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

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MAR 16 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Imazalil, Dermal absorption in rats

TO: Kathryn Davis PM 52
Reregistration Branch
Special Review and Reregistration Division (H7508C)

FROM: Robert P. Zendzian Ph.D. 3/15/94
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (H7509C)

THROUGH: Karl Baetcke Ph.D. Karl D. Baetcke 3/15/94
Chief
Toxicology Branch I
Health Effects Division (H7509C)

Compound;Imazalil | Tox Chem #Not given

Registration #;11901-043813 | Registrant;Janssen

MRID;429134-01 | DP Barcode;D195542

Action Requested

Review the following study;

Dermal absorption of ^{14}C-imazalil in male rats after topical application of its Fungaflor 500 EC formulation, L. van Beijsterveldt, L.V. Leemput & J. Heykents, Janssen Research Foundation, R23979/FK1326, Feb 1, 1993

Core Classification Acceptable

Conclusions

^{14}C-imazalil in male rats at doses of 0.004, 0.04, 0.4 and 4.0 mg/cm^2, exposure durations of 0.5, 1, 2, 4, 10 and 24 hours. Blood concentrations increased with time in a dose/duration related pattern. Percent absorption, at 24 hours, 47.93, 39.39. 20.92 and 29.23 respectively. Percent skin residue, at 24 hours, 18.3, 10.4, 5.14 and 4.51 respectively.

(C)

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Data Evaluation Report

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Compound Imazalil

Citation

Dermal absorption of ^{1C}-imazalil in male rats after topical application of its Fungaflor 500 EC formulation, L. van Beijsterveldt, L.V. Leemput & J. Heykents, Janssen Research Foundation, R23979/FK1326, Feb 1, 1993, MRID 429134-01

3/15/94

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

^{1C}-imazalil in male rats at doses of 0.004, 0.04, 0.4 and 4.0 mg/cm^2, exposure durations of 0.5, 1, 2, 4, 10 and 24 hours. Blood concentrations increased with time in a dose/duration related pattern. Percent absorption, at 24 hours, 47.93, 39.39. 20.92 and 29.23 respectively. Percent skin residue, at 24 hours, 18.3, 10.4, 5.14 and 4.51 respectively.

Materials

^{14}C-labeled imazalil base
^{14}C-R23979
Batch # 886
specific activity 2.05 GBq/mmole or 6.9 MBq/mg
(554. mCi/mmole or 186 uCi/mg)
radiochemical purity 99.9%

Unlabeled imazalil
R239679
Lot # V890-275

Blank formulation

Young adult male Wistar rats
From Janssen Animal Breeding Center

Experimental Design

Four animals per dose/duration of exposure were dosed at 0.004, 0.04, 0.4 and 4 mg/kg for durations of 0.5, 1, 2, 4, 10 and 24 hours.

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Dosing formulations

Dosing formulations were prepared by appropriate mixture of cold and ^{14}C-labeled imazalil in ethanol solution. Ethanol was removed under nitrogen. The residue was dissolved in formulation blank and in order of decreasing dose was diluted zero, 10, 100 or 1000 times in de-ionized water.

Dose application

"Approximately 24 h before dosing, rats were anaesthetised with diethylether. An area of the dorso-lumbar skin (approximately 10 cm X 7.5 cm) of each animal was clipped carefully free of hair with electrical veterinary clippers without abrading the skin. The clipped area was washed with acetone. As a protective cover, a brown glass spacer with a perforated screw cap to allow air circulation, was used. the protective cover (prepared from a storage bottle) was glued to the shaved rat skin in the middle of the back with cyanoacrylate adhesive (Perma Bond , Eastleigh, Hampshire U.K.). The enclosed area was 12 cm^2."

"Rats were weighed and dosed; 100ul formulation was applied with a positive displacement pipette and spread evenly over the skin inside the protective cover with the tip of the pipette. The radioactivity remaining on the outside of the tip was rinsed with 1 ml methanol."

Rats were housed individually in stainless steel cages provided with a system for the seperate collection of urine and feces for the entire duration of the exposure period.

The end of the exposure period, individual rats were anesthetised with diethylether and 3ml of blood collected from the orbital plexus. The protective device was removed and the application site washed with soap and water and rinsed with water. After washing the application site skin was removed. The following individual samples were analyzed for radioactivity;

Skin wash, including protective device wash
Skin of aplication site
Blood
Carcass
Urine
Feces
Cage Wash

Results

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Table 1 and Figure 5 (from the report) present blood concentration with dose and time data. Table 2 presents mean percent dose distribution with dose and time.

Blood concentration increases with increasing dose but the pattern with time changes with dose. At doses of 0.004 and 0.04 mg/cm^2 blood the concentration peak is observed at 1-2 hours and then declines with further exposure. At 0.4 mg/cm^2 the peak concentration is observed at 1, 2 and 4 hours and then declines. At 4 mg/cm^2 the peak concentration is not observed until 10 hours exposure and is maintained at 24 hours. To a certain extent the percent of dose (and subsiquently the concentration) in the carcass follows a similar pattern.

RW 1067-98

Imazalil Tox Review

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Pages 5 through 7 are not included.

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