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

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(Excerpt)
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MEMORANDUM

August 23, 1989

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Paclobutrazol, Review of Dermal Absorption Study

TO: Roger Gardner
Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

FROM: Robert F. Zendzian PhD 5/23/89
Senior Pharmacologist
Health Effects Division (H7509C)

Compound; Paclobutrazol — Tox Chem #628C

Registration #10182-EAT — Registrant; ICI

MRID #410482-02 — Tox Project #9-1212

Action Requested

Review the following study;

Paclobutrazol: In Vivo percutaneous absorption study in the rat. B.K. Jones; ICI Central Toxicology Laboratory; Report No. CTL/P/2285; Nov 10, 1988; MRID 410482-02

Conclusions

Core Classification Acceptable

Male rats (five/dose/exposure period) were dosed dermally on an area of 10 cm^2 per rat. The percent of dose absorbed and remaining on the washed application site, for exposures of 10 and 24 hours, are as follows.

Dose mg/rat	Total Absorbed 10hrs	Total Absorbed 24hrs	Application Site 10hrs	Application Site 24hrs
12.49	1.12	2.78	2.57	2.40
1.23	3.3	3.2	1.6	0.8
0.125	11.6	10.4	0.8	1.6
0.025	16.0	20.8	2.4	2.4
0.011	15.1	24.5	3.6	2.7

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Disussion

In addition to the expected relationship of dose and absorption, increased mass absorption with dose but decreased proportional (percent) absorption, an effect was observed which can be attributed to solvent. At the two lowest doses and the high dose, absorption increased with time. At the two remaining doses, absorption was essentially identical at 10 and 24 hours. Also at these doses the quantity remaining in/on the skin following the wash was approximately half that at the other doses. At the high dose the test compound was dosed in the use formulation, a solution of the compound in an organic solvent. At the two low doses the formulation had been sufficiently diluted with water to assure us that the dose was applied as a suspension. At the remaining doses we were very possibly dealing with a mixed solution/suspension.

Attachments

DER
One-liner

Data Evaluation Report

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Compound Paclobutrazol

Citation
Paclobutrazol: In Vivo percutaneous absorption study in the rat. B.K. Jones; ICI Central Toxicology Laboratory; Report No. CTL/P/2285; Nov 10, 1988; MRID 410482-02

Reviewed by Robert P. Hendzlian Ph.D
Senior Pharmacologist

Core Classification Acceptable

Conclusions
Percent of dose absorbed and remaining on the washed application site, for exposures of 10 and 24 hours, are as follows.

Dose	Total Absorbed		Application Site	
mg/rat	10hrs	24hrs	10hrs	24hrs
12.49	1.12	2.78	2.57	2.40
1.23	3.3	3.2	1.6	0.8
0.125	11.6	10.4	0.8	1.6
0.025	16.0	20.8	2.4	2.4
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Materials

Unlabeled test substance;
Paclobutrazol, (2RS,3RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)) penta-3-ol
CLT reference Y00001/097/001
Purity 99.1%

Labeled test substance;
[^{14}C]-triazole labeled paclobutrazol1
CLT reference Y00001/099/001
Specific activity 1.70GBq/mmol

A 'blank' formulation concentrate
CTL reference Y06378/001/001

Water for dilution
deionised and sterile
CTL reference Y04517/012/004

Male adult rats, Alpk:APfsd from Animal Breeding Unit, ICI Pharmaceuticals

Experimental Design
Animals were dosed and exposed as in the table. The highest dose consisted of the formulation concentrate (25% paclobutrazol w/v) and the lower doses were prepared as aqueous dilutions thereof (nominally 1/10, 1/100, 1/451 and 1/1000).

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Dose mg/rat	Number of Rats 10 hour	24 hour exposure
12.49	5	3
1.23	5	5
0.125	5	5
0.025	5	5
0.011	5	5

Dosing suspensions were prepared prior to dosing and samples were collected before, during and after dosing for analysis. Actual doses applied were calculated based on this analysis and corrected for quantity remaining in the tip of the application pipette.

"Approximately 24 hours before dosing the fur from the shoulders and back of each rat was shaved. After several hours the condition of the shaved skin was examined and only animals with undamaged skin were retained in the study. The shaved area of skin was washed with acetone to remove sebum and two 22.5mm internal diameter, 3mm thick nitrile rubber 'O' rings (----) were glued to the skin surface, one behind each shoulder, using cyano-acrylate glue (----). The internal surface area of skin encompassed by each ring was approximately 5 cm^2, giving a total defined skin application area of approximately 10 cm^2 per rat. A Queen Anne plastic collar was secured around each animal's neck and the rats were transfered to individual stainless steel metabolism cages (----) and were allowed to acclimatise overnight."

Each application site was dosed as follows; "Using a 25ul capacity positive displacement pipette (----) and disposable plastic tips, 25ul of the dose suspension was applied to the skin surface with one 'O' ring and was spread over the 5 cm^2 application area using the side and end of the pipette tip, which was retained for analysis. The applied suspension was allowed to dry. The application site was then protected by applying cyano-acrylate glue around the surface of the 'O' ring and superimposing a second similar 'O' ring covered with a fine permeable nylon gauze (----), glued to the surface of the ring with Bostik." "The amount of radioactivity applied to each rat was calculated as the mean amount of radiolabel in 50ul of dose suspension plus the mean amount of radioactivity retained in the pair of pipette tips used to transfer samples to volumetric flasks minus the amount of label retained on the pair of pipette tips used to apply the dose to each individual animal."

Total urine and feces were collected from each animal for the duration of exposure.

"Animals with detached or damaged protective rings were deemed unacceptable and were excluded from the study."

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"Ten hours after dosing, five acceptable rats were selected and anaesthetised with FLUOTHANE vapour. For each rat the nylon gauze covering both application sites was detached and retained and the skin surface was carefully washed with a 3% aqueous solution of Teepol-L using cotton wool swabs. The surface was then rinsed with water which was also recovered on cotton wool swabs. All swabs used for each animal were retained in a single vial and were subsequently serially extracted with solvent for radioactivity analysis. Under deeper anaesthesia a sample of blood was taken by cardiac puncture and divided between two heparinised vials. Each rat was then killed by cervical dislocation. The bladder was exposed and any residual urine was removed and added to the corresponding urine collection vessel in the metabolism cage. The rubber 'O' rings were detached and were retained in the same vial as the nylon gauze covers for subsequent solvent extraction. The skin encompassing both application sites was then removed and transferred to a single vial for each animal. The carcass was transferred to a polythene bag.

Twenty four hours after dosing the five lowest numbered acceptable rats were processed as described above."

The metabolism cages were individually washed immediately after removal of the rats and the wash retained for analysis.

Samples analysed for each rat were; skin wash, 'O' rings + gauze, skin at the application site, carcass, urine, feces and cage wash.

Results

Tables 1 through 5 from the report present the analytical results. Selected percent values were calculated and are written in by hand. Table A summarizes the percent distrobution data and Figure 1 presents the absorption data graphically.

Disussion

In addition to the expected relationship of dose and absorption, increased mass absorption with dose but decreased proportional (percent) absorption, an effect was observed which can be attributed to solvent. At the two lowest doses and the high dose, absorption increased with time. At the two remaining doses, absorption was essentially identical at 10 and 24 hours. Also at these doses the quantity remaining in/on the skin following the wash was approximately half that at the other doses. At the high dose the test compound was dosed in the use formulation, a solution of the compound in an organic solvent. At the two low doses the formulation had been sufficiently diluted with water to assure us that the dose was applied as a suspension. At the remaining doses we were very possibly dealing with a mixed solution/suspension.

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Table A. Summary of the dermal absorption of paclobutrozol. The highest dose consisted of the use formulation concentrate (25% paclobutrazol w/v) and the lower doses were prepared as aqueous dilutions thereof (nominally 1/10, 1/100, 1/451 and 1/1000). Values are percent of dose applied and are calculated from the mean analytical values of Tables 1 - 5 from the report. Total values do not necessarily 'add up'.

Ten hour exposure

Dose mg/rat	Skin wash	'O' Rings + Gauze	Total Unabsorbed[1]	Application Site	Carcass	Total Excreted[2]	Total Absorbed[3]	Total
12.49	92.07	1.32	93.43	2.57	0.96	0.16	1.12	97.11
1.23	88.6	7.3	91.1	1.6	3.3	0.4	3.3	96.0
0.125	76.0	3.2	79.6	0.8	11.2	0.72	11.6	92.0
0.025	68.0	4.0	72.0	2.4	16.0	1.6	16.0	90.4
0.011	78.2	4.5	81.8	3.6	13.6	1.8	15.1	100.5

Twenty four hour exposure

Dose mg/rat	Skin wash	'O' Rings + Gauze	Total Unabsorbed[1]	Application Site	Carcass	Total Excreted[2]	Total Absorbed[3]	Total
12.49	93.27	1.72	95.03	2.40	2.32	0.48	2.78	100.2
1.23	88.6	2.4	91.9	0.8	2.4	0.8	3.2	92.6
0.125	80.0	3.2	83.2	1.6	8.0	2.4	10.4	95.2
0.025	64.0	4.0	72.0	2.4	13.2	8.0	20.8	95.2
0.011	68.2	4.5	72.7	2.7	11.8	13.6	24.5	99.9

1. Sum of skin wash and 'O' rings + gauze
2. Sum of urine feces and cage wash
3. Sum of total excreted and carcass

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Figure 1

x 10 Loss = excessive

+ 35 Loss = excessive

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