DATA EVALUATION RECORD

9/6/05

BAS 670H

Study Type: §85-2a; Dermal Penetration Study - Rats

Work Assignment No. 1-01-11 W (MRID 45902307)

Prepared for
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U.S. Environmental Protection Agency
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Disclaimer

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DATA EVALUATION RECORD

STUDY TYPE: Rodent *In Vivo* Dermal Penetration Study - Rat; OPPTS 870.7600 [§85-2]; OECD (none).

PC CODE: 123009 **DP BARCODE:** D292904

TEST MATERIAL (RADIOCHEMICAL PURITY): BAS 670H technical (>98%)

SYNONYMS: [3-(4,5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-phenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone-[pyrazole-4-^{14}C]

CITATION: Beimborn, D., and E. Leibold (2002) ^{14}C-BAS 670H - study of the dermal absorption in rats. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory Project No.: 01B0022/996052, May 27, 2002. MRID 45902307. Unpublished

SPONSOR: BASF Corporation, P.O. Box 13528, Research Triangle Park, NC

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 45902307), [pyrazole-4-^{14}C] BAS 670H (>98%, batch/lot #706-1013) was administered to the shaved intact skin (10 cm^2) of 4 male CrlGlxBrlHan:WI rats/time point/dose at dose levels of 0, 0.004, 0.068, or 3.36 mg ai/cm^2. Exposure durations were 1, 4, 10, and 24 hours. Additional groups of rats were exposed for 10 hours and sacrificed after 24 (only at low dose) and 72 hours.

Recovery of the applied dose was acceptable, 95.9-105.5% for each group at each sampling interval. Following all exposure periods up to 24 hours, the majority of the applied dose for each group was not absorbed (91.0-98.3% dose), with the greatest amount of the non-absorbed material being recovered from the skin wash (90.8-96.0% dose). Absorbed radioactivity was low and accounted for 0.16-2.60% of the dose for all groups for all exposures (Table a)..

In all dose groups, skin residues ranged from 3.04-6.52% dose after 1 hour of exposure, and increased an additional 2% dose after 24 hours exposure duration (4.99-8.73% dose). Only limited absorption of these skin residues was evident, with residues remaining in the skin

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accounting for 1.78-5.19% dose in animals exposed for 10 hours and sacrificed after 72 hours (Table b).

Table a. Mean percent radioacivity absorbed.

Exposure Time (h)	Sacrifice Time (h)	3.36 mg/cm^2	0.068 mg/cm^2	0.004 mg/cm^2
		% abs	% abs	% abs
1	1	0.16	0.85	2.19
4	4	0.24	0.56	1.07
10	10	0.22	1.23	0.99
24	24	0.31	0.60	2.6
10	24	---	---	1.53
10	72	1.23	1.73	1.88

Table B. Mean percent radioactivity in washed skin

Exposure Time (h)	Sacrifice Time (h)	3.36 mg/cm^2	0.068 mg/cm^2	0.004 mg/cm^2
		% skin	% skin	% skin
1	1	2.53	5.99	6.45
4	4	2.54	6.84	6.50
10	10	2.89	6.61	6.92
24	24	47.58	8.12	8.16
10	24	---	---	4.63
10	72	1.67	4.33	4.87

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided.

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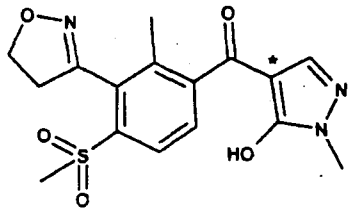
I. MATERIALS AND METHODS

A. MATERIALS:

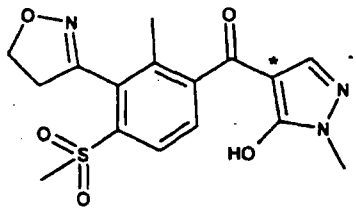
1. Test material: [pyrazole-4-^{14}C] BAS 670H

Description:	Powder (radiolabeled)
Lot/Batch #:	706-1013 (radiolabeled
Purity:	>98% a.i.
Compound stability:	Not provided
CAS # for TGAI:	210631-68-8
Structure:	

* indicates position of ^{14}C-label within molecule

Vehicle/solvent used:	Tap water was used as the vehicle, if necessary (low and intermediate dose levels).
Specific activity:	5.76 MBq/mg (346,000 dpm/µg)
Radiochemical purity:	>98%
Source:	BASF AG, Ludwigshafen, Germany

[pyrazole-4-^{14}C] BAS 670H

Description:	Liquid (unlabeled)
Lot/Batch #:	2000-2 (unlabeled)
Purity:	>99% a.i.
Compound stability:	Not provided
CAS # for TGAI:	210631-68-8
Structure:	

Vehicle/solvent used:	Tap water was used as the vehicle, if necessary (low and intermediate dose levels).
Source:	BASF AG, Ludwigshafen, Germany

2. Relevance of test material to proposed formulation(s): Dose formulations were comprised of the end-use product (EPA Reg. No. 375-080) mixed with different amounts of radiolabeled pure compound, depending upon the dose. Additionally, in the low and mid dose groups, dose formulations were diluted with water, to simulate exposure to dilute aqueous sprays.

3. Test animals:

Species:	Rats, male	
Strain:	CrlGlxBrlHan:WI	
Approximate age/weight at study initiation:	10 weeks; 240-287 g	
Source:	Charles River Laboratories (Sulzfeld, Germany)	
Housing:	Individually in Metabowl all-glass metabolism cages (Jencons, Leighton Buzzard, UK)	
Diet:	Kliba lab diet for rat/mouse/hamster Certified Rodent Chow® #8728CM (Harlan Teklad), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not reported
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	Not provided	

B. STUDY DESIGN

1. Dose

Rationale and nominal doses: Doses were selected to cover a broad range of potential exposure scenarios. The low nominal dose, 0.004 mg/cm^2 (1/900 aqueous dilution of formulation concentrate), was selected to represent the spray dilution for field use; the mid dose, 0.068 mg/cm^2 (1/49 aqueous dilution of formulation concentrate) was intended to represent hands-only operator exposure to the formulation concentrate (derived from POEM considering a dermal exposure of 55 mg/person to an 800 cm^2 area); and the high dose, 3.36 mg/cm^2 (formulation concentrate) represented more extensive operator exposure to the formulation concentrate.

Actual Doses: 0.005, 0.074, and 3.45 mg ai/cm^2 skin were the mean (over all durations) administered doses.

Dose volume: 10 µL/cm^2 skin

Duration of exposures (time from dose to skin wash): Dermal exposure was terminated immediately prior to sacrifice at 1, 4, 10, and 24 hours post-dose. Additional recovery groups were included that were exposed for a duration of 10 hours and then sacrificed at 24 hours (low dose only, 14 hours after skin wash) or 72 hours (62 hours after skin wash).

Number of animals/group: 4 rats/time point/dose

2. Animal preparation: Twenty-four hours before dosing, the back and shoulders of each rat was shaved, and the shaved area was washed with acetone. The site of application (approximately 10 cm^2) was defined and protected by a silicone ring glued to the skin.

3. Dose preparation, administration and quantification

Preparation: Dose formulations were prepared by mixing the appropriate amount of the radioactive test material with the formulation concentrate to achieve the intended radioactivity per animal (approximately 1, 0.7, and 0.1 MBq/rat for the high, mid, and low doses, respectively; Table 1). The low and mid dose mixtures were then brought up to volume with tap water; the high dose mixture was administered neat. Dose formulations were stirred and sonicated in order to achieve homogeneity.

Table 1. Dosing [a]

Nominal Dose (mg ai/cm^2)	Amount of BAS 670H in dosing solution (mg/animal)			Specific Activity (dpm/µg) [e]	Actual Dose (mg ai/cm^2) [f]
	Radio-labeled [b]	Non-labeled [c]	Total [d]		
0.004	0.023	0.026	0.049	157655	0.005
0.068	0.117	0.617	0.735	1608	0.074
3.36	0.160	34.377	34.537	1608	3.45

a Data were obtained from pages 17 and Tables 4-19 on pages 30-45 in the study report.
b The amount of ^{14}C-labeled test substance added to the dosing solution was calculated by the reviewers by dividing the average MBq administered/animal by the original specific activity of the ^{14}C-test substance (5.76 Mbq/mg).
c The amount of non-labeled test substance in dosing solution was calculated by the reviewers by subtracting the ^{14}C-labeled amount from the amount in the total mixture.
d The total amount of test substance in the dosing solution was calculated by the reviewers as an average of the mean dose administered (mg/animal) presented in Tables 4 through 19 on pages 30-45 of the study report.
e Specific activity of BAS 670H in the final dosing solution.
f Calculated by the reviewers as an average of the actual doses for each exposure duration presented in Tables 1 through 3 on pages 27-29 of the study report.

Application: 100 µL was applied within the dose site enclosure using a syringe which was weighed before and after application. The dosing site was then covered by nylon mesh glued to the surface of the silicone ring, and a porous bandage was used to encircle the trunk of the animal. Treated animals were placed in Metabowl metabolism cages, for collection of excreta. CO_2 was not collected.

Quantification: Samples of each dosing solution were taken before and after application to determine the amount of radioactivity in each solution and to verify the stability, homogeneity, and concentration of test substance in each dosing solution. These parameters were determined using liquid scintillation counting (LSC) for the low dose preparation and using an unspecified analytical method for the high and mid dose preparations. Results from these analyses were not provided.

4. **Skin wash (pre-sacrifice):** At the end of the exposure period, the protective cover was removed and the treated skin was washed with a mild soap solution. For recovery group animals,

a fresh gauze and nylon bandage was applied after the post-exposure skin wash, and an additional skin wash was performed immediately before the scheduled sacrifice.

5. **Sample collection:** At the end of the exposure (or recovery) period, animals were sacrificed and the following specimens/tissues were collected for radioanalysis: urine, feces, blood cells, plasma, liver, kidneys, carcass, treated (application site) and non-treated (surrounding application site) skin, skin wash(es), cage wash, and the protective cover (including the silicone ring).

6. **Sample preparation and analysis:** The protective cover, silicone spacer, and skin wash pads were extracted with SOLUENE (Packard). Weighed aliquots of these extracts and of the liquid samples (plasma, urine, cage wash) were mixed with scintillation cocktail and analyzed for radioactivity without any additional treatment.

Feces and carcass were homogenized with water, and aliquots of these suspensions were lyophilzed. The resulting powder and homogenates of the other tissues or aliquots of the skin were solubilized in SOLUENE. In order to bleach these samples, as well as blood samples, a solution of isopropanol and H_2O_2 was added and left for 24 hours at room temperature.

After addition of scintillation cocktail, the samples were counted for 10 min in a liquid scintillation counter (Wallac type 1409), and the disintegration rate was corrected for the respective background. The limit of detection was taken as twice background disintegration rate.

II. RESULTS

A. **SIGNS AND SYMPTOMS OF TOXICITY:** No information was provided regarding the clinical condition of the animals during the study.

B. **DERMAL ABSORPTION:** Dose distribution is presented in Tables 1, 2 and 3 from the report. Recovery of the applied dose was 95.89-105.48% for each group at each sampling interval (Table 2). Following all exposure periods up to 24 hours, the majority of the applied dose for each group was not absorbed (90.99-98.29% dose), with the greatest amount of the non-absorbed material being recovered from the skin wash (90.80-96.03% dose).

Estimates of dermal absorption were based on the sum of radioactivity in the body (blood + plasma + kidney + liver + carcass) and excreted (urine + cage wash + feces). Regardless of exposure duration, absorbed radioactivity was low for each group, accounting for 0.99-2.6% dose for the low dose groups, 0.56-1.73% dose for the mid dose groups, and 0.16-1.23% dose for the high dose groups. The actual amount of dose absorbed increased with increasing dose, with 0.05-0.13 $\mu g/cm^2$ in the low dose, 0.42-1.26 $\mu g/cm^2$ in the mid dose, and 5.46-43.54 $\mu g/cm^2$ in the high dose.

For each dose and exposure duration, the majority of the absorbed radioactivity was associated with the carcass, liver, and kidneys. Together these tissues accounted for 63.6-98.2% of the

absorbed radioactivity at exposures up to 24 hours. Of the selected tissues analyzed, concentrations of radioactivity were highest in the kidneys in all groups at each exposure interval. Average concentrations of radioactivity (µg Equivalents/g) in kidneys were 0.031-0.158 µg/g for the low dose groups, 0.257-0.412 µg/g for the mid dose groups, and 1.58-3.45 µg/g for the high dose groups.

Although the majority of the radioactive dose remained in the body for the duration of the study, the % dose excreted increased incrementally with exposure duration in the low dose group (0.03-0.37% dose). Except for this trend, there was neither dose nor time dependence regarding the % dose excreted. The percent of the absorbed dose that was excreted ranged from 11-27% in all dose groups after 10 or 24 hours exposure and 14-52% after a 10-hour exposure and 72-hour sacrifice.

Elimination of the absorbed radioactivity occurred via the urine. For animals sacrificed at 72 hours, following a 10-hour exposure, radioactivity recovered in the urine accounted for approximately 35% of the absorbed dose for the mid and high dose groups, and 10% of the absorbed dose for the low dose group.

Residues retained on or in the skin at and around the application site were considered available for potential absorption, and accounted for 3.04-6.52% dose after 1 hour of exposure in all groups. At the longest exposure interval (24 hours), radioactivity associated with the skin increased by an additional 2% dose, for a total of 4.99-8.73% dose. However, continued absorption of radioactivity associated with the skin was limited. Radioactivity remaining in or on the skin immediately following the 10-hour exposure period accounted for 3.25-8.20% dose and declined to 1.78-5.19% dose by the 72-hour sacrifice, for a decline of 1.5-3.5% dose. However, there was only a concomitant increase in absorption of 0.5-1.0% dose.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Following a single dermal administration of [^{14}C] BAS 670H in the formulation concentrate and at 1/49 and 1/900 aqueous dilutions thereof, very limited dermal absorption was observed, amounting to a maximum of 1.88% of the administered dose after a 10-hour exposure (and 72 hour depuration period) and 2.6% dose after a 24-hour exposure period. The mean relative amount of radioactivity absorbed was neither time nor dose dependent. Percentages of absorption at the high dose were considerably lower than the low dose, indicating a saturation effect of increasing dose on dermal penetration.

B. REVIEWER COMMENTS: Recovery of the applied dose was acceptable, 95.9-105.5% for each group at each sampling interval. Following all exposure periods up to 24 hours, the majority of the applied dose for each group was not absorbed (91.0-98.3% dose), with the greatest amount of the non-absorbed material being recovered from the skin wash (90.8-96.0% dose). Absorbed radioactivity was low and accounted for 0.16-2.60% of the dose for all groups. The actual amount of dose absorbed increased with increasing dose, with 0.05-0.13 µg/cm^2 in the

low dose, 0.42-1.26 µg/cm^2 in the mid dose, and 5.46-43.54 µg/cm^2 in the high dose. However, there was neither dose nor time dependence regarding the % dose absorbed.

In all dose groups, skin residues ranged from 3.04-6.52% dose after 1 hour of exposure, and increased an additional 2% dose after 24 hours exposure duration (4.99-8.73% dose). Limited absorption of these skin residues was evident, with residues remaining in the skin accounting for 1.78-5.19% dose in animals exposed for 10 hours and sacrificed after 72 hours. The % dose excreted increased incrementally with exposure duration in the low dose only (0.03-0.37% dose). The percent of the absorbed dose that was excreted ranged from 11-27% in all dose groups after 10 or 24 hours exposure and 14-52% after a 10-hour exposure and 62-hour depuration period.

C. **STUDY DEFICIENCIES:** The following study deficiencies were noted but do not affect the conclusions of this DER:

- It was stated that the concentration, homogeneity, and stability of the test substance in the dosing preparations were verified analytically; however, these data were not provided.

TABLE 1: MEAN EXCRETION AND RETENTION OF RADIOACTIVITY AFTER A SINGLE DERMAL ADMINISTRATION OF ^{14}C-BAS 670 H TO RATS AT A NOMINAL DOSE LEVEL OF 3.36 MG/CM^2.

If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/cm²]	3.36				
Exposure time [h]	1	4	10	24	10
Sacrifice time [h]	1	4	10	24	72
Actual dose [mg/cm²]	3.41	3.36	3.51	3.44	3.54
Urine	0.01	0.06	0.05	0.06	0.14
Feces	0.00	0.00	0.00	0.01	0.21
Cage wash	0.00	0.01	0.01	0.00	0.29
Bloodcells	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00
Kidney	0.01	0.02	0.02	0.02	0.01
Liver	0.04	0.07	0.06	0.06	0.08
Carcass	0.10	0.09	0.09	0.14	0.50
Material absorbed	0.16	0.24	0.22	0.31	1.23
Surrounding skin	0.51	0.49	0.36	0.41	0.11
Protective cover	0.28	0.18	0.24	0.47	0.53
Skin (application site)	2.53	2.54	2.89	4.58	1.67
Skin wash	97.10	98.11	95.44	96.94	92.04
2nd skin wash	—	—	—	—	0.31
Total recovery	100.59	101.55	99.42	102.70	95.89

TABLE 2: MEAN EXCRETION AND RETENTION OF RADIOACTIVITY AFTER A SINGLE DERMAL ADMINISTRATION OF ^{14}C-BAS 670 H TO RATS AT A NOMINAL DOSE LEVEL OF 0.068 MG/CM^2.

If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/cm²]	0.068				
Exposure time [h]	1	4	10	24	10
Sacrifice time [h]	1	4	10	24	72
Actual dose [mg/cm²]	0.070	0.075	0.076	0.074	0.073
Urine	0.10	0.09	0.27	0.10	0.41
Feces	0.04	0.01	0.01	0.01	0.07
Cage wash	0.03	0.01	0.03	0.03	0.22
Bloodcells	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00
Kidney	0.06	0.07	0.09	0.06	0.06
Liver	0.34	0.18	0.43	0.13	0.59
Carcass	0.27	0.21	0.41	0.27	0.37
Material absorbed	0.85	0.58	1.23	0.60	1.73
Surrounding skin	0.20	0.20	1.59	0.48	0.40
Protective cover	1.20	0.83	0.32	0.07	0.14
Skin (application site)	5.99	6.84	6.61	8.12	4.33
Skin wash	95.01	94.25	94.22	93.12	94.57
2nd skin wash	—	—	—	—	0.56
Total recovery	103.24	102.67	105.48	102.40	101.71

TABLE 3: MEAN EXCRETION AND RETENTION OF RADIOACTIVITY AFTER A SINGLE DERMAL ADMINISTRATION OF ^{14}C-BAS 670 H TO RATS AT A NOMINAL DOSE LEVEL OF 0.004 MG/CM^2.

If not stated otherwise, results expressed as % of the radioactivity administered.

Nominal dose [mg/cm²]	0.004					
Exposure time [h]	1	4	10	24	10	10
Sacrifice time [h]	1	4	10	24	24	72
Actual dose [mg/cm²]	0.00475	0.00473	0.005	0.0049	0.0052	0.0049
Urine	0.00	0.03	0.04	0.27	0.20	0.10
Feces	0.00	0.01	0.01	0.05	0.05	0.08
Cage wash	0.03	0.01	0.06	0.05	0.03	0.09
Bloodcells	0.02	0.01	0.01	0.01	0.01	0.01
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.60	0.15	0.12	0.46	0.30	0.14
Liver	0.80	0.21	0.25	0.66	0.47	0.25
Carcass	0.75	0.65	0.50	1.09	0.48	1.22
Material absorbed	2.19	1.07	0.99	2.60	1.53	1.88
Surrounding skin	0.07	0.49	0.32	0.57	0.45	0.32
Protective cover	0.08	0.06	0.05	0.19	0.18	0.22
Skin (application site)	6.45	6.50	6.92	8.16	4.63	4.67
Skin wash	92.73	93.76	91.92	90.80	94.66	94.26
2nd skin wash	—	—	—	—	1.37	0.21
Total recovery	101.51	101.87	101.24	102.32	102.81	103.81