10/31/78 RD-1009 TXR-1519

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Hummel Roth Fale petition

DATE: October 31, 1978

SUBJECT: Petition 8G2087 for Temporary Tolerance of 20 p.p.m. for Iprodione and its Isomer on Stone Fruits (Apricots, Sour and Sweet Cherries, Nectarines, Peaches, Plums and Prunes.

FROM: John E. Preston, Ph.D.
Toxicology Branch

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TO: E. Wilson, Ph.D.
PM-21

Reference numbers: Reg/EUP No. 359-EUP-58. PP # 8G2087. Product Name: ROVRAL®.

Active ingredient: Iprodione, R.P. 26019, Chemical Name 3-(3,5-dichlorophenyl)-N-(1-Methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide.

Caswell Number: 470 A

Chemical Name of the isomer of Iprodione,

(R.P. 30228): 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide. Caswell No. 568 D

Applicant: Rhodia, Inc.
P.O. Box 125
Monmouth Junction NJ 08852

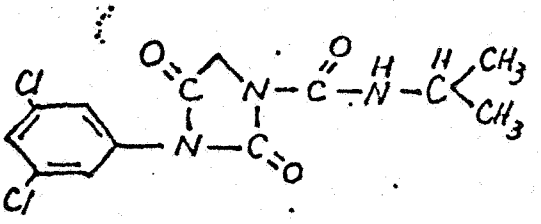
Chemical and Physical Properties:

Iprodione

Chemical name: 3-(3,5 dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide

Common and Proprietary names: Iprodione, Anfor, BSI, Glycophene, R.P. 26019, Chipco®, ROVRAL®.

Chemical Structure:



Iprodione, R.P. 26019
Caswell No. 470 A

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EPA FORM 1320-6 (REV. 3-76)

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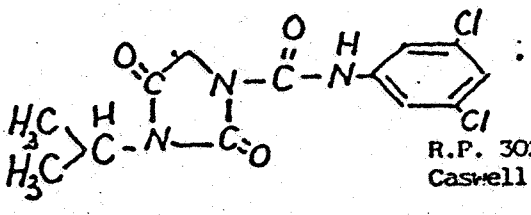
Chemical structure of the isomer of Iprodione:



R.P. 30228
Caswell No. 568 D

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Chemical name of isomer: 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide.

Pesticide class: Fungicide vs. Septoria, Botrytis spp., Monilia spp., Sclerotinia, Tilletia spp. wheat smut, Fusarium roseum, Alternaria spp.

Mol. Wgt. 330.17g Density 1.4g/cc M.P. 136°C
Vapor press. $<1x10^{-5}$ mm Hg @ 20°C
Soluble in : water, ethanol, acetone, methyl chloride

Physical State: nonhydroscopic powder, off white to cream colored, ordorless and stable.

Formulation: ROVRAL®, a wettable powder.

Statement of formula:

Ingredients	Percent
3-(3,5 dichlorophenyl)-N-(1-methylethyl) 2,4-dioxo-1-imidazolidine carboxamide	53.1%
[redacted]	

Composition of Technical Product (Iprodione)

Identity

[redacted]

Iprodione, the active ingredient 95.00%
100.00%

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NOTE: The two batches of technical Iprodione (R.P. 26019) used for the oncogenic studies in Rat and Mice were stated to be 99.6% pure.

Source of physical/chemical data: 359-EUP-58, PP #8G2087
Acc. No. 097200, Tabs A-1 & A-4. ✓
Data on Isomer: 359-684 Acc. No. 232781 Vol II, Book 1 Tab. 13

Background: The product, ROVRAL a 50% WP, containing Iprodione (R.P. 26019) and its isomer (R.P. 30228) has been tested in the U.S. from 1974-1977 as a foliar applied fungicide. The present action is a petition to establish a temporary tolerance for the subject active ingredient and its isomer of 20 p.p.m. in/on stone fruits, apricots, sweet and sour cherries, nectarines, peaches, plums and prunes.

Recommendation:

Based upon a review of the toxicity studies, especially the sub-chronic feeding studies, and the calculation of the acceptable Daily Intake (ADI) and the Theoretical Maximal Residue Contribution (TMRC) (attatched) the temporary tolerance of 20 p.p.m. Iprodione and its isomer in/on stone fruits (as shown above) is toxicologically supported.

Summary of Toxicity Data

1. Acute Studies

	Result
✓ Acute Oral LD 50 in mice, Carworth CF-1, male, 3-10 mice/dose level, 5 dose levels, 1000-6340 mg/kg Technical Iprodione, 99.6% purity.	LD 50 = 3050 (2630-3540) mg/kg Core Minimum Data -range of LD 50 exceeds ± 10% of LD 50 value. Source: 359-684, Vol. II, Book 1, Tab 3, Access #23270

II. Acute Oral LD 50 in Mice.

Charles River, CD males and females. 5 M and 5 F/dose level, 6 dose levels, 1.3-10 g/kg. Technical Iprodione (99%) purity, implied)	LD 50 = 4(3.3-4.8)g/kg males = 4.4(3.3-5.9)g/kg females Core Minimum Data-range of LD 50 ± 10% of LD 50 value. Source: as above but Tab. 2.
Acute Oral LD 50 in Rats Charles River, CD males and females. 10 M & 10 F per dose level, 2 dose levels, 2 & 1 g/kg.	Atoxic at highest dose administered, i.e. 2g/kg Supplementary-dose too low. Source: as above.
Acute Oral LD 50 in Dogs, Beagle or common dogs, males and females. Tech. Iprodione. 2 M & 2 F/dose level, 2 dose levels : 1 & 2 g/kg.	Atoxic at highest dose, i.e. 2 g/kg Supplementary-doses are too low. Source: as above.
Acute Dermal LD 50 in Rats, CD males and females, 10 M & 10 F /dose level. One dose level: 2.5 /kg. Technical Iprodione.	Atoxic @ 2.5g/kg Supplementary-Iprodione was in acetone and olive oil. Source: as above.
Acute Dermal LD 50 in Rabbits, New Zealand White males and females. 8 rabbits/dose level. 1 dose level: 1 g/kg (in acetone and peanut oil 2:1) Technical Iprodione	Atoxic at 1g/kg Supplementary-as above. Source: as above
Primary Dermal Irritation in Rabbit. 4 M and 4 F/dose level. 1 dose level: 1g/kg. Iprodione in acetone and olive oil. Iprodione Technical	Not an irritant @1g/kg Supplementary-abraded area not used. Source: 359-634 Acc. # ~~232701 Tab~~ 2
Primary Dermal Irritation in Rabbit. 6 rabbits/dose level. One dose level: 0.5 ml per rabbit (B.W. 2.5-3 kg) Suspension of Iprodione (Technical) in acetone: olive oil.	Not an irritant Minimum Data Source: 359-684 Access #23270 Vol II Book 1 Tab 2 (Study by Rhône-Poulenc in France.)

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Primary Dermal Irritation - Rabbits.	
0.5 ml/dose level, One dose level: 0.5g. 6 rabbits per dose level. Iprodione, Technical.	Not a dermal irritant. Supplementary- a summary report. Source: as above but Tab. 6. Study by FDRL.
Primary Eye Irritant in Rabbits.	
New Zealand White. Six/dose level 1 dose level: 100 mg in left eye. Obs.@ 1 hr and at 1,2,3, 4 and 7 days after appl'n Iprodione, Technical	Not an Eye Irritant. Core Minimum Data Source: As above, but Tab. 2 and Tab 7
Acute Inhalation LC 50 in Rats	
Sprague Dawley, albino. 7 M & 7 F per dose level. Single 4 hr. exposure/ per dose level. Two dose levels: 0.65g/ M^3 & 3.29 g/m^3 14 d observation. Iprodione Technical	No significant difference between test and control animal: Core Minimum Data Source: 359-684 Acc #232701 Vol. II Book 1 Tab. 8.
Dermal Sensitization in Guinea Pig	
Dunkin Hartley strain. 5 M & 5 F exposed to 0.3 ml/d X 5 d/w X 2 wks. waited 2 weeks then challenged with 0.3 ml (dissolved in Dimethylformamide). Iprodione Technical.	No evidence of sensitization Supplementary— Not given by intradermal injection, used 2 w instead of 3 weeks. Source: As above but Tab 10.
II Subchronic Studies	
Subchronic Oral Feeding in Mice, CF-1 strain for 28 days. 5M & 5F per dose level. 5 dose levels: 15,000 9,000, 6000, 1900 & 600 p.p.m. Iprodione, Technical	NOEL= 1,900 p.p.m. Dec. wgt. gai inc. liver wgt and stippled liver above 6000 p.p.m. Supplementary-duration too shor Source: as above but Tab 15.
Subchronic Feeding Study in Mice,	
Carworth CF-1 strain for 28 days. 10 M & 10 F per dose level, 5 dose levels: 15,000, 9,500, 6,000, 1,900 & 600 p.p.m. Technical, Iprodione, R.P. 26019.	NOEL = 1,900 p.p.m. Hypertrophy of liver, stippled liver at dosed above 6000 p.p.m. white foci in liver at 1900 ppm or higher. Supplementary-duration too sho

Subchronic Feeding Study in Mice (cont.)

Source: 359-684
Access # 232702 Vol II
Book 2 Tab 16

Subchronic Dog Feeding Study

Beagle dogs- duration 90 days. 2 M & 2 F dogs were used per dose level, three dose levels: 7200, 2400, & 800 p.p.m.

Iprodione (R.P. 26019, glycophene) technical was used. Initially iprodione was mixed with feed; after 6 weeks the 7200 ppm dose was administered directly using gelatin capsules since it rendered the food less palatable when mixed with feed.

Parameters observed and results

Clinical examination (general condition)

General condition and food consumption were monitored daily. No deaths occurred, one male in 7200 ppm group showed general fatigue with muscular atony from the 5th to the last week. Apart from this one animal there was no significant difference between test and control animals. Specificaly, there were no other effects on behavior the CNS or autonomic nervous systems or on the digestive system.

Bodyweight, consumption of food, eye effects and rectal temperatures.

No significant differences, test vs. control animals.

Hematological examinations.

The following blood tests were conducted initially and at 1, 2, and 3 months:

Hematocrit and Hemaglobin
Erythrocyte and Leucocyte counts
Differential White cell count
Reticulocyte and platelet counts
Prothrombin time

Also at 3 months bone marrow examinations were done. Results: A slight anemia resulted in one dog in the hi dose group at two months and in the same dog and one additional dog (both in the 7200 ppm group) at the end of the study (3 months). Other than the above there was no significant difference between test and control animals.

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Biochemical blood tests (Blood Chemistry).

Results: From the first month to the end of the study (90 d) the alkaline phosphatase level in 3 out of 4 animals was elevated. In one of these 3, the level returned to normal at 3 months. Also in 2 of the 3 animals referred to above there was an increase in transaminase activity.

Urinalysis

All tests were normal during the first two months. During the third month the following was observed:

- proteins and bile pigments in one animal in the low dose group.
- presence of bile pigments in one animal of four in group II and in group III.

Necropsy and gross Pathology

In the mid dose (2400 ppm) group there was congestion of mesenteric lymph nodes. In the high dose group, 3 of the 4 animals showed slight hypertrophy of the liver and the fourth showed: pale liver, anemia, hypertrophy of prostate and gonads.

Histological Examination

Only common and trivial changes were apparent- not dose related.

General Conclusions

Treatment was well tolerated at the two lower dosage levels i.e., 800 and 2,400 ppm. In the highest dose group only minor effects were noted, namely:

- A transient increase in alkaline phosphatase.
- Slight liver hypertrophy.

The NOEL was 2400 p.p.m.

Classification: Core Minimum Data

Source: 359-684 Acc. #232702, Vol II, Book 2, Tab 18

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Subchronic Oral Feeding in Rats

Charles River (Fr.) CD strain. Fifteen male and 15 female per dose level, 3 dose levels: 1000, 500, and 150 p.p.m. Administered technical grade Iprodione (R.P. 26019) in diet for 5 months.

Examinations carried out: (frequency shown in parentheses)

General condition of rats (daily)
Food consumption (weekly)
Body weights (weekly)
Eye (weekly after 2 months)
Hematological (at end of treatment)
- hematocrit
- RBC & WBC count
- Coagulation time

Blood (at end of treatment)
- glucose
- urea nitrogen
- BSP assay
- GOT & GPT (transaminases)

Urine (at end of treatment)
- glucose
- albumin
- urobilin
- bile salts

Gross and Histopathological examination:

Weight of principal organs, i.e. those underlined: (at end of treatment)

esophagus
stomach
sm. & lg. intestine
liver
pancreas
salivary glands
trachea
lungs
heart
aorta
bladder
epididymus
seminal vesicles
brain
eye
spleen
mesenteric lymph nodes
thymus
thyroid
parathyroid
suprarenals
straited muscle
kidney
gonads
prostate
uterine horns
spinal cord
optic nerve

Results:

There was no deaths. Behavior (observed daily) was normal. Food consumption-(obs. daily) of test animals was the same as controls except that females in the 2 highest dose groups showed a decrease in food consumption which was less than 15% except during the 6th week when the decrease was 25-27%.

Body weight (determined weekly)

No significant differences in growth of treated and control animals except for 3 out of 60 animals in the 2 highest dose groups, and the depression was not greater than 8%.

Eye Condition (tested weekly after 2 months).

No abnormalities were observed

Organ Weights-

There were no significant differences in relative organ weights of test animals compared with controls.

Blood tests

There were no significant differences between test and control animals in the parameters tested (glucose, urea, B.S.P., transaminases, alkaline phosphatases).

Urinalysis (biochemical tests)- there was no sigrificant difference between test and control animals.

Histological examinations- no significant differences were found between test and control animals.

The NOEL was 1000 p.p.m.

Classification: Minimum data- study would be improved by using at least 20 animals of each sex.

Source: 359-684, Acc. #232702, Vol. II Book 2, Tab 17 and page 3 of toxicological summary.

III Chronic Toxicity Studies in Rats,

Charles River, CD outbred albino. 60 M & 60 F rats per dose level, three dose levels: 1000, 250 and 125 p.p.m. Duration: 24 months
Iprodione, Technical, lot 7 CA 7331900 & 46 A 7507700- purity 99.5

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Examinations conducted:

General condition
Food consumption dec'd in M & F @ all doses.
Body weight dec. in hi dose M & in F.
Eye condition no effect.

Cholinestarase activity

Necropsy, Gross & Histopathology

Organs- weight & micro exam.

adrenals, brain, liver, pancreas, aorta, lung, heart, kidney, spleen, testes, bone, pituitary, prostate

Tissues

bladder, urinary; bone marrow; eye; esophagus; skin; thyroid; trachea; mammary gland; large intestine; small intestine; main stem bronchi; salivary gland; spleen; sciatic nerves; skeletal muscl; stomach; thymus; spinal cord; ovary; cecum; uterus; mesentary lymph nodes; seminal vesicles

growth of tissue masses

Clinical testing

Hematology
- hematocrit (Hct) sl. dec. M & F
- hemaglovin sl. dec. M & F
- erythrocyte count-N.S.D.
- total leucocyte count-N.S.D.
- differential leucocyte count N.S.D.

Blood Chemistry
- calcium, potassium
- phosphorous, chlorides
- glucose (fasting), sodium
- urea nitrogen (BUN), prothrombin
- total protein, bilirubin
- Hepatic enzymes, cholesterol
- serum alkaline phosphatase
- serum glutamic-pyruvic transaminase (GPT)
- serum glutamic-oxaloacetate transaminase (GOT)

Urinalysis
- glucose
- albumin
- microscopic elements
- pH
- specific gravity

N.S.D. = no sig. diff.

Results:

Clinical observations- incidental findings which were not treatment related. Animals were observed daily.

Clinical laboratory findings- (det'd @ 3, 12, 18 & 24 months) control and 125 ppm groups had hi glucose values which resulted in an apparently significant decrease in glucose values in the 250 and 1000 p.p.m. male groups.

At 18 months one male in 125 p.p.m. group had elevated SGOT & died about 3 months later and was found to have a liver mass.

Onset of Palpable Tissue Masses- (observed weekly)

Tumor incidence increased with age and was not related to treatment with iprodione.

Mortality and Necropsy findings- No significant difference between treated and control groups.

Organ Weights-

None of the organ weight changes appeared related to treatment except the decrease in spleen weights for treated males, (at all dose levels).

Histopathology Finding's-

There was no pathology which appeared to be treatment or dose related.

NOEL= 1000 p.p.m.

Classification: Core Guidelines

Source: 359-EUP-58 PP # 8G2087 Acc. # 097201 Vol. II Sec. C, Book 1 TAB C-3.

Chronic Toxicity and Oncogenicity Study in Mice, Carworth CF-1 albino.

60 M & 60 F per dose level, three dose levels: 1250, 500, and 200 p.p.m. Duration: 18 months, using Iprodione, technical, purity 99.5%.

NOEL should be the highest level tested which is predicted not to impair survival, longevity due to effects other than tumor

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Examinations conducted:

General condition
Food consumption

Body weight

Eye condition

Clinical testing
Hematology
hematocrit
hemoglobin
erythrocyte count
total leucocyte count
differential leucocyte count
reticulocyte count (if anemia is present)
Blood Chemistry
calcium
phosphorous
glucose (fasting)
urea nitrogen (BUN)
total protein
Hepatic enzymes
serum alkaline phosphatase
serum glutamic-pyruvic transaminase (GPT)
serum glutamic-oxaloacetate transaminase (GOT)
Urinalysis
glucose
albumin
microscopic elements
pH
specific gravity

Cholinestarase activity

Necropsy, Gross & Histopathology

Organs- weight & micro exam.

adrenals	lung	bone femur
brain	heart	pituitary
liver	kidney	prostate
pancreas	spleen	
aorta	testes	
gall bladder		

Tissues

bladder, urinary	salivary gland
bone marrow	spleen
eye	sciatic nerves
esophagus	skeletal muscle
skin	stomach
thyroid	thymus
trachea	spinal cord
mammary gland	ovary
large intestine	cecum jejunum
small intestine	uterus colon
main stem bronchi	duodenum

mesenteric lymph node

Results

NOEL ≧ 1250 p.p.m.

Animals were observed dialy and tests conducted as indicated.

Body Weights and Food Consumption-

No sig. diff. between test and control groups. Body weights were determined weekly and Food Consumption was det'd daily.

Clinical Observations- no sig. dif. in appearance, behavior and general condition between test and control animals.

Clinical Laboratory findings- hematology and urinalysis (Det'd @ 3,6,12 mo.)

Values for hematocrit, alkaline phosphatase, serum GOT, BUN, were significantly different for certain test animals when compared with controls, but the values were considered within the normal range of values for the Hess and Clark lab (where the study was conducted).

Onset of Palpable Tissue Masses- (checked weekly)

The incidence of neoplasms was low and was comparable between the treated and the control groups.

Mortality

No sig. dif. between control and treated animals. (checked daily or more often if necessary).

Gross Necropsy

Conducted on animals that died and @ 6, 12 and 18 months.

There was no significant differences in gross necropsy findings during the first 12 months of the study when control and treated animals were compared.

Animals necropsied during the last 6 months and at the end of the study (18 month) revealed the following:

- significantly enlarged livers among treated female mice compared with controls. Most of these enlarged livers were due to metastasised lymphosarcoma . However since the incidence of lymphosarcoma was the same in treated and control groups the liver enlargement was not considered to be treatment related.

- Male mice in the 200 p.p.m. treatment group had significaty enlarged lymph nodes, spleens, and lungs with white nodules compared with controls. The enlarged spleens and lymph nodes was due to microscopically confirmed lymphosarcoma. Alghough there was no occurrance of lymphosarcoma in control males at 18 months the overall incidence of lymphosarcoma was comparable for treated and control male mice. Also, the number of neoplastic and non-neoplastic findings in the lungs were comparable between 200 p.p.m. treated mice and control males.

Eye examination-

Examined initially and at 6, 12 and 19 months. No significant differences between test and control animals.

Organ Weights (Determined at 6, 12 and 18 months).

Significant differences did occur in the mean absolute and relative organ weights in different treatment groups during different time periods (1st-6 mo, 2nd-6 mo, at sacrifice at 18 months) compared with controls. However, the findings appear to be random and not treatment or dose related.

Histopathological Findings (Det'd at 6, 12, and 18 months)

Analysis of the total neoplastic findings did not reveal a significantly greater frequency of benign or malignant neoplasms in the treated group compared with controls.
Treated animals had a greater frequency of malignant neoplasms than controls which, however, was not statistically significant by Chi-Square.

In Summary - there were numerous non-neoplastic processes present, the most common findings were focal interstitial inflammatory cell infilration of the kidney, stomach, lung, salivary gland, and bladder. The distribution of these findings showed no apparent dose relationship.

Lymphosarcoma was the most common malignant process involving the spleen, lymph nodes or thymus gland with metastases to many other organs. Adenoma of the lung was a common benign tumor.

Based on the data iprodione (R.P. 26019) is not carcinogenic. The No Observable Effect Level = 1250 p.p.m.

Classification: Core guidelines

Source: 359-EUP-58, PP # 8G2087 Acc. # 097201 Vol II, Sec. C, Book 1 Tab C-3
Study Conducted by: Hess & Clark Laboratories of Ashland, Ohio. A division of of Rhodia, Inc., whose parent company is Rhône-Poulenc, of Vitry, France. Study No.: Project CH-42 Report No. SEH 75:133 of.6 March 1978.

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Teratogenicity Study in Rat,

Sprague Dawley females. 30 F, 30 F & 25 F per 400, 200 & 100 mg/kg p.p.m. respectively.
Iprodione, technical

Batch GD 5740 99.6%-100%

No evidence of teratogenicity
NOEL = 200 mg/kg/day Core Minimum
Source: 359-684
Acc # 232712, Vol. II, Book 3,

Slight decrease in food consumption, conception rate & mean no. of implantation in hi dose group

maternal & fetal toxic effects NOEL at which doses or at all doses

Teratogenicity in Rabbit,

New Zealand albino, 10 F 13 F & 12 F at dose levels: 400, 200 & 100 p.p.m respectively.
Iprodione, technical

mg/kg

No evidence of teratogenicity 400 mg/kg dose was too hi since 9/17 females died. Animals in low and med. dose groups showed decreased or (in gp II) loss of weight. Group I fetuses normal Group II 3/13 resorption of litter. One fetus showed multiple malformations out of 68. NOEL = 100 mg/kg/day. Core Minimum.
Source: 359-684 Acc # 232712
Vol II Book 3, Tab 20

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Mutagenicity Study in Mice, Carworth CF-1 Males were treated (25 M/dose level, 2 dose levels: 6000, & 1500) and each male was mated with 2 females (untreated). Iprodione technical.

Study by Hess & Clark Labs. Div. of Rhodia Inc. Ashland, OH. (Parent Co. is Rhône-Poulenc, Vitrey, France)

* Conducted by : Centre de Recherche et d'Elevage des Oncins.

No evidence of mutagenicity or adverse effect on fertility.

Results:

Clinical observations- There was no related difference in average body weight gain between control and test animals. Male mice in high dose group showed slight depression from day 8 through day 15.

Postmortem observation- There was no significant reduction in the number of early fetal deaths per pregnant female nor was there a reduction in the number of implants per pregnant female where treated and control mice were compared.

Core Minimum Data Source 359-684 Acc # 232712 Vol II Book 3, Tab 25.

Reproduction Study - 3-Generation, Rat, Sprague Dawley, 10 M & 20 F per dose level. 3 dose levels: 2000, 500 & 250 p.p.m. Iprodione, technical.

No evidence to toxicity of doses used. Postnatal pup growth from hi dose females was dec. 7%.

Core Minimum Data Source: 359-684 Acc # 232712, Vol II Book 3, Tab 24.

Mutagenicity study in microbiologic system, (Bacillus subtilis strains H 17 & M 45, E. coli & Salamonella typhimurium. Iprodione, technical (99.4% purity).

Rec-assay test was negative. Reverse Mutation test-negative. Host Mediated Assay-negative.

Supplementary. Source: 395-684 Acc # 232712 Vol II, Book 3, Tab 26.

Inerts:

ROVRAL wettable powder [redacted] ingredients as shown below:

Iprodione 53.16

[redacted]

[redacted] been certified inactive toxicologically.

Source: 359-EUP-58, PP # 8G2087 Acc. # 097200. Attachment: Calculation of ADI & TMRC.

Temporary Tolerance Petition 8G2087.

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RD inital
Reto Engler 10/21/78:lf

11/3/78