DATA EVALUATION RECORD

^{14}C BAS 510 F/128008

STUDY TYPE: DERMAL PENETRATION - RAT
[OPPTS: 870.7600 (§85-3)]
MRID 45404920

2/5/2002

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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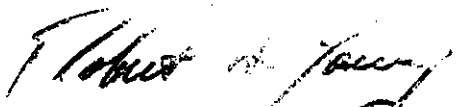
Task Order No. 02-06

Primary Reviewer: Robert A. Young, Ph.D., D.A.B.T.	Signature: Date:	 FEB 0 5 2002
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(1)

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DATA EVALUATION RECORD
TXR#: 0050193

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

PC CODE: 128008 **DP BARCODE:** D278384
SUBMISSION NO.: S604279

TEST MATERIAL (PURITY): BAS 510 F (>99% chemical purity; >95% radiochemical purity)

SYNONYMS: 2-chloro-*N*-(4'-chloro-biphenyl-2-yl)nicotiniamide-[diphenyl-U-^{14}C]

CITATION: Liebold, E., Hoffmann, H.D. (2001) ^{14}C-BAS 510-F Study of the dermal absorption in rats. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, D-67056 Ludwigshafen/Rhein, FRG. Laboratory report NO. 01B0426/976047, February 16, 2001. MRID 45404920. Unpublished

SPONSOR: BASF Corporation, Agricultural Products Division, Research Triangle Park, NC 27709.

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 45404920), [^{14}C]-BAS 510 F (diphenyl label; Lot/Batch no. 641-2017; >95% radiochemical purity) in distilled water was applied to the shaved dorsal surface (~10 cm^2) of male rats (four/group) at nominal doses of 0.01, 0.10, or 1.0 mg/cm^2 for periods of 1, 4, 10, or 24 hours. At the low dose two groups were washed at 10 hours and sacrificed at 24 and 72 hours. At the intermediate and high-dose one group at each dose was washed at 10 hours and sacrificed at 72 hours.

Percent mean dose distribution, as absorbed and remaining in the washed application site skin, is presented in the table below;

Exposure Time (hours)	1	4	10	24	10	10
Sacrifice Time (hours)	1	4	10	24	24	72
0.01 mg/cm^2						
Absorbed % ug/cm^2	0.52 0.052	2.02 0.202	8.07 0.807	10.93 1.093	6.26 0.626	5.72 0.527

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Skin	2.80	2.36	2.69	3.76	0.77	0.50
0.1 mg/cm^2						
Absorbed % ug/cm^2	0.37 0.37	0.25 0.25	0.63 0.63	2.63 2.63	— ---	2.07 2.07
Skin	1.45	1.42	1.99	3.32	---	0.49
1.0 mg/cm^2						
Absorbed % ug/cm^2	0.17 1.7	0.33 3.3	0.42 4.2	0.41 4.1	— ---	1.48 14.8
Skin	2.65	2.13	2.05	2.22	---	0.15

The percent of the dose absorbed increased with duration of exposure to 24 hours but decreased with increasing dose. This latter pattern is indicative of approaching saturation of absorption. However, since the quantity absorbed increased with each dose, one cannot determine directly if saturation was reached at the high dose. By plotting the quantity absorbed by dose with time, it was determined that the absorption from the washed skin at the high dose continued at the same rate as before washing. This showed that absorption was saturated at the high dose. Test material remaining in the washed skin decreased significantly in the animals that were washed at 10 hours and then sacrificed at 24 or 72 hours.

This dermal penetration study (MRID 45404920) in rats is **Acceptable/Guideline** and satisfies the requirements for a Dermal Penetration Study [OPPTS 870.7600 (§85-13)].

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

I. MATERIALS AND METHODS:

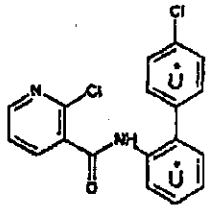
portions of this section are extracted from the report and are indicated as " "

A. MATERIALS:

1. TEST SUBSTANCE

labeled material

Code:	^{14}C-BAS 510 F
Chemical name:	2-Chloro-N-(4'-chloro-biphenyl-2-yl)nicotinamide[diphenyl-U-^{14}C]
Test substance No.:	97/426-2
Molecular formula:	$C_{18}H_{12}Cl_2N_2O$
Origin:	Synthesis; isotope laboratory BASF AG, Ludwigshafen
Batch/Lot No:	641-2017
Radiochemical purity:	> 95 %; verified analytically prior to all experiments
Physical state:	Solid
Storage:	at 4°C in the dark
Stability:	Verified analytically prior to all experiments
Structure:	



*designates label

unlabeled material

Code:	BAS 510 F
Origin:	Synthesis at BASF AG, Ludwigshafen
Batch/Lot No.:	01183-190
Test substance No.:	971179-5
Chemical purity;	> 99 % (analysis of May 1999)
stability	stability confirmed in February 2001
Physical state:	Solid
Storage:	At ambient temperature

The analyses of the test substances were carried out by BASF Aktiengesellschaft, Agricultural Center, Limburgerhof, FRG.

2. VEHICLE

Doubly distilled water was used as vehicle.

3. STABILITY AND HOMOGENEITY OF THE TEST SUBSTANCE PREPARATIONS

Stability in vehicle: verified analytically in all experiments

Homogeneity and correctness of the concentrations: verified analytically in all experiments

The analyses of the test substance preparations were carried out by Experimental Toxicology and Ecology, Bioanalytical Laboratory, BASF Aktiengesellschaft, Ludwigshafen, FRG.

4. TEST SYSTEM

Animals:	rats
Strains:	Crl:WI (GLX/BRL/HAN) IGS BR
origin:	Charles River *Laboratories, Sulzfeld, Germany*
Sex:	Male
Age:	About 14-17 weeks at application
Weight:	Ca. 248 - 377 g (weight was measured prior to dosing)

B. STUDY DESIGN:

The experimental groups, their respective treatment duration and observation periods, and actual doses are summarized in Table 1.

TABLE 1. Arrangement of experimental groups for assessment of dermal penetration of ^{14}C-BAS 510 F in male rats.

Experiment 1 (0.01 mg/cm² nominal)						
Duration of exposure (hrs)	1	4	10	24	10	10
Termination period (hrs)	1	4	10	24	24	72
No. of animals	4	4	4	4	4	4
Actual dose (mg/cm²)	0.01±0.0	0.01±0.0	0.01±0.0	0.01±0.0	0.01±0.0	0.01±0.0
Experiment 2 (0.10 mg/cm² nominal)						
Duration of exposure (hrs)	1	4	10	24	-	10
Termination period (hrs)	1	4	10	24	-	72
No. of animals	4	4	4	4	-	4
Actual dose (mg/cm²)	0.1±0.0	0.1±0.0	0.1±0.0	0.1±0.0	-	0.1±0.0
Experiment 3 (1.00 mg/cm² nominal)						
Duration of exposure (hrs)	1	4	10	24	-	10
Termination period (hrs)	1	4	10	24	-	72
No. of animals	4	4	4	4	-	4
Actual dose (mg/cm²)	1.1±0.1	0.9±0.1	1.1±0.1	0.9±0.1	-	0.9±0.1

Data taken from pp. 17-19, and Tables 4-19, pp. 30-45, MRID 45404920.

Rationale for dose selection

"The dermal application was selected in order to simulate user specific exposure scenarios. According to the relevant guidelines, experiments shall be performed using doses expected in field exposure."

"Using model calculations (BBA-model, POEM), doses of 35-145 mg/person were estimated. If it is assumed, that exposure will predominantly occur on the hands and forearms (2 x 800 cm^2) this will correspond to doses of approximately 0.02 - 0.116 mg/cm^2. Based on these data and to cover this range, the doses were chosen."

C. PREPARATION OF TEST SUBSTANCE

"A stock solution was prepared for the labeled material in toluene. If necessary, the unlabeled test substance was added to appropriate aliquots of the toluene stock solution in order to achieve the required specific activity and the intended dose level. The organic solvent was evaporated to dryness at 300°C under vacuum and the respective amounts of blank formulation (BAS 510 01F) and doubly distilled water were added. Prior to administration the preparation was stirred and sonicated in order to produce a homogeneous preparation. Before start of and at the end of the administrations samples were taken to determine the amount of radioactivity in the solution and to show the homogeneity."

D. ADMINISTRATION OF TEST MATERIAL

"Twenty-four hours prior to dosing the back shoulders of the rats were clipped free of hair and the area (about 10 cm^2) was washed with acetone. A silicone ring was glued to the skin, the test substance preparation (about 10 ul/cm^2) was administered with a syringe which was weighed before and after application. A nylon mesh was then glued to the surface of the silicone ring and a porous bandage used to encircle the trunk of the animal."

E. EXPOSURE, TERMINATION AND SAMPLE COLLECTION.

"In this set of experiments, animals were treated and then placed in metabolism cages in order to collect excreta up to 72 hours. After the respective exposure period, the protective cover was removed and the exposed skin was washed with a mild soap solution. For animals with a post-observation period, a new gauze and a new bandage was applied and an additional skin wash was performed before sacrifice. At the end of the various collection periods animals were sacrificed and the following specimens/tissues were checked for remaining radioactivity-."

"excreta, blood cells, plasma, liver, kidneys, carcass, skin [treated (= application site) and non-treated areas (surrounding skin)]"

"For balance estimates the cage wash and skin wash(es) as well as the protective cover (including the silicone ring) were also checked for radioactivity"

II. RESULTS

A. SIGNS OF TOXICITY:

The study reported no signs of toxicity in rats following dermal exposure to BAS 510 F at the doses tested.

B. SUMMARY TABLES:

Mean dose distribution, as percent of dose, is presented in Table 2 and summarize in Table 3. Note that mean totals in these tables do not always 'add up'. This is due to rounding from the individual values and obtaining the total absorbed and recovered as the mean of the individual values rather than as the totals of the mean sample values.

C. DOSE DISTRIBUTION:

Recovery of the applied dose was acceptable (group means ranged from 95-116 %). .

The majority of the applied dose for all dose groups were recovered from the skin washes with ranges of 87-101% for the low dose, 90-112% for the intermediate dose and 85-112% for the high dose. At the high dose mean skin wash was comparatively less for the 4, 24 and 72 hour groups with the missing material being found on the protective cover. 2/4, 3/4 and 2/4 individual animals in the respective groups accounted for the high values on the protective covers.

The total absorbed dose was determined as the sum of radioactivity in the urine, feces, tissues, carcass, and cage wash. Absorption ranged from 0.52-10.93% low dose, 0.25 -2.63 intermediate dose and 0.17-1.48% high dose. At each dose percent absorption increased with duration of exposure but decreased with increasing dose (Figure 1). This is indicative of increasing saturation of absorption with increasing dose. However, the quantity absorbed per unit area continued to increase with increasing dose indicting that a saturated dose had not yet been reached (Table3).

Further, data from the washed animals indicated that absorption from the skin residue continued after washing. Test material in washed skin at 10 hours and carried to 72 hours went from 2.69-0.5%, 1.99-0.49% and 2.05-0.15% for the respective doses. The quantity of test material in the skin decreased and the quantity absorbed increased.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Low dose (0.01 mg/cm²)

"Following a single dermal administration of ^{14}C-BAS 510 F at a nominal dose level of 0.01 mg/cm² (0.1 mg/animal or 0.4 mg/kg body weight), the mean recovery of radioactivity in the different groups was between 100.36 % and 113.98 %,"

"In all groups, the largest proportion of radioactivity was recovered from the skin wash. Recoveries in skin wash amounted to 87.07 - 100.63 % of the radioactivity applied. In the groups with 10 h exposure and either 24 or 72 h post observation period, 87.07 - 96.00 % were found in the 10 h skin wash, whereas the second skin wash after 24 and 72 h contained 5.23 % and 0.40 %, respectively."

"The protective cover contained 0.62 - 1.12 % of the radioactivity applied, In the animals with immediate sacrifice after end of exposure, the portions of radioactivity recovered from the application site ranged from 2.36 - 3.76 %, At the end of the 24 and 72 h post observation periods, radioactivity in the application site amounted to 0.77 and 0.50 % of the radioactivity applied, respectively. The amounts of radioactivity in the skin surrounding the application site ranged from 0. 12 - 1.65 % of the radioactivity applied. The amount of radioactivity absorbed (including excreta, cage wash. tissues/organs and carcass) was 0.52 % after 1 h, 2.02 after 4 h, 8.07 % after 10 hours and 10.93 % after 24 h, respectively. At 24 and 72 hours after beginning of a 10 h exposure, absorbed material amounted to 6.26 % and 5.72 % of the dose applied, respectively."

"Due to the variation of results in the groups with 10 h exposure, no evaluation is possible concerning the fate of the radioactivity remaining in the skin after the skin wash at the end of the exposure period."

"Seventy two hours after beginning of exposure, the absorbed radioactivity was excreted mainly via the feces."

"Due to the very limited skin penetration, concentrations of radioactivity in organs and tissues analyzed were very low with the remaining carcass and liver showing the highest values and the maximum level of 0.085 ug eq/g being found in liver after 10 h."

Intermediate dose (0.1 Mg/ cm²)

"Following a single dermal administration of ^{14}C-BAS 510 F at a nominal dose level of 0.0 mg/cm² (1.0 mg/animal or about 4 mg/kg body weight), the mean recovery of radioactivity in the different groups was between 96.90 % and 116.74 %."

"In all groups, the largest proportion of radioactivity was recovered from the skin wash. Recoveries in skin wash amounted to 90.03 - 112.28 % of the radioactivity applied. In the group with 10 h exposure and post observation period, 90.03 % were found in the 10 h skin wash and 1.89 % in the 72 h skin wash."

"The protective cover contained 0,20 - 2.27 % of the radioactivity applied. In the animals with immediate sacrifice after end of exposure, the portions of radioactivity recovered from the application site ranged from 1.42 - 3.32 %. At the and of the 72 h post observation period, radioactivity in the application site amounted to 0.49 % of the radioactivity applied. The amounts of radioactivity in the skin surrounding the application site ranged from 0.45 - 1.82 % of the radioactivity applied."

"The amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) was 0.37 % after 1 h, 0.25 after 4 h, 0.63 % after 1 0 hours and 2.63 % after 24 h, respectively. At 72 hours after beginning of a 10 h exposure, absorbed material amounted to 2.07 % of the dose applied."

"These results together with the skin wash data and the amounts in the application site indicate that at this dose level a considerable portion of the radioactivity remaining in the skin after end of exposure can be washed off and does not penetrate through the skin during the post-observation period."

"Seventy two hours after beginning of exposure, the absorbed radioactivity was excreted mainly via the feces."

"Due to the very limited skin penetration, concentrations of radioactivity in organs and tissues analyzed were very low with the remaining carcass and liver showing the highest values and the maximum level of 0. 1 09 ug eq/g being found in carcass after 24 h."

High dose (1.0 Mg/cm²)

"Following a single dermal administration of ^{14}C-BAS 510 F at a nominal dose level of 1.00 mg/cm² (10 mg/animal or about 36 mg/kg body weight), the mean recovery of radioactivity in the different groups was between 95-54 % and 116.02 % of the applied radioactivity."

"In all groups, the largest proportion of radioactivity was recovered from the skin wash. Recoveries in skin wash amounted to 82.74 - 112.28 % of the radioactivity applied. In the group with 10 h exposure and post observation period, 85.56 % were found in the 10 h skin wash and 0.31 % in the 72 h skin wash."

"The protective cover contained 0.77 - 9.93 % of the radioactivity applied. In the animals with immediate sacrifice after end of exposure, the portions of radioactivity recovered from the application site ranged from 2.05 - 2.65 %. At the end of the 72 h post observation period, radioactivity in the application site amounted to 0. 1 5 % of the radioactivity applied. The amounts of radioactivity in the skin surrounding the application site ranged from 0.33 - 8.24 % of the radioactivity applied."

"The amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) was 0. 1 7 % after 1 h, 0.33 after 4 h, 0.42 % after 1 0 hours and 0.41 % after 24 h, respectively.

At 72 hours after beginning of a 10 h exposure, absorbed material amounted to 1.48 % of the dose applied."

"These results together with the skin wash data and the amounts in the application site imply that at this dose level most of the radioactivity remaining in the skin after end of exposure penetrates through the skin during the post-observation period."

"Seventy two hours after beginning of exposure,, the absorbed radioactivity was excreted mainly via the feces."

"Due to the very limited skin penetration, concentrations of radioactivity in organs and tissues analyzed were very low with the remaining carcass and liver showing the highest values and the maximum level of 0.226 ug eq/g being found in carcass after 72 h."

"Overall, a comparison of skin penetration at the three dose levels applied showed that the relative amount of radioactivity absorbed increased with increasing exposure and sacrifice time. With increasing dose the percentage of radioactivity absorbed decreased. This becomes most evident when comparing skin penetration at the low and intermediate dose level. These results clearly indicated saturation of penetration with increasing dose. The variation of results did not allow make a firm evaluation of the fate of the radioactivity remaining in the skin after the skin wash at the end of the exposure period."

Conclusion

"Following single dermal administration of ^{14}C-BAS 510 F mixed with the blank of a commercial formulation (BAS 510 01F) and taken up in water there was limited absorption through the skin amounting at maximum to about 8 % of the dose applied after a 10 h exposure period and to about 11 % after a 24 h exposure period, respectively. With increasing dose the percentage of radioactivity absorbed decreased indicating saturation of skin penetration with increasing dose."

B. REVIEWER COMMENTS:

In a dermal penetration study (MRID 45404920), [^{14}C]-BAS 510 F (Lot/Batch no. 641-2017; >95% radiochemical purity) was applied to the shaved dorsal surface (~10 cm^2) of male rats (four/group) at doses of 0.01, 0.10, or 1.0 mg/cm^2 for periods of 1, 4, 10, or 24 hours. For the 10-hour exposure groups, the experimental protocol included post-exposure observation periods to 24 and 72 hours after dosing (low-dose group) and to 72 hours after dosing (intermediate and high-dose groups).

Absorption was low at all doses with the majority of dose being removed by washing. The percent of dose absorbed increased with duration of exposure but decreased with increasing dose. This latter pattern is generally indicative of saturation of absorption but is not sufficient in itself to prove saturation. Saturation can generally be said to have occurred if the quantity absorbed does not increase between the intermediate and the high dose. In this study the quantity absorbed

increases with each dose. The presence of wash off doses in this study allows another way of determining if saturation occurred at the high dose. Saturation can occur at either of two steps in the process of dermal penetration; entry into the outer layer of the skin (the stratum corneum) or subsequent exit from the stratum corneum into the systemic space. Saturation at this second step can be detected by washing the application site and following the fate of the skin residue to determine the rate at which it continues to enter the systemic space. If this rate is the same as the rate before washing, saturation at the second step has been demonstrated. Figure 2 plots the mass absorbed by dose with time. At the high dose the portion of the curve defined by 4, 10 and 72 hours is straight indicating that absorption is saturated at the second step.

In all three doses, washing the application site and continuing the animals for up to 72 hours post dose results in a decrease in the quantity of material in the washed skin and an increased absorption. This clearly indicates continued absorption of skin residue.

This dermal penetration study (MRID 45404920) in rats is **Acceptable/Guideline** and satisfies the requirements for a Dermal Penetration Study [OPPTS 870.7600 (§85-13)].

RIN-0870-05

DER For MRID No. 45404920

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