011645

5-22-95

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

MEMORANDUM

May 22, 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Iprodione, Dermal Absorption in Rats

TO: Linda Taylor Ph.D.
Review Section II
Toxicology Branch II
Health Effects Division (7509C)

5/23/95

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (7509C)

Action Requested

Review the following study;

Study Type Demal Absorption Guideline 85-3

Citation

Demal absorption of ^{14}C-Iprodione (ROVRAL®) in male rats (Preliminary and Definitive Phases) T. Cheng: Hazleton Wisconsin HWI 6224-208, Oct 25, 1994, MRID 435350-03

Core Classification Acceptable

Conclusions

Male rats dermally exposed at 0.4, 4.0 and 40 mg/rat (12.5cm^2 /rat). At each dose subgroups of four rats exposed for 0.5, 1, 2, 4, 10 and 24 hours. Skin residue increased with duration of exposure to 5 to 10 % of applied dose, no apparent dose relation. Portion absorbed increased with duration of exposure to 7.41, 3.16 and 0.19% of applied dose respectively. Absorption appears to be saturated at 4 and 40 mg/rat.

Attachment
DER

Data Evaluation Report

Compound Iprodione

Study Type Demal Absorption Guideline 85-3

Citation

Demal absorption of ^{14}C-Iprodione (ROVRAL®) in male rats (Preliminary and Definitive Phases) T. Cheng. Hazleton Wisconsin HWI 6224-208, Oct 25, 1994, MRID 435350-03

5/22/95

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Male rats dermally exposed at 0.4, 4.0 and 40 mg/rat (12.5cm^2 /rat). At each dose subgroups of four rats exposed for 0.5, 1, 2, 4, 10 and 24 hours. Skin residue increased with duration of exposure to 5 to 10 % of applied dose, no apparent dose relation. Portion absorbed increased with duration of exposure to 7.41, 3.16 and 0.19% of applied dose respectively. Absorption appears to be saturated at 4 and 40 mg/rat.

Materials

ROVRAL Brand 4 Flowable Fungacide
[Phenyl-^{14}C]Irpodione
3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide
CAS # 36734-19-7
Lot #
Formulation: X06228006(Analytical Code/Log No 029706)
Radiolabeled: CLS-92-354-81-3
Purity
Formulation; 42.4% Irpodione
Data files 93107STM, 93021STM and 36LJH103-106)
Radiolabeled: >98% by UV-HPLC
Specific activity 19.86 mCi/mmol
Molecular wt 220.15
Physical state:
Formulation; Tan viscous liquid
Radiolabeled: White Powder

Male Charles River Crl:CD®BR rats
approximately 7 weeks of age
From Charles River

2

Experimental Design

Phase	Group	Number of Animals	Dose Level	Dose ai (mg)	Microliters /rat
Preliminary	1	4	1:99 dilution	0.4	100
	2	4	Concentrate	40	100
Definitive	3	2	Carrier only	0	100
	4	24	1:99 dilution	0.4	100
	5	24	1:9 dilution	4	100
	6	24	Concentrate	40	100

In groups 4, 5 and 6, subgroups of four animals each were exposed dermally for 0.5, 1, 2, 4, 10 and 24 hours.

Dose Preparation and Verification

"The radiolabeled dosing solutions were prepared by measuring the appropriate amount of a ^{14}C-Iprodione solution into a serum vial, evaporating the organic solvent (acetonitrile) under a stream of nitrogen gas, and adding Rovral 4F formulation and 1.0% carboxymethylcellulose (CMC) solution (except groups 2 and 6). The group 3 solution was 1% CMC. The doses were prepared as follows:

Group	^{14}C-Iprodione (mg)	Rovral 4F Fungicide (ul)	^{12}C-Iprodione (mg)	1% CMC (ml)	Iprodione (mg/ml)
1	0.83	9.4	4.48	1.20	4.4
2	0.83	1000	476.6	0	477
4	1.99	20.99	10.0	2.98	4.0
5	2.49	309.6	148	3.41	40.5
6	2.49	3857	1838	0	477

The radiolabeled dosing solutions were analyzed for homogeneity, concentration and specific activity.

Dose Administration

"One day before dosing (preliminary and definitive phases) the back and shoulders of each animal were shaved and the shaved area washed with water. Care was taken not to abrade the skin. The site for application of the test material was defined by a plastic enclosure (aproximately 12.5cm^2) which was affixed to the back with cyanoacrylate-based glue. Medical silicone adhesive Type Q was applied on the outside of hte enclosure for sealing. An Elizabethan collar was placed around the animal's neck to prevent ingestion of the test material."

"The radiolabeled dosing suspensions were sonicated and mixed using a vortex mixer before aliquots were taken. At dosing, approximately 100 ul of the dosing suspension was applied

within the enclosure along the midline of the skin site. The weight of the dosing syringe was recorded before and after dosing. The test material was spread across the surface of the skin site using a glass rod(spreader). The spreader was then rinsed with approximately 3 ml of methanol (groups 3 and 4 were rinsed with acetone) and wiped with a qauze pad; the rinse and wipe were collected for analysis. Duplicate predose and postdose aliquots for each treated group were taken for dose verification."

"After administration of the test material, the application site was covered with a nonocclusive (filter paper) cover." Animals were placed in individual metabolism cages for the duration of exposure and total urine and feces collected.

Skin wash (presacrifice)

"Approximately 10 to 15 minutes prior to the scheduled skin wash the animals were anesthetized with ketamine via an intramuscular injection in the thigh. The animals were removed from their individual cages and placed in a plastic box for collection of any excreta. The Elizabethan collar was removed. The nonocclusive cover was removed from the plastic enclosure and placed in a 100-ml container. For preliminary and difinitive phases, 25 guaze pads and four cotton-tipped applicators were placed in a 500 ml prelabeled plastic container and then all were tarred. The gauze pads and cotton-tipped applicators were removed form the plastic container. The skin was washed with gauze pads and applicators immersed in water with a mild soap solution then dried with gauze pads."

Sample Collection

"The acumulated postdose feces and urine from each animal were collected. The nonocclusive cover and skin wash were collected for analysis. Immediately following the skin wash, all animals were anesthetized with halothane and exsanguanated by cardiac puncture and the blood collected. Residual urine was collected form the urinary bladder and added to the urine sample. The skin from the dose site (enclosure included) was excised and collected. The residual carcass was retained. Cages were washed with a 1% trisodium phosphate solution and wiped with a gauze pad(cage wipe). All samples collected were retained for radioanalysis."

"Preliminary phase (Groups 1 and 2) Urine, feces, cage wash and cage wipe were colected from 0 to 0.5 hours postdose. The nonocclusive cover, enclosure, skin wash, skin at application site and carcass were collected.

"Definitive phase control (Group 3) The nonocclusive cover, enclosure, skin wash, skin at application site, blood,

A

carcass, cage wash, cage wipe, urine and feces were collected from each control animal through 24 hour post dose."

Definitive phase (groups 4, 5 and 6) Four animals/group/time point were sacrificed immediately following skin washes at 0.5, 1, 2, 4, 10 and 24 hours post dose. The nonocclusive cover, enclosure, skin wash, skin at application site, blood, carcass, cage wash, cage wipe, urine and feces were collected."

Results

Results from the definitive phase (groups 4, 5 and 6) are summarized in Table A. The actual dose absorbed per rat indicates saturation of absorption at 4.0 and 40 mg/rat.

Table A. Mean percent dose distribution of male rats receiving a dermal dose of Iprodione. Values are the means of four rats. Dosing area 12.5 cm^2. Data are from tables 6 through 11 of the report.

Exposure (hours)	Enclosure and Cover	Skin Wash	Skin	Blood	Carcass	Cage Wash Wipe	Urine	Feces	Absorbed[1] %	Absorbed[1] ug	Total Recovery
0.4 mg/rat											
0.5	0.40	94.3	2.85	<0.005	0.12	ND	<0.005	ND	0.12	0.5	97.7
1	0.67	93.3	2.28	<0.005	0.41	ND	0.1	ND	0.43	1.7	96.7
2	0.78	88.6	5.71	0.01	0.82	0.02	0.03	ND	0.87	3.5	96.0
4	0.93	92.6	2.79	0.01	0.94	0.04	0.07	<0.005	1.06	4.2	97.4
10	0.62	90.9	2.20	0.02	2.13	0.19	0.83	0.04	3.21	12.8	96.9
24	0.91	79.8	8.34	0.03	2.43	0.65	2.23	2.06	7.41	29.6	96.5
4.0 mg/rat											
0.5	0.32	96.6	3.94	ND	1.09	ND	<0.005	ND	1.09	43.6	101
1	0.96	94.6	6.81	ND	0.16	0.02	0.01	ND	0.18	7.2	102
2	0.31	93.1	7.86	<0.005	0.33	ND	0.02	ND	0.36	14.4	101
4	0.43	86.5	16.1	<0.005	0.38	ND	0.07	ND	0.46	18.4	103
10	0.73	94.7	6.25	0.01	0.82	0.07	0.28	ND	0.26	10.4	102
24	1.11	88.4	9.12	0.01	0.95	0.19	1.11	0.90	3.16	126.4	101
40 mg/rat											
0.5	0.24	96.4	0.75	ND	ND	ND	ND	<0.005	<0.005	<2.0	97.4
1	0.43	97.9	1.03	ND	0.11	ND	<0.005	<0.005	0.11	44.0	99.5
2	0.30	96.9	1.81	ND	ND	ND	<0.005	<0.005	<0.005	<2.0	99.1
4	0.72	93.6	3.80	ND	ND	ND	0.01	ND	0.01	4.0	98.2
10	0.67	94.5	4.29	ND	ND	ND	0.04	0.04	0.05	20.0	99.5
24	0.79	92.5	4.81	ND	ND	0.02	0.09	0.09	0.19	76.0	98.3

1. Sum of Blood, Carcass, cage wash and wipe, urine and feces.

6