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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Aciflourfen (Blazer®) Registrant's Response to Review of Dermal Absorption Study

TO: Richard Mountfort PM-23
Registration Division (TS-767)

FROM: Robert P. Lendzian PhD 2/6/86
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HED (TS-769)

THROUGH: Reto Engler PhD, Head 2/6/86
Mission Support Staff

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Toxicology Branch

Compound; Acifluorfen (Blazer®) Tox Chem #&55D

Registration #707-149, -150 Registrant; Roham and Haas

Accession #N/A Tox Project #1049, 1050

Action Requested

The Registrant submitted the report of a dermal absorption study on Blazer which was reviewed and judged 'Unacceptable'. Additional data was requested by the reviewer. The Registrant has submitted a reply to the data request and commented on the review of the dermal absorption study.

Conclusion and Recommendation

The Registrant has not submitted the data requested, possibly because of a misunderstanding of the request. The study remains classified as 'Unacceptable' as it is impossible to untangle the internal inconsistancies in the data reported with the information available. We repeat our request, which is explained in detail in the Discussion below, for the basic analytical (counting) data for each sample for each animal and the steps by which the Registrant generated the numbers, percent of dose per sample, found in the table of Appendix F of the report. If this data is not available a laboratory audit of the study may be necessary.

Background

In 1985 the Registrant submitted the following dermal absorption study which was reviewed in a DER by Zendzian dated 9/11/85.

Dermal Absorption Study in Male Rats, R.B. Steigerwalt & S.L. Longacre, Rohm and Haas Co, Protocol No. 85P-058, Report No. 85R-063, April 26, 1985

Zendzian concluded that; "The results presented are internally inconsistant and inconsistant with the pattern expected for this type of study. Additional data are required to further evaluate the study and determine if it can be utilized." The Study was classified 'Unacceptable".

The following is the discussion and data-request from the DER.

"The data generated in this study are inconsistant with what one usually expects in the study of the dermal absorption of a foreign compound. The quantity absorbed at each dose is small, as is the percentage of dose absorbed. This is to be expected by the physical/chemical properties of the compound. Aciflourfen is the water soluble sodium salt and is ionized at neutral pH. However the relative absorption in relation to time and dose in this study do not follow the pattern expected in this type of study.

For any single dose of a compound which is absorbed dermally the percent absorbed can be expected to increase with time. Conversely for a compound that is absorbed dermally the percent absorbed per unit time can be expected to decrease with increasing dose. These relationships may not hold at extremes of dose or duration of exposure but are generally true throughout the middle ranges. Experience has shown that the percent absorption at half or one hour exposures for varying doses often does not follow this rule.

Both the urinary excretion data and the blood content date differ, in a nonuniform manner, from the expected pattern. The skin recovery data is of no assistance in verifying or disputing these results. Skin recovery is generally a rather crude measure which does not indicate differences in the order of a few percent or less. In this study the skin recovery data for the 756 ug dose adds to the confusion reflecting an absorption in the order of 20-30 percent while the urine and blood data for this dose indicate absorption in the order of 0.1-2.3 percent.

A further complication is present in the comparative data from blood and urine. Absorbed acifluorfen passes through the skin, enters the blood and is excreted in the urine. Because of its' physical/chemical properties one can expect

urinary excretion to be rather rapid. However, the data do not reflect such expectations. For example the data for a dose of 75.6 ug show 3.9 and 5.8 percent of the dose in the blood at 1 and 2 hours respectively but the excretion data show only 1.8 percent excreted at the end of 10 hours. There are additional but less obvious inconsistancies in the data from other doses. In general the blood data appear to be higher than expected in an order(s) of magnitude relationship to the excretion data.

In order to clearify these inconsistencies the following data is requested.

1. The complete individual animal and sample values for radioactivity recovary and a stepwise presentation showing how they were converted into the data format as presented in the report.

2. Data on the excretion of acifluorfen, particularly kinetic data. Blood half-life data and/or urinary excretion half-life data would be of particular value in resolveing the apparent inconsistencies between the blood and urine data presented in the report."

Registrant's Reply and Reviewer's Comments

The Registrant noted that the metabolism data has been submitted. It is now available to the reviewer.

The Registrant agreed that " no clear time course of ^{14}C-label in blood or urine was observed." and explained this as, "This was due to the small amount of dermal absorption of acifluorfen, and to animal to animal variation observed. Indeed, a study design in which different groups of rats are killed at different time intervals introduces more variation into the results, for both the time course of ^{14}C-excretion, compared to a design in which blood and excreta samples are collected from the same animals at different times. In addition the variation in the present study was accentuated by the relatively short time of the in-life phase (10 hr.)."

In reviewing a dermal absorption study following this protocol, this reviewer utilizes experience gathered over a period of six years in reviewing approximately 20 dermal absorption studies performed in different laboratories. Various data manipulations are undertaken to determine if a pattern of absorption is shown and if this pattern follows that which has been seen and expected in the majority of the studies reviewed. If, as sometime occurs, it doesn't follow the pattern there is usually a physical/chemical reason for this deviation. Manipulation of the data from this study showed no obvious reasons for the variability of the results. Compounds of similar physical/chemical properties

have been evaluated and internally consistant results obtained at similar penetration rates. Much smaller quantities have been followed in blood and urine at similar radio-activities. All of the available information indicates the possibility of problems in performance of the study. Considering only the variation of the blood and urine data, problems in sample collection, handling, analysis and the data conversion used to produce the tables in the report are possible. For this reason I requested the basic individual data. That is the radio-analytical data from which the information in Appendix F was ultimately derived.

Tables A and B, which were not used in the DER on this study, show part of the process used for concluding that there are problems associated with the data produced in this study. Blood and urine data as percent of dose found therein were combined to produce Table A. Experience has shown that the data from the 10 hour exposure period and from the high dose at all exposure periods are most likely to be internally consistent with the expected pattern of results. Quantitative 'experimental' errors will have the least proportional effect under these circumstances. If no consistancy is found we have an unusual, but not unique compound. This data from the study are generally consistant with expectations with only one outlieing value in each set. Both of these outliers are higher then expected. The rest of the data are then examined looking for outliers that are higher then expected. A total of nine outliers were identified with a particular concentration in the 2 hour exposure group and the 756 ug dose group.

The data in table A can also be evaluated graphically. Experience has shown that if one plots the dose against the percent absorbed on log-log paper for each exposure period one obtains a family of curves. The curves are essentially linear for each exposure period and the curves are parallel. As expected this relationship was not observed with the data from this study.

Outlieing values identified by either of these methods can be further examined by looking at the individual animal data to see if a single extreme value has distorted the mean value. One can often compensate for such distortion. In the case of this study this process was not helpful but further indicated the possibility of problems in the performance of the study.

Table A. Mean absorption as percent of dose. Obtained by adding mean percent of dose in urine and blood for each dose-interval. Microgram (ug) calculated from dose applied.

Dose ug/rat		Exposure time (hr) 0.5	1.0	2.0	4.0	10.0
7.56	%	1.5855	4.0900	5.8094	4.8818	4.3664
	ug	0.12	0.31	0.44	0.37	0.33
75.6	%	0.5744	1.2153	7.8004	0.5694	1.5141
	ug	0.43	0.92	5.90	0.43	1.14
756.0	%	1.7023	0.5699	1.6644	0.8193	3.3216
	ug	12.87	4.31	12.58	6.19	25.11
7560.0	%	0.0185	0.0263	0.0581	0.0311	0.0563
	ug	1.40	2.00	4.39	2.35	4.26

Table B. Data from Table A. Marked and footnoted to show outlieing values. Outliers are selected as being higher than expected based on high dose all intervals and 10 hour exposure all doses.

Dose ug/rat		Exposure time (hr) 0.5	1.0	2.0	4.0	10.0
7.56	%	1.5855	4.0900	5.8094†	4.8818	4.3664
	ug	0.12	0.31	0.44†	0.37	0.33
75.6	%	0.5744	1.2153*†	7.8004*†	0.5694	1.5141
	ug	0.43	0.92*†	5.90*†	0.43	1.14
756.0	%	1.7023*†	0.5699	1.6644†	0.8193*	3.3216*
	ug	12.87*†	4.31*	12.58*†	6.19*	25.11*
7560.0	%	0.0185	0.0263	0.0581†	0.0311	0.0563
	ug	1.40	2.00	4.39†	2.35	4.26

* higher then expected in the same exposure duration.
† higher then expected for the same dose.

way out by dose	way out by exposure