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SECTION HEAD

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

008258

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPTC, Dermal Absorption Study in Rats

TO: Terri Stowe PM-74
Reregistration Branch
Special Review and Reregistration Division (H7508C)

FROM: Robert P. Zendzian Ph.D. 1/31/91
Senior Pharmacologist
SACB, HED (H7509C)

THROUGH: Albin Kocialski Ph.D. ABK 1/28/91
Head
Registration Standards and Special Review Section

Reto Engler Ph.D.
Chief
Science Analysis and Coordination Branch

Compound; EPTC | Tox Chem #435 | MRID #416862-01

Registration #041401 | Registrant; ICI | Tox Project #1-0221

Action Requested

Review the following study;

Dermal Absorption of EPTAM® in Rats, A.R. Jeffcoat, RTI, Laboratory Project ID 3586-40, T-13013, 5/9/88, MRID 41686201.

Conclusions

For applied doses of 254, 26.1, 5.68 and 2.73 mg/rat and exposure durations of 1 to 24 hours, 75 to 85% is rapidly lost by evaporation, up to 8% is absorbed and up to 4% remains on the skin after washing. Dose-duration of exposure does not appear to produce a discernable pattern of absorption.

The study is acceptable.

Attachments
DER
1-liner

1 of 9

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Data Evaluation Report

008258

Compound EPTC (Eptam)

Citation
Dermal Absorption of EPTAM® in Rats, A.R. Jeffcoat, RTI, Laboratory Project ID 3586-40, T-13013, 5/9/88, MRID 416862-01.

Reviewed by 11/13/91
Robert P. Zendzian Ph.D.
Senior Pharmacoalogist

Core Classification Acceptable

Conclusions
For applied doses of 254, 26.1, 5.68 and 2.73 mg/rat and exposure durations of 1 to 24 hours, 75 to 85% is rapidly lost by evaporation, up to 8% is absorbed and up to 4% remains on the skin after washing. Dose-duration of exposure does not appear to produce a discernable pattern of absorption.

Materials

[Propyl-1-^{14}C]EPTC Lot #EHC-0804-17
Specific activity 35 mCi/nmole (185 uCi/mg)
from Stauffer Apr 4, 1987

Unlabeled EPTC Lot # M-997-C
from Stauffer Apr 4, 1987

EPTAM® 7E Lot # NE1-2661
from Stauffer Mar 20, 1987

Male CD rats [Crl: CD® (SD)BR]
from Charles River

Experimental design

Dose group	Dose Preparation	Mean Dose per Animal (mg)	Number Animals per Dose
A	Neat EPTAM® 7E	254 ± 5	28
B	1 to 10 dilution	26.1 ± 0.3	28
C	1 to 50 dilution	5.68 ± 0.19	28
D	1 to 100 dilution	2.73 ± 0.05	28

The dose was applied to an area of 29 cm^2 on the back. Four animals from each dose group were exposed for 1, 4 and 10 hours. The remaining 16 animals were washed at 24 hours and 4 animals terminated. Groups of 4 of the remaining animals were terminated at 48, 72 and 96 hours after dose administration.

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Application site preparation

"Approximately 24 h before the animals were to be dosed, the rats were sedated (ketamine/xylazine, 7/1), and the fur on their backs was removed ---- The clipped area on each rat was washed with soapy water, rinsed with water and dried. ---- Next a 4.9 x 6.0 cm rectangular piece of cardboard was placed in the center of the clipped area and an outline of the cardboard was made on the rat with a permanent type felt tip marker. This ourline defined the dose area."

"Just prior to dosing-------- An appliance was then attached to the back of each rat with Hollister® medical adhesive ---- so that the inside edge of the appliance was about 0.5 cm outside the area were the dose was to be applied."

Dose Preparations

Dose A, Neat EPTAM® 7E

0.407 g [^{14}C]EPTC in methanol (containing 3.6 mg EPTC) plus 13.597 g EPTAM® 7E to give a total weigh of 14.004 g dose frmulation

Dose B, 1 to 10 Dilution of EPTAM® 7E with Water

0.407 g [^{14}C] EPTC in methanol (containing 3.5 mg EPTC) with 1.401 g EPTAM® 7E and deionized distiled water to give a total of 14.014 g dose formulation

Dose C, 1 to 50 Dilution of EPTAM® 7E with water

0.419 g [^{14}C] EPTC in methanol (containing 3.7 mg EPTC) with 0.288 g EPTAM® 7E and deionized distiled water to give a total of 14.102 g dose formulation

Dose D, 1 to 100 Dilution of EPTAM® 7E with water

0.427 g [^{14}C] EPTC in methanol (containing 3.7 mg EPTC) with 0.142 g EPTAM® 7E and deionized distiled water to give a total of 14.203 g dose formulation

All dosing preparations were analyzed for radiochemical purity and concentration of carbon-14 at frequent intervalus during use.

Dosing

The protective device.

"The protective device was constructed as follows. First, a frame was prepared from 8 x 9 x 1 cm (length x with x

thickness) rectangular section of Reston® self-adhering foam pad (3M™ Company). A 6 x 7 cm window was cut in the center section of the pad to form a frame having sides ca. 1 cm wide. Second, strips of double sided carpet tape (Manco Tape, Inc Cleveland OH, Cat. #DFC-1) ca. 6mm wide were attached to the top (nonadhesive side) and outer sides of the frame so that there were no gaps in the tape strips. Similarly, carpet tape strips were attached to the sides of the frame. After the frame had been secured around the dose area (cf. section 2.1.5), the test chemical was applied. The adhesive on the surface of the top carpet tape strips was then exposed. A rectangular piece of charcoal nuisance odor mask filter (3M™ Company, Cat. No. 9913) was placed over the frame and held securely to the frame by the carpet tape. Any excess charcoal filter that extended beyond the frame was trimmed away. Finally, the adhesive surface of the side carpet tape strips was exposed. A rectangular piece of 50/50 polyester/cotton sheeting was placed over the frame and charcoal-impregnated filter and secured to the frame by carpet tape."

Application of the dose

"The dose was applied to the animals with an 18 gauge gavage needle (ball-tipped) attached to a 500 ul glass syringe equipped with a Teflon®-tipped plunger"

"For each dose the syringe/needle combination was filled to the 300 ul mark with the dosing formulation. After excess formulation was removed from the outside of the needle with a Kimwipe®, the filled apparatus was weighed. The dose was then applied to the premarked area of the rat's back and spread evenly over the area with the side of the needle. After dosing was complete, the needle was wiped again with a Kimwipe® swab and the syringe/needle reweighed. The Kimwipe® swab was placed in a scintillation vial containing 2 ml ethanol and was analyzed--. The dose was calculated --as the difference in the weight of the syringe/needle before and after dosing multiplied by the concentration of carbon-14 in the dosing formulation minus the carbon-14 removed from the needle by the Kimwipe® swab after dosing."

Dosed animals were placed in individual glass metabolism cages. Urine and feces were collected individually. Collection periods ended at 1h, 4h, 10 h, 24h and each subsequent 24 h period until the animals were sacrificed. Cages were washed at termination.

Termination and application site wash

Animals in the first three time groups were sacrificed 1, 4 and 10 hours after dosing. The animals were anesthetized, a blood sample taken by cardiac puncture and the animal sacrificed by lethal injection. Bladder contents were collected

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and added to the urine collection. The skin in the dose area, including skin to which the protective appliance had been attached was excised. The remaining carcass was collected.

"After removal from the carcass, the skin in the dose area was separated from the protective appliance. The skin was clamped (inner side down) to the inside upper edge of a 12 cm diameter glass funnel that drained into a wide mouth jar containing ca. 20 ml of ethanol. The protective appliance was placed in a second jar containing ca. 50 ml 0.5% EPTAN® 7E in ethanol. The skin was then washed with soapy water (ca., 30 ml of Liquid Ivory® per liter) and scrubbed with swabs of cotton gauze (26 x 5.1 cm)--- The skin was next rinsed with water and scrubed with additional gauze."

The remaining animals were anesthatized at 24 hours after dosing. The charcoal filters and fabric covers collected individuallly. The dose site was washed with soapy water and a water rinse. The protective appliance was removed and collected. Blood samples were collected from 4 animals at each dose, the animal sacrificed and the skin at the application site and the carcass collected. Fresh protective appliances and covers were afficted to the remaining animals and they were returned to their metabolism cages. The remaining animals "were sacrificed at the apropriate times after they had been sedated and a blood sample withdrawn by cardiac puncture. The dose site skin was excised and washed."

Samples collected for analysis

The following samples were collected from each animal on the study and analyzed for [^{14}C]EPTC;

charcoal-impregnated cover
appliance
skin wash
skin at the application site
blood sample
carcass
urine
feces

Results

Means of the actual doses applied are presented in Table 11 (page 43) from the report. Blood concentration is presented in Table 1. Dose distribution and absorption are presented in Table 2.

RTI Study No.: 3586-40
ICI Americas Study No.: T-13013

Table 11

Nominal Amounts of EPTC (Target Doses) and Dose Means ± SD (mg) of EPTC for EPTAM® 7E Dose Groups

Exp. Time (h)	Neat EPTAM® 7E (Dose A)	1 to 10 Dilution (Dose B)	1 to 50 Dilution (Dose C)	1 to 100 Dilution (Dose D)
Target Dose	263	26.3	5.27	2.63
1	259 ± 2	26.2 ± 0.1	5.85 ± 0.14	2.71 ± 0.03
4	250 ± 5	26.1 ± 0.1	5.78 ± 0.28	2.74 ± 0.09
10	254 ± 7[a]	25.7 ± 0.4[a]	5.45 ± 0.18[a]	2.68 ± 0.05[a]
24	254 ± 8[a]	26.0 ± 0.2[a]	5.73 ± 0.02[a]	2.72 ± 0.02[a]
48	249 ± 2[a]	26.4 ± 0.1[a]	5.69 ± 0.02[a]	2.73 ± 0.02[a]
72	254 ± 3[a]	26.1 ± 0.0[a]	5.49 ± 0.11[a]	2.75 ± 0.02[a]
96	254 ± 5[a]	26.3 ± 0.1[a]	5.74 ± 0.05[a]	2.75 ± 0.08[a]
All Time Points	254 ± 5[a]	26.1 ± 0.3[a]	5.68 ± 0.19[a]	2.73 ± 0.05[a]

[a] Does not include animals whose experimental results were not used. See Tables 1-4 and Section 2.1.4 for explanation.

Table 1. Mean blood concentrations of EPTC as nanagram equavalants per gram of blood.

Wash 1 Time (hrs)	Sacrifice Time (hrs)	Dose A Neat	Dose B, 1 to 10 Dilution	Dose C 1 to 50 Dilution	Dose D 1 to 100 Dilution
1	1	4830	985	212	88
4	4	13300	1270	238	101
10	10	12500	983	167	89
24	24	17100	992	184	103
24	48	16000	881	142	65
24	72	12800	796	148	57
24	96	10300	810	131	51
Mean		12400	960	175	79
Ratio		A/B 13	B/C 5	C/D 2	

Discussion

EPTC is a volatile liquid which rapidly vaporizes when placed on a warm surface such as a rat's back. The potential problems associated with a dermal absorption study of such a compound appear to have been effectively handled by the use of activated charcoal impregnated filter paper to cover the protective appliance. This mimics the field exposure in that the compound is allowed to vaporize off and is trapped so that it can be quantitated and so that it can not enter the animal through another route/site. The filter paper also allows free circulation of air over the application site.

There are two deficiencies in the study which may distort the data. However, considering the overall nature of the data generated in this study, they are not considered significant. First, it would have been helpful to have added a trap to the air flow out of the metabolism chamber to trap expired and/or vaporized radioactivity. Second, the application site skin for the 1, 4 and 10 hour exposures was removed from the animal and then washed rather than washed in situ. We have learned that in vitro washing can give excessive skin binding values as the test material will bind to the cut surface and/or the inner face of the skin. However, considering that the majority of the test compound had vaporized off the application site before the wash, this procedure will not significantly effect the skin 'binding' data in this study.

Blood concentrations appear to have no relation to the duration of exposure and are relatively consistant throughout the exposure periods. This may be a function of a slow excretion rate but we have no data on excretion rates. The ratio of relative blood concentrations are quite close to the ratio of the applied doses. We have no data on compounds of comparable physical properties and so cannot determine if

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this is consistant with the general physical properties or if it is unique to the compound.

There is one anomalous data set in the dose distribution data in Table 1. For Dose B one hour exposure the skin, skin wash and protective appliance values are not distributed as one would expect from the rest of the data of that and the other doses. The skin and skin wash data appear to be to high and the protective appliance data to low. The individual animal data appear to have more variation than that of the other doses at this duration of exposure but no single values of B one hour stand out as sufficiently different than the other three to allow one to say that is an erroneous value. With this in mind the general obervations will set this aside as puzzleing, neither ignoring nor trying to incorporate it.

The largest part of the applied dose is rapidly lost by evaporation. Considering the largest dose differences, 100 fold for A and D, there is a relatively small difference in the portion of dose lost by evaporation. Overall the dose differences can hardly be considered a trend. Skin wash and skin residue decrease with time through 10 hours with little change beyond. There is little dose related difference in the portion of dose absorbed. This does not agree with the absorption pattern usually seen with nonvolatile compounds but we do not have enough data to determine if this is consistant with volatile compounds.

Table 2. Dose distribution, as percent of dose, following a single dermal dose of EPTC. Values are means of four animals.

Wash 1 Time (hrs)	Sacrifice Time (hrs)	Skin	Carcass	Urine	Feces	Total[a] Absorbed	Skin Wash 1	Protective Appliance 1	Skin Wash 2	Protective Appliance 2	Total Recovery
Dose A, Neat											
1	1	2.04	1.00	0.12	0.00	1.12	10.0	86.8	-	-	100
4	4	1.85	2.35	2.37	0.01	4.73	6.66	86.9	-	-	100
10	10	1.15	1.21	3.72	0.01	4.94	0.97	88.4	-	-	96
24	24	0.68	0.89	7.56	0.14	8.59	0.35	81.9	0.25	-	92
24	48	0.12	0.22	7.22	0.11	7.55	0.27	83.6	0.02	0.93	93
24	72	0.07	0.15	7.36	0.54	8.05	0.12	81.0	0.01	0.50	90
24	96	0.02	0.13	6.46	0.14	6.73	0.15	84.6	0.01	0.25	92
Dose B, 1 to 10 dilution											
1	1	8.50	1.99	0.23	0.00	2.22	22.9	59.9	-	-	94
4	4	3.47	2.39	1.79	0.11	4.29	2.27	82.6	-	-	93
10	10	2.40	0.84	3.54	0.03	4.41	1.13	85.3	-	-	93
24	24	1.35	1.02	4.49	0.24	5.75	0.66	85.3	0.30	-	93
24	48	1.09	0.24	4.33	0.19	4.76	0.61	86.9	0.09	0.78	94
24	72	0.75	0.21	4.11	1.76	6.08	0.86	84.7	0.11	0.90	93
24	96	0.64	0.18	4.14	0.19	4.51	0.58	88.0	0.07	0.70	95
Dose C, 1 to 50 dilution											
1	1	3.85	2.17	0.24	0.00	2.41	6.80	77.1	-	-	90
4	4	1.41	1.94	2.08	0.00	4.02	2.06	82.1	-	-	90
10	10	1.15	0.89	2.49	0.01	3.36	1.59	85.6	-	-	92
24	24	0.62	0.60	2.30	0.16	3.06	0.84	86.1	0.33	-	91
24	48	0.44	0.39	2.79	0.08	3.26	0.90	88.4	0.06	0.57	94
24	72	0.60	0.37	3.70	0.09	4.16	0.92	83.1	0.10	0.65	90
24	96	0.30	0.26	2.88	0.10	3.24	0.79	84.5	0.05	0.80	90
Dose D, 1 to 100 dilution											
1	1	2.70	1.98	0.15	0.00	2.13	4.72	75.6	-	-	85
4	4	1.62	2.03	1.81	0.01	3.85	1.72	79.8	-	-	87
10	10	1.52	1.21	3.36	0.01	4.58	1.53	83.7	-	-	91
24	24	1.02	1.18	4.16	0.25	5.59	1.11	79.4	0.43	-	87
48	48	0.60	0.48	3.27	0.07	3.82	1.37	80.2	0.11	0.56	87
72	72	0.47	0.49	3.40	0.11	4.00	1.25	82.2	0.12	0.46	88
96	96	0.58	0.31	3.03	0.17	3.51	1.16	82.7	0.09	0.57	89

a. Total of carcass, urine and feces.