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

004407

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cyromazine (Larvadex), Review of Dermal Absorption Study in Rats

TO: Timothy Gardner PM-17
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD, Acting head 4/22/85
Review Section IV
Toxicology Branch
HED (TS-769)

THROUGH: Theodore M. Farber PhD, Chief
Toxicology Branch

Compound Cyromazine (Larvadex) Tox Chem #167B

Registration #100-ALU Registrant Ciba-Geigy

Accession #257488

Action Requested

Review the following dermal absorption study. This is a revision of Accession #257251.

Percutaneous Absorption of Cyromazine in Rats, T.G. Murphy and B.J. Simoneaux, Biochemistry Dept., Agricultural Div., Ciba-Geigy Corp, M7-329-5A, 329950 Report No. ABR-85022. Mar 13, 1985

Conclusion

The dermal absorption study as submitted is aceptable. Cyromazine is rapidly absorbed into the skin and more slowly into the body, with total absorption in the range of 30 to 44 percent of doses of 0.1 and 1.0mg/rat over durations of 1 to 10 hours. Data from the 100mg/rat dose was extremely variable and cannot be used.

Attachment DER

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Data Evaluation Report

Compound Cyromazine (Larvadex)

Citation
Percutaneous Absorption of Cyromazine in Rats, T.G. Murphy & B.J. Simoneaux, Biochemistry Dept, Agricultural Division, Ciba-Geigy, M7-329-5A, 329950. Report No. ABR-85022, 4/3/85

Reviewed by Robert P. Zendzian PhD 4/22/85
Pharmacologist

Core classification Acceptable

Conclusion

Cyromazine is rapidly absorbed into the skin and more slowly into the body, with total absorption in the range of 30 to 44 percent of doses of 0.1 and 1.0mg/rat over durations of 1 to 10 hours. Data from the 100mg/rat dose was extremely variable and cannot be used.

Materials

Cyromazine (CGA-72662), ^{14}C labeled in the tirazine ring.
75WP formulated product
Specific activity 16.6 uCi/mg, low dose
2.26 uCi/mg, mid dose
0.0176 uCi/mg, high dose

Male Harlan Sprague-Dawley albino rats weighing 225 gms.

Methods

The hair on the back of the rats was shaved 24 hours prior to dosing and the shaven area washed with acetone. "A 10 sq. cm area, 2.5 by 4 cm, was marked before the dose was applied." The hind legs of the rats were restrained with jewelers chain.

Dermally applied doses were 0.1, 1.0 or 100mg/rat.

"The low dose was prepared by throughly mixing 25mg of ^{14}C-cyromazine with 75 mg of blank formulation (WP) and 12.5ml deionized water. The mid-dose was prepared by throughly mixing 200mg of ^{14}C-cyromazine and 66mg of blank formulation (WP) and 10 ml deionized water. The resutant mixtures are representative of a typical 75WP formulation."

"The high dose was prepared by throughly mixing 50gm 75WP which contains 37.5 g of unlabeled cyromazine and 40 mg of ^{14}C-cyromazine and 30ml of deionized water. The resultant mixture would contain one percent of ^{14}C-cyromazine and 99.9% (sic) unlabled cyromazine to give a representative 75WP formulation. This mixture had the consistancy of a smooth paste."

Zero-time sampling

In order to test the effectiveness of the skin washing procedure, samples of skin were taken from live rats ($10cm^2$, three rats per dose) and treated with the low and medium doses of ^{14}C-cyromazine. The skin was allowed to dry and immediately rinsed with water. The rinse water and the solubilized, digested skin were radioassayed.

Dose application

1. Low (0.1 mg/rat) and the mid (1.0 mg/rat) dose.

"Fifty microliters of an aqueous suspension containing the low (0.1 mg/rat) and the mid (1.0 mg/rat) dose levels were applied with a 50 ul Hamilton Syringe equiped with a teflon tip coated needle and plunger assembly." " The tip of the syringe was used to uniformly spread the suspension over the entire treatment area. The amount of ^{14}C-cyromazine applied to the rat was calculated by radioassay of 50 ul of the ^{14}C-cyromazine delivered with the same syringe. The amount of ^{14}C-cyromazine remaining on the teflon coated needle was considered to be minimal and not measured directly."

2. High dose level (100 mg/rat)

"The high dose level (100 mg/rat) was applied with the blunt end of a glass rod used for packing columns that measured 1.75cm in diameter. Two hundred and eighty milligrams of an aqueous paste (100 mg ^{14}C-cyromazine, 37.5 mg of formulant and 142.5 mg of deionized water) was applied by touching the surface of the paste with the blunt end of the glass rod until the exact amount was transferred. The amount of paste on the tared rod was determined by weighing on an analytical balance. Two drops of deionized water was placed on the treatment area with an eye dropper before the dose was applied. The glass rod tip was rubbed over the wet treatment area until a uniform application took place and by visual inspection very little residue paste remained on the glass rod. The transfer of ^{14}C-cyromazine appeared quantitative and was not measured directly."

Preliminary study

A preliminary study was done on two rats at the mid-dose (1.0mg/rat) for an eight hour exposure. Animals were placed individually in metabolism cages and volatiles, urine and feces collected. At eight hours the rats were sacrificed and blood (plasma and RBCs), carcass, skin, skin wash and cage wash collected for analysis. CO_2 was not collected since metabolism studies have shown that cyromazine metabolism does not produce CO_2.

Main Study

In the main study three rats per dose per time point were used. For each dose three rats were sacrificed at 1, 2, 4 or 10 hours after dosing. Animals were placed individually in metabolism cages and urine and feces collected. At sacrifice blood (plasma and RBCs), carcass, skin, skin wash and cage wash collected for analysis. The preliminary study showed that collection of volitiles was not necessary.

Analysis of samples

Liquid samples were radioassayed directly. Carcasses and feces were homogenized and aliquits combusted.

Results

Zero-time sampling

Table 1. Mean (of two rats) recovery from skin of low and intermediate dose as percent of applied dose. Data from Appendix Table XIII of the report.

	Dose	
	0.1mg/rat	1.0mg/rat
Skin Rinse	99.60	92.58
Skin dissolved	7.52	3.99
Total	107.12	96.57

Preliminary study

Table 2. Mean (of two rats) recovery following a dose of 1.0mg/rat and an eight hour exposure as percent of dose. Date from Table I in the report.

Tissues and Collections	% Dose
Plasma	<0.00
RCB	<0.03
Carcass	4.71
Skin Wash	53.40
Skin Dissolved	18.83
Cage Wash	7.86
Volitiles	<0.44
Urine	1.67
Feces	0.01
Total Recovered	86.95
Missing	13.05

% Dose Absorbed = 25.25 (Totals; Plasma, RCB, Carcass, Skin Dissolved, Urine Feces.)

% Dose Not Absorbed = 61.7 (Totals; Skin Wash, cage wash, volitiles)

Main Study

Table 3. Mean quantity absorbed, as percent of dose, three rats per dose. Date from Appendix Tables I through XIII in the report.

Dose (mg/rat)		0.1	1.0	100.0
Duration (hours)				
1	Total*	36.86	21.98	9.87
	Skin**	29.14	18.50	7.64
2	Total	39.16	30.71	37.41
	Skin	34.69	25.87	26.29
4	Total	38.27	26.61	9.64
	Skin	30.14	20.04	6.37
10	Total	44.68	38.80	22.29
	Skin	34.69	27.37	15.21

*Plasma, RBC, Carcass, Urine, Feces & Skin dissolved.
**Skin after washing (skin dissolved).

Table 4. Mean quantity not absorbed (skin wash) as percent of dose, three rats per dose. Date from Appendix Tables I through XIII in the report.

Dose (mg/rat)	0.1	1.0	100.0
Duration (hours)			
1	50.51	63.82	89.79
2	52.13	56.41	44.17
4	59.00	58.55	88.37
10	41.04	47.88	79.05

Discussion

The compound shows a rapid and high absorption into the skin followed by a slower release into the body. The variation with time of the 100mg dose indicates a possible problem in consistancy of dose appplication, perhaps in spreading. Because of this variation and a general inability to determine its cause the 100mg/rat data should be discarded.