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

006727

APR 19 1988

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 707-EPE:ERN;EPP/7F3476:7H5524. RH-3866 (Rally™)
Fungicide. Response to Additional Data Submitted on
Dermal Penetration Study

Tox. Chem. No. 723Y

TO: Lois Rossi, PM #21
Fungicide-Herbicide Branch
Registration Division (TS-767c)

FROM: Pamela M. Hurley Ph.D., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Pamela M. Hurley

*Budd/88
4/19/88
16/2/88 TB*

Background and Request:

Rohm and Haas filed an application for registration of a new pesticide, RH-3866 Technical, and two end-use products, Rally™ 40W fungicide and Rally™ 60DF fungicide, all containing the active ingredient, myclobutanil. In its review of the toxicity studies submitted with the application, the Toxicology Branch (TB) stated that the dermal penetration study was inadequate because analysis of the application site skin and residue in the carcass were needed to verify recovery. Rohm and Haas subsequently submitted additional data on the dermal penetration study. TB has been asked to review the submitted data on the study and revise its conclusions concerning the study, if appropriate.

Response:

The submitted data has been reviewed by TB see attached memorandum. TB's conclusion is that due to a lack of data on the material remaining in the carcasses, it is impossible to perform a material balance on the dose in the treated animals. Therefore, the rating of the study remains unacceptable.

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MEMORANDUM

April 15, 1988

SUBJECT: RH-3866, Additional Comments re the Dermal Absorption Study

TO: Pamela H. Hurley Ph.D.
Review Section II

FROM: Robert F. Zendzian PhD *4/15/88*
Senior Pharmacologist
Toxicology Branch
HED (TS-769)

Action Requested

The Registrant submitted the following dermal absorption study which was considered unacceptable. A complete material balance had not been performed and one was unable to quantitate the total material absorbed. However, it was noted that if the Registrant analyzed the application site skin samples and the carcasses from the study, thus completing the material balance, it might be possible to find the study acceptable.

RH-3866 Dermal Absorption study in male rats, Protocol No 85P-394, L.J. DiDonato & R.B. Steigerwalt, Rohm and Haas Co, Report No. 85R-179, Aug 26, 1986. Accession #266104.

The Registrant has submitted the following report which includes analysis of the application site skins but reports that the carcasses have been discarded unanalyzed.

RH-3866: ¹⁴C-Analysis of application site skins following dermal application of ¹⁴C-RH-3866 to male rats. Supplement A to RH-3866 Dermal Absorption study in male rats, Report No. 85R-179, Protocol No 85P-394. S.L. Longacre, Rohm & Haas, Mar 10, 1988.

Conclusion

Lacking data on the material remaining in the carcasses, it is impossible to perform a material balance on the dose in the treated animals and the study remains unacceptable.

Discussion

The basic deficiency noted in the review of this dermal absorption study was the failure to analyze the application site skin and the carcasses of the treated animals. Experience has shown that significant quantities of test compound can remain on/in the application site after washing and are potentially absorbable. Studies on the absorption of such residue have shown varying degrees of absorption, in the extreme case approximately 50% of the dose remained on the skin and was absorbed over two week. In addition the relatively slow entry of test compound into the body from the application site could tend to favor redistribution of test compound into slow exchanging tissue of the body. Thus carcass residue data is also necessary.

Obtaining this information would enable one to overcome a fundamental and serious deficiency, obvious and uncorrectable errors in dosing. Based on available recovery data, but lacking data on the test material in the carcass, at least 9 of the 12 animals appear to have been overdosed (Table 1).

Table 1. Total recovery as percent of nominal dose. Data from Table II of the report plus skin data from Table 2 of the supplementary report.

<u>Animal Number</u>	<u>Route</u>	<u>Nominal Dose (ug/rat)</u>	<u>Total recovery (% dose)</u>	<u>Calculated Dose_a (ug/rat)</u>
6245-1	dermal	15,000	109.09	16363
7270-2	dermal	15,000	117.35	17602
6272-3	dermal	15,000	116.19	17428
6246-4	dermal	15,000	94.55	14183
		Mean	109.20	16380
6259-5	dermal	37.5	140.20	52.59
6255-6	dermal	37.5	136.11	51.04
6261-7	dermal	37.5	101.91	38.22
6260-8	dermal	37.5	124.97	46.86
		Mean	125.62	47.1
6243-9	iv	30	149.92	44.98
6250-10	iv	30	135.05	40.52
6247-11	iv	30	109.07	32.73
6241-12	iv	30	100.59	30.18
		Mean	123.66	37.1

a. Nominal dose X percent recovered.

It is particularly important to note the dosing variation in the intravenous group. This group was dosed by dissolving the test material in dimethylsulfoxide and injecting 60 ul of the solution. This was not only the easiest group to dose, but the only group in which it appears, from the kinetics of excretion, that recovery is essentially complete (see below). Yet, actual doses, based on recovery data, range from 100 to 149 % of nominal dose or 30 to 45 ug/rat. Since the concentration of the solution was verified, the errors are in measurement of dose volume and/or delivery of the dose. Measurement and delivery of the dermal doses have even greater possibilities for error. No attempt was made to measure the actual dose delivered such as by weighing the pipette before and after dosing or delivering a dose into a measured quantity of solvent and analyzing. Since we have serious doubts as to the dose delivered we cannot say that all of it is accounted for by simply adding up the quantities detected and comparing them to the nominal dose.

The pattern of dose excretion following the intravenous dose allows one to conclude that essentially all of the dose had been excreted at the end of the experiment. However, comparison of this data with the excretion pattern of the dermal doses leads one to conclude that up to 8 percent of the dermal dose can remain in the carcass at the end of the experiment.

Excretion following the intravenous dose follows a typical biphasic pattern (Fig. 1)¹. Ninety two percent, of the total percent of dose excreted², is excreted in 2 days, 99 percent is excreted in 5 days and less than 1 percent in the remaining two days (Table 2). This is typical of rapid excretion of readily available compound followed by excretion of compound from a slowly exchangeable tissue store. In contrast the excretion of the high dermal dose shows a monophasic, linear, pattern with no indication that excretion has been completed on the 7th day (Fig. 2). This pattern of excretion is typical of excretion from depot administration of a compound. In this case the depot is skin where, despite the six hour wash, compound continues to be absorbed and 1.25 percent of the dose remains at sacrifice. The low dermal dose excretion pattern is biphasic, but the latter half gives no indication that excretion has been completed on the 7th day (Fig. 3). Again compound continues to be absorbed from the washed skin where 13.5 percent of the dose remains at sacrifice.

At the same time that test compound is being slowly absorbed into the animal from the dermal site it can be expected to be entering into and equilibrating with the slow exchange compartment identified by the excretion kinetics of

1. Figures 1-3 from the Aug 26, 1986 report.
2. This conversion is utilized to compensate for the errors in dosing.

the intravenous dose. Considering that the slow exchange compartment identified in the intravenous dosing held up to 8 percent of the dose, additional test material equivalent of up to 8 percent of the dose may remain in the dermally dose animals. Because we are uncertain as to the dose that was actually delivered we cannot quantitate this material by material balance. Because the carcasses were not analyzed we cannot quantitate this material directly.

Thus the data available can underestimate dermal absorption by up to 8 percent of the dose delivered.

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Pages 6 through 8 are not included.

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Table 2. Mean ¹⁴C-Cumulative Excretion (Total of urine and feces). Expressed as percent of nominal dose. Data from Appendix C of the first report. Dermal dose washed off after 6 hours.

RH-3866		Dose ¹⁴ C-RH-3866		DURATION (Hours)									
2EC		(ug/cm ²)		(ug/rat)		6	24	48	72	96	120	144	168
Route	Dilution												
Dermal	None	3,750	15,000	0.19	2.54	5.87	9.77	13.24	16.28	22.30	25.49		
Dermal	1:400	9.4	37.5	1.08	11.17	21.37	26.26	31.31	35.51	37.93	40.85		
iv	---	-----	30	31.93	89.91	107.57	113.15	114.70	115.97	116.52	116.93		