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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Isoxaflutole, dermal absorption in the rat.

TO: Sanju Diwan Ph.D.
Review Section I
Toxicology Branch II
Health Effects Division (7509C)

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

THROUGH: William Burnam
Chief
Science Analysis Branch
Health Effects Division (7509C)

DP Barcode #D228282 Case #046754 Submission #S508413

Chemical #Isoxaflutole ID #000264-LAA

Registrant #Rhone-Poulenc MRID 440447-02

Action Requested

Review the following study;

Study type Dermal Absorption 85-3

Citation

Dermal Absorption of ^{14}C-Isoxaflutole in Male Rats. (Preliminary and Difinitive Phases) T. Cheng. Corning Hazleton. CHW 6224-225 April 25, 1996 MRID 440447-02

Core Classification Acceptable

Conclusions

Male rats were dosed at 0.865, 7.32 and 79.00 ug/cm^2. Four animals per dose were exposed for 0.5, 1, 2, 4, 10 and 24 hours. Although test material continued to enter the skin throughout the exposure period (up to 11.9, 6.3 & 2.11 % at

24 hrs), only a relatively small portion of the dose was absorbed, 4.42, 0.88 and 0.20 % at 24 hours exposure. Approximatley 50% of the skin residue can be expected to be absorbed over 3 weeks. The remainder will be lost by exfoliation. The test chemical bioaccumulates.

Discussion

Absorption of isoxaflutole of very slow being very close to saturation. However, test chemical continues to enter the skin throughout the exposure period. As a result a relatively large amount of isoxaflutole remains in the washed skin after 24 hours exposure, 2.7, 7.1 and 10.6 times the absorbed dose. Considering the slow rate of penetration into the systemic compartment from the skin, one may conclude that approximately half of the skin residue will enter the systemic compartment during the three weeks following dosing. Three weeks is the turnover time for the stratum cornium. The remaining dose will be lost by exfoliation of the stratum cornium during that period.

In this study isoxaflutole shows bioaccumulation at all three doses. The quantity of test chemical in the carcass increases with increasing duration of exposure. This occurs because the rate of urinary excretion is significantly less than the rate of absorption.

Attachment

DER

Data Evaluation Report

Chemical Isoxaflutole

Study type Dermal Absorption 85-3

Citation

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9/13/96

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Male rats were dosed at 0.865, 7.32 and 79.00 ug/cm^2. Four animals per dose were exposed for 0.5, 1, 2, 4, 10 and 24 hours. Although test material continued to enter the skin throughout the exposure period (up to 11.9, 6.3 & 2.11 % at 24 hrs), only a relatively small portion of the dose was absorbed, 4.42, 0.88 and 0.20 % at 24 hours exposure. Approximatley 50% of the skin residue can be expected to be absorbed over 2 weeks. The remainder will be lose by exfoliation. Chemical bioaccumulates.

Materials

^{14}C-Isoxaflutole ([Phenyl-U-^{14}C] RPA 201772)
68.24 uCi/mg
white solid
Lot Number GXR395A
99.7% radiopure

Isoxaflutole CAS No. 141112.29-0
white solid
LOt No. 40ADM93
99.8% chemically pure

Male Charles River Rats from Charles River, Portage, Michigan
7 weeks of age, 153.4 to 198.6 gm

Experimental Design

Phase	Group	Number of Animals	Dose Level	Dose (nominal) (mg/rat)	Dose (nominal) (ug/cm^2)
Preliminary	1	4	1:99 dilution	0.01	0.8
	2	4	concentrate	1.0	80.0
Definitive	3	2	vehicle	0.0	0.0
	4	24	1:99 dilution	0.01	0.8
	5	24	1:9 dilution	0.1	8.0
	6	24	concentrate	1.0	80.0

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Four animals per groups number 4, 5 and 6 were exposed for 0.5, 1, 2, 4, 10 and 24 hours.

Dose preparation

"Dose suspensions were prepared by combining appropriate amounts of ^{14}C-isoxaflutone, nonlabeled isoxaflutone, and aqueous 1.0% carboxymethylcellulose (CMC). The dose suspension was throughly mixed using a magnetic stir bar, vortex-mixing and sonication.-- Radioactivity concentration, radiochemical purity and homogeneity of the doses were determined before dosing."

Site preparation and dose application

"At least 16 hours before dosing the back and shoulders of each animal were shaved and the shaved area washed with water.-- The site for application of the test material was defined and protected by a rectangular plastic enclosure (approximately 12.5 cm^2) which was affixed to the back of each rat with cyanoacrylic-based glue. A 100% silicone sealent was applied on the outside of the enclosure for sealing purposes and an Elizabethan collar was placed on each animal's neck to protect the dose site."

"The radiolabeled dosing suspensions were stirred constantly and mixed using a vortex mixer before aliquots were taken. Prior to dosing, the Elizabethian collar was removed and approximately 120-180 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 evenly across the surface of the skin site using a glass rod (spreader). The glass rod was then rinsed with approximately 10 ml of ACN:H_2O (20:80, v/v) and wiped with a gauze pad; the rinse and wipe were collected for analysis. Duplicate predose and post dose aliquots were taken for dose verification. After test material application, rubber cement was applied to the top of the enclosure and was covered with a nonocclusive filter paper. An Elizabethan collar was placed on the animals neck to protect the application site."

Animals were placed individually in metabolism cages and total urine and feces collected separately.

At the end of the exposure period the animals were anethetized with ketamine, the skin washed and the wash collected for analysis. The animals were exsangunated by cardiac puncture. Residual urine was collected from the urinary bladder and added to the excreted urine. The skin from the exposure site was excised with the protective cover. The cage was washed.

The following samples were analysed;

Skin Wash	blood
Protective device wash	residual carcass
Application site skin	urine
Cage wash	feces

Results

Results of the definitive phase, groups 4, 5 and 6, are presented in Table A.

Discussion

Absorption of isoxaflutole of very slow being very close to saturation. However, test chemical continues to enter the skin throughout the exposure period. As a result a relatively large amount of isoxaflutole remains in the washed skin after 24 hours exposure, 2.7, 7.1 and 10.6 times the absorbed dose. Considering the slow rate of penetration into the systemic compartment from the skin, one may conclude that approximately half of the skin residue will enter the systemic compartment during the three weeks following dosing. Three weeks is the turnover time for the stratum cornium. The remaining dose will be lost by exfoliation of the stratum cornium during that period.

In this study isoxaflutole shows bioaccumulation at all three doses. The quantity of test chemical in the carcass increases with increasing duration of exposure. This occurs because the rate of urinary excretion is significantly less than the rate of absorption.

Table A. Isoxaflutole. Mean dose distribution. Mean of four male rats. Data from tables 6, 7 and 8 of the report.
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Exposure (hours)	Cover/ Rinse %	Skin Wash %	Skin %	Skin ug/cm^2	Blood %	Carcass %	Cage Wash/ Wipe %	Urine %	Feces %	Absorbed[a] %	Absorbed[a] ug/cm^2	Recovery %
0.865 ug/cm^2 (0.011 mg/rat)												
0.5	0.27	92.2	2.81	0.024	ND	ND	ND	<0.005	ND	ND	ND	95.6
1	0.17	86.7	4.09	0.035	ND	ND	ND	0.03	ND	0.03	0.001	91.3
2	0.30	92.9	7.53	0.065	ND	ND	ND	0.03	ND	0.03	0.001	102
4	0.38	86.2	8.78	0.075	ND	1.69	ND	0.12	ND	1.81	0.016	97.2
10	0.42	82.6	12.0	0.104	ND	3.14	ND	0.32	ND	3.46	0.030	98.5
24	0.83	84.1	11.9	0.103	ND	3.86	ND	0.56	ND	4.42	0.038	101
7.32 ug/cm^2 (0.092 mg/rat)												
0.5	0.06	100	2.01	0.147	ND	ND	ND	ND	ND	ND	ND	102
1	0.32	92.1	1.86	0 136	ND	ND	ND	<0.005	ND	<0.005	<0.001	94.4
2	0.41	86.5	1.11	0.081	ND	0.14	ND	<0.005	ND	0.14	0.010	88.1
4	0.33	96.0	2.89	0.209	ND	0.25	ND	0.02	ND	0.28	0.020	99.5
10	0.15	92.0	3.54	0.259	ND	0.49	ND	0.05	ND	0.54	0.040	96.2
24	0.91	82.8	6.30	0.461	ND	0.78	ND	0.10	ND	0.88	0.064	91.0
79.0 ug/cm^2 (0.987 mg/rat)												
0.5	0.20	106	1.13	0.893	ND	ND	ND	ND	ND	ND	ND	109
1	0.40	95.0	1.38	1.090	ND	ND	ND	ND	ND	ND	ND	96.8
2	0.23	98.2	0.92	0.727	ND	ND	ND	<0.005	<0.005	<0.005	<0.004	99.3
4	0.34	103	1.35	1.067	ND	0.08	ND	<0.005	ND	0.08	0.063	105
10	0.29	95.9	2.47	1.951	ND	0.02	ND	<0.005	ND	0.03	0.024	98.7
24	0.30	92.2	2.11	1.667	0.05	0.12	ND	0.03	ND	0.20	0.150	94.8

a. Sum of blod, carcass, urine, cage wash/wipe and feces.

Tox Chem No. Isoxafludtole File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA MRID No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Dermal Absorption,Rat; Hazleton Wisconsin, CHW 6224-225, Api 25, 1996	^{14}C-labeled chem pure	440447-02	Male rats were dosed at 0.865, 7.32 and 79.00 ug/cm^2. Four animals per dose were exposed for 0.5, 1, 2, 4, 10 and 24 hours. Although test material continued to enter the skin throughout the exposure period (up to 11.9, 6.3 & 2.11 % at 24 hrs), only a relatively small portion of the dose was absorbed, 4.42, 0.88 and 0.20 % at 24 hours exposure. Approximatley 50% of the skin residue can be expected to be absorbed over 2 weeks. Remainder will be lose by exfoliation. Chemical bioaccumulates.	N/A	Aceptable

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