DATA EVALUATION RECORD

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.7600 [§85-2]; Dermal Penetration Study in Rats

Work Assignment No. 4-1-125 (MRID 46808304)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: *In Vivo* Dermal Penetration Study in Rats; OPPTS 870.7600 [' 85-2]; OECD none.

PC CODE: 129108 **DP BARCODE:** D331116
TXR#: 0054348

TEST MATERIAL: XDE-570 (Florasulam; 98-99% radiochemical purity)

SYNONYMS: *N*-(2,6-difluorophenyl)-8-fluoro-5-methoxy[1,2,4]triazolo[1,5-*c*]pyrimidine-2-sulfonamide

CITATION: Bounds, S.V.J. (1997) XDE-570: Dermal absorption of [^{14}C]-XDE-570 in male Fischer 344 rats following exposure to undiluted EF-1343 and a spray solution – final report. Huntingdon Life Sciences Ltd., Eye, Suffolk, England. Laboratory Study No.: DWC/891; Report No.: DWC891/972958, October 14, 1997. MRID 46808304. Unpublished.

SPONSOR: DowElanco Europe, Letcombe Laboratory, Letcombe Regis, Wantage, Oxfordshire, England.

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 46808304), [^{14}C]-XDE-570 (Florasulam; 98-99% radiochemical purity as applied; Batch Nos. B463-145 and C237-7B) was applied to the skin (12 cm^2) of Fischer 344 rats (4 males for each time point at each dose level). Nominal doses were 0.001 or 0.5 mg/cm^2 skin. The high dose (EF-1343 commercial formulation) was included to assess exposure to mixer/loaders. The low dose (spray dilution, using an EF-1343 blank as a vehicle) represented a dose that was 2.39-fold more concentrated than the highest anticipated spray concentration for use on field crops, which was necessary in order to provide sufficient analytical sensitivity. The exposure duration was 24 hours, after which one group of 4 males for each dose level was sacrificed. The remaining 2 groups/dose were sacrificed at 48 or 72 hours post-application.

Recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Increasing the dose 200-fold resulted in only

approximately 2-fold increase in absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable.

The compound isolated in the treated skin after 72 hours (including the 24 hour exposure period) would be absorbed in negligible amounts. The highest dermal absorption noted was 0.45% of the applied dose. This value is considered appropriate for use in risk assessment, with the appropriate uncertainty factors applied.

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

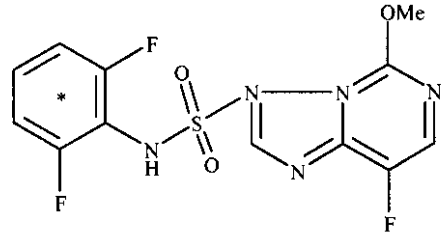
COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: XDE-570

Description: White solid (low dose) or milky white suspension (high dose)
Batch Nos.: B463-145 (low dose); C237-7B (high dose)
Compound Stability: Data not reported
Vehicle/Solvent used: EF-1343 blank formulation
Radiolabelling:



* denotes the position of [^{14}C]-labeled atoms

Specific Activity: 54.6 mCi/mmol (low dose); high dose not reported
Radiochemical Purity: 99% (low dose); 98% (high dose)
Source: DowElanco Europe, Oxfordshire, England

Test material: XDE-570
Description: Fine off-white powder
Lot No.: RMM 2184
Purity: 99.9% (w/w)
Compound stability: Data not reported
CAS # for TGAI: 145701-23-1
Source: Not reported

2. Relevance of test material to proposed formulation(s):
EF-1343 is a commercial formulation and as such is relevant in the preparation of the testing formulations. The high dose formulation was supplied by the Sponsor as EF-1343, containing [^{14}C]-XDE-570. The low dose was made using the EF-1343 blank.

3. Test animals:

Species: Rat
Strain: Fischer 344
Age/weight at study initiation: Approximately 61-75 days old/205-235 g males
Source: Charles River (UK) Limited, Margate, Kent
Housing: Individually housed in all-glass metabolism cages with removable metal mesh flooring
Diet: Laboratory Animal Diet No. 1 SQC expanded rodent diet (Special Diet Services, Essex, UK), *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 19-25EC
Humidity: 40-70%
Air changes: ≥15/hr
Photoperiod: 12 hours dark/ 12 hours light
Acclimation period: At least 5 days

B. STUDY DESIGN: At the end of the acclimatization period, the rats were re-weighed, and the rats nearest the mean bodyweight were arbitrarily allocated to the treatment groups (4 males/termination period/dose).

1. Dose

Rationale: The high dose (formulation concentrate) was included to assess exposure to mixer/loaders. The low dose (spray dilution) represented a dose that was 2.39-fold more concentrated than the highest anticipated spray concentration for use on field crops, which was necessary in order to provide sufficient analytical sensitivity.

Nominal doses: 0.001 or 0.5 mg/cm^2 skin

Actual doses: 0.0009 or 0.53 mg/cm^2 skin

Dose volume: 10 µl/cm^2

Duration of exposures (time from dose to skin wash): 24 hours

Termination periods (time from dose to sacrifice): 24, 48, or 72 hours

Number of animals/group: 4

2. Animal preparation: On the day before dosing, an area of dorsal skin was clipped. Immediately prior to dosing, a silicone rubber saddle with an interior area of approximately 12 cm^2 was attached to the clipped area using cyanoacrylate adhesive.

3. Dose preparation, administration and quantification:

Preparation: The high dose formulation was supplied by the Sponsor as EF-1343 (commercial formulation), containing [^{14}C]-XDE-570. The formulation was stored at 4°C with dessicate. The low dose (spray dilution) was prepared by mixing the blank formulation with [^{14}C]-XDE-570 for 30 minutes just prior to sampling and dosing. Both formulations had a radiochemical purity of 98% at the time of application.

Application: The dose formulations were applied (120 µL) with pipettes, and the doses were evenly distributed with a dose spreader. Following dose application, the application site was semi-occluded with stainless steel gauze held in place over the silicone rubber saddle by surgical tape. The rats were housed individually in metabolism cages, and urine and feces were collected over dry ice. CO_2 was not collected.

Quantification: The radiolabelled concentration of both dose preparations was determined throughout dosing, and the radiochemical purity was assayed at each dosing. Homogeneity was not determined. The actual doses are reported in Table 1.

TABLE 1. Dosing [a]		
Nominal dose level (mg/cm^2)	Specific activity (KBq/mg XDE-570)	Actual dose (mg/cm^2)
0.001	5590	0.0009
0.5	110	0.53

a Data (mean of 3 groups of 4 rats) were obtained from page 28 of MRID 46808304.

4. **Skin wash (pre-sacrifice):** After 24 hours, the gauze was removed and retained for analysis. The application sites were swabbed with the animals held over the metabolism cages, or after the scheduled 24 hour sacrifice. The sites were swabbed with 4% (by volume) soap solution and dried with cotton wool. The swabs were retained for analysis. Clean gauzes were attached to the silicone rubber saddles with surgical tape for groups scheduled for termination at 48 or 72 hours post-application.

5. **Sample collection:** Following dosing, urine and feces were frozen upon excretion by collection over dry ice. Urine and feces were collected at 24 hour intervals until termination. At the end of each collection period, the cages were washed with distilled water, and the cage washes were retained. At the scheduled termination, a sample of blood was removed from the tail vein, the animals killed by an overdose of halothane, and the application site tape stripped. The rats were carefully dissected separating treated skin (plus approximately 1 cm of surrounding skin), untreated skin, liver, kidneys, and residual carcass into individual containers. The saddle, gauze, and surgical tape were also retained for analysis.

6. **Sample preparation and analysis:** When samples were not analyzed immediately, they were stored at -20°C. Details of sample preparation are provided in Table 2. Duplicate weighed aliquots of each sample were assayed for radioactivity using liquid scintillation counting (LSC). The liquid scintillation spectrometer was calibrated using a quenched carbon-14 toluene series and external standard spectral quench parametric analysis. The limit of detection (LOD) was twice the background counts. At the low dose, the LOD was 4.27 ng eq/g in blood and 0.16-1.33 ng eq/g in other samples. At the high dose, the LOD was 230.7 ng eq/g in blood and 7.9-69.8 ng eq/g in other samples. The oxidizer was calibrated for combustion efficiency and $^{14}CO_2$ recovery using SPEC-CHECK™ carbon-14 standard. Total amounts of radioactivity in samples were reported as a percentage of the total dose applied and, for blood, as a concentration (µg eg/g).

TABLE 2. Sample preparation details [a]	
Sample type	**Preparation method**
Dose formulation, urine, and cage wash	Direct liquid scintillation counting (LSC) was conducted.
Feces	Samples were homogenized in water and combusted prior to LSC.
Whole blood and treated skin	Samples were solubilized prior to LSC. Whole blood was solubilized in Soluene-350, and treated skin was solubilized in 2 M NaOH in H_20: MeOH (1:1 v/v).
Skin swabs and cellophane tape strips	The swabs and tape strips were soaked in acetone immediately after collection and then extracted in acetone for 3 hours by Soxhlet extraction prior to LSC.
Gauze, saddle, and surgical tape	Samples were soaked overnight in acetone and sonicated for approximately 15 minutes prior to LSC.
Livers, kidneys, residual carcass	Samples were homogenized in water and then solubilized in Soluene-350 prior to LSC.

a Information was obtained from pages 20, 25, and 26 of MRID 46808304. Further details were not provided.

II. RESULTS

A. SIGNS AND SYMPTOMS OF TOXICITY: No mention of observations was made in the methods, and no signs or symptoms were reported for any animal.

B. SUMMARY TABLES: Results are summarized in Tables 3a and 3b.

TABLE 3a. Amount of [^{14}C]-XDE-570 in each matrix at specified hours post-application of 0.001 mg/cm^2 (skin wash at 24 hours) [a]			
Matrix analyzed	**Residues in matrix (% of applied dose; n=4)**		
	24 h	**48 h**	**72 h**
Urine	0.18±0.16	0.26±0.16	0.29±0.08
Feces	ND	ND	ND
Cage wash	ND	ND	ND
Skin (untreated)	ND	ND	ND
Carcass	ND	ND	ND
Liver	ND	ND	ND
Kidneys	ND	ND	ND
Skin (treated)	12.2±0.90	21.8±2.27	20.9±2.51
Gauze wash	2.58±0.55	7.29±7.47	3.22±1.82
Skin swab	85.1±1.80	71.4±6.78	75.0±3.84
Tape strips	0.26	1.17±0.68	0.91±0.32
Recovery (sum of above)	100.3±0.89	101.9±2.27	100.3±1.01
Dermal absorption (based on sum of skin (untreated) + tissues and residual carcass + urine + feces + cage wash)	0.18±0.16	0.26±0.16	0.29±0.08

a Data were obtained from Tables 1-3 on pages 36-38 of MRID 46808304.

TABLE 3b. Amount of [^{14}C]-XDE-570 in each matrix at specified hours post-application of 0.5 mg/cm^2 (skin wash at 24 hours) [a]

Matrix analyzed	Residues in matrix (% of applied dose; n=4)		
	24 h	48 h	72 h
Urine	0.02±0.01	0.14±0.20	0.07±0.03
Feces	ND	ND	0.02
Cage wash	0.05±0.05	0.12	0.02
Skin (untreated)	0.27±0.25	0.18±0.33	0.02
Carcass	0.04	ND	ND
Liver	ND	ND	ND
Kidneys	ND	ND	ND
Skin (treated)	11.1±4.28	9.88±0.57	10.0±1.27
Gauze wash	4.71±3.09	3.20±3.60	1.45±0.79
Skin swab	85.4±5.77	87.6±6.22	90.1±1.45
Tape strips	0.59±0.40	0.84±0.30	1.00±0.34
Recovery (sum of above)	102.2±1.94	102.0±1.45	102.7±0.57
Dermal absorption (based on sum of skin (untreated) + tissues and residual carcass + urine + feces + cage wash)	0.39±0.32	0.45±0.77	0.13±0.08

a Data were obtained from Tables 4-6 on pages 39-41 of MRID 46808304.

C. **TOTAL ABSORBED DOSE:** Recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Generally, increasing the dose 200-fold resulted in only approximately 2-fold increase in absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS= CONCLUSIONS:** The potential for dermal absorption of XDE-570 is very low in the rat. The absorbed dose was rapidly removed from the site and excreted in the urine. The proportion of dose remaining in the treated skin beyond 24 hours after the skin swabbing is significantly more than was absorbed and excreted, and did not decrease at the

48 and 72 hour time points. Therefore, it is considered unlikely that the dose remaining in the skin would be absorbed, but would probably be removed with natural epidermal turnover.

B. REVIEWER COMMENTS: Recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Increasing the dose 200-fold resulted in only approximately 2-fold increase in absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable.

The reviewers agree with the Sponsor that the compound isolated in the treated skin after 72 hours would be absorbed in negligible amounts. The highest dermal absorption noted was 0.45% of the applied dose. This value is considered appropriate for use in risk assessment, with the appropriate uncertainty factors applied.

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

C. STUDY DEFICIENCIES: The following deficiencies were noted in this dermal penetration study, but were considered minor and do not affect the conclusions of this review:

- The doses were not selected at log intervals.
- Duration of exposure was not tested at 1 and 10 hours.
- Stability and homogeneity data were not reported but were not considered crucial as the test substance was radiolabeled.
- No formal randomization procedure was indicated.