LD_{50} = 3700 ± 300 mg/kg - M = 4400 (3200-6100) mg/kg -F	III	Minimum
Acute oral LD_{50}, dog	TECH	232701	Atoxic at 2000 mg/kg	III	Supplementary
Acute dermal LD_{50}, rat	TECH	232701	Atoxic at 2.5 g/kg	III	Supplementary
Acute dermal LD_{50}, rabbit	TECH	232701	Atoxic at 1 g/kg LD_{50} > 30,000 mg/kg - M > 5,000 mg/kg - F	IV	Supple-mentary
Primary dermal irritation - rabbit	TECH	232701	Not irritating at 1 g/kg	IV	Supple-mentary
Primary dermal irritation - rabbit	TECH	232701	Not an irritant	IV	Minimum
Primary dermal irritation - rabbit	TECH	232701	Not an irritant (Summary)	IV	Supple-mentary
Primary eye irritation - rabbit	TECH	232701	Not an irritant	IV	Minimum
Acute inhalation LD_{50}, rat	TECH	232701	LC_{50} = > 3.29 mg/L/4 hr.	IV	Minimum
Sensitization dermal - guinea pig	TECH	232701	Negative	IV	Supple-mentary
28-Day Oral - mice	TECH	232701	NOEL = 1,900 ppm		Supple-mentary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
~~90-Day feeding, mice~~	TECH	232701	NOEL = 1,900 ppm		Supplementary
90-Day feeding, dog	TECH	232701	NOEL = 2,400 ppm LEL = 7,200 ppm		Minimum
5-Month feeding, rat	TECH	232701	NOEL $\geq$ 1,000 ppm (highest dose tested)		Minimum
24-Month feeding, rat	TECH	097201	NOEL $\geq$ 1,000 ppm (highest dose tested)		Minimum
18-Month feeding - oncogenicity, mice	TECH	097201	NOEL $\geq$ 1,250 ppm (highest dose tested) Not carcinogenic.		Minimum
Teratogenic - rat	TECH	232712	Teratogenic NOEL $\geq$ 400 mg/kg/day (highest level tested) Fetotoxic NOEL = 200 mg/kg/day Fetotoxic LEL = 400 mg/kg/day (decrease in mean number of implantation sites) Maternal NOEL = 200 mg/kg/day Maternal LEL = 400 mg/kg/day (decrease in conception rate and food consumption)		Minimum
Teratogenic - rabbit	TECH	232712	Teratogenic NOEL $\geq$ 400 mg/kg/day (highest level tested) Fetotoxic NOEL = undetermined Maternal LEL = undetermined		Supple-mentary 000614

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity dominant lethal - mice	TECH	232712	No evidence of mutagenicity or adverse effects on fertility at 1500 or 6000 ppm dose males		Minimum
Mutagenicity - microbiologic	TECH	232712	Negative		Supplementary
3-Generation reproduction - rat	TECH	232712	NOEL = 500 ppm		Minimum

SECTION F

PROPOSED PERMANENT TOLERANCES FOR RESIDUES OF THE FUNGICIDE IPRODIONE, ITS ISOMER AND METABOLITE IN OR ON THE RAW AGRICULTURAL COMMODITY STONE FRUITS INCLUDING FRESH AND PROCESSED FRUITS

Stone Fruits

It is hereby proposed a tolerance for the combined residues of iprodione [3-(3,5-dichlorophenyl)-N-(1-methyl ethyl)-2,4-dioxo-1-imidazolidinecarboxamide], its isomer [3-(1-methyl ethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide], and its metabolite [3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine-carboxamide] in and/or on:

apricot, cherries (sour and sweet), nectarines, peaches, plums (fresh prunes)	10 ppm

Animal Products

It is hereby proposed a modified use to restrict grazing livestock in treated orchard and to restrict the feeding of cover crops, therefore, no tolerances for residues in meat, milk, poultry and eggs would be needed. Section 180.6 (a) (3).