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

APR 29 1988

006684

MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 707-ERE;ERN;ERR/7F3476;7H5524. RH-3866 (RallyTM)  
Fungicide. Response to Comments Submitted By  
Registrant on Dominant Lethal Study

Tox. Chem. No. 723K

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

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

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

*Edg  
4/29/88  
4/29/88*

Background and Request:

Rohm and Haas filed an application for registration of a new pesticide, RH-3866 Technical, and two end-use products, RallyTM 40W fungicide and RallyTM 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 dominant lethal assay on Technical RH-3866 was unacceptable because current positive control data was not submitted with the study. Rohm and Haas submitted comments on TB's decision and included a statement from the testing laboratory which conducted the study. TB has been asked to respond to the Registrant's comments.

Response:

TB has reviewed the submitted comments and is responding to each point discussed by the testing laboratory which conducted the study (see attachment). The testing laboratory stated that it had submitted positive control data with another study submitted to the Agency. TB has located the submitted data and acknowledges that the positive control data were generated in the appropriate time frame for the dominant lethal study conducted on RallyTM. Therefore, the classification of the study is upgraded from unacceptable to acceptable.

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PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

**SUBJECT:** Response to Registrant Comments concerning EPA  
Review of Rally - Dominant Lethal Assay

**FROM:** Kerry L. Dearfield, Ph.D. *Kerry Dearfield*  
Geneticist  
Scientific Mission Support Staff  
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Hazard Evaluation Division (TS-769C) *4-22-88*

**TO:** Pamela Hurley, Ph.D.  
Section II  
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Hazard Evaluation Division (TS-769C)

**THRU:** Reto Engler, Ph.D.  
Chief  
Scientific Mission Support Staff  
Toxicology Branch  
Hazard Evaluation Division (TS-769C) *Reto Engler*  
*4/25/88*

Rohm and Haas Company had submitted a dominant lethal assay in support of their registration for Rally fungicide. The assay was performed for Rohm and Haas by Argus Research Laboratories. The assay was apparently well conducted and presented and obtained negative results. However, the assay was considered unacceptable by OPP as no concurrent or historical positive controls were submitted with the assay results. Most guidelines for the performance of the dominant lethal assay are uniform in their guidance for performing a positive control with at least one dominant lethal assay in a specified time period, usually one year, of any other dominant lethal assay that laboratory may perform. This reasoning was relayed to Rohm and Haas and eventually to Argus.

Rohm and Haas and Argus have responded to OPP's decision in a letter (March 11, 1988; MRID #'s 405482-00, 405482-01). They present four points of discussion:

1. The primary purpose of a positive control group is to demonstrate the proficiency of the laboratory personnel in performing a dominant lethal assay and to confirm the capability of the test species to demonstrate dominant lethal effects. They suggest that this is a practical exercise and does not generate new scientific information of interest.

2. Argus Research Laboratories, Inc. is an established laboratory that routinely performs reproductive and developmental toxicity studies. To assess their ability, many of their studies are available through the Freedom of Information Act after a study is evaluated by the EPA or FDA. One such dominant lethal assay that has been conducted for submission to EPA used a positive control (triethylenemelamine (TEM)).

3. It is documented that the strain of rat used, Sprague-Dawley, responds to dominant lethal effects and there is little reason to prove this fact again.

4. The use of a positive control would require the unnecessary wastage of a large number of additional animals just to redocument the abilities of the laboratory, to test an agent already known to produce dominant lethal effects and to demonstrate again the ability of the Sprague-Dawley rat to respond to dominant lethal effects.

The following will respond to these points.

The Toxicology Branch has looked to its files to locate the dominant lethal study that Argus states has been conducted for EPA purposes to locate the positive control data using TEM. The search was successful and the particular study was located and reviewed (Data Evaluation Record; Ethoprop, Mutagenicity - Dominant Lethal Assay in Rats; Reviewed for Toxicology Branch, OPP, April, 18, 1988; Document #006677). This study was performed in the appropriate time frame relative to when the Rally dominant lethal assay was performed. The TEM positive control, at 0.5 mg/kg, had a significant effect on dead implants and the dominant lethal index (percent of dead implants/total implants) at the majority of mating weeks. It appears that the positive control was adequate and demonstrated the ability of the laboratory personnel and test species to evaluate a dominant lethal effect. This periodic check is important as part of quality assurance for performing any biological assay. As a result of this submission with an adequate positive control, the dominant lethal assay performed with Rally should be upgraded to acceptable with negative results.

While Argus Research Laboratories, Inc. may be a well recognized laboratory performing many reproductive and developmental studies a year, it does not appear to have performed as many dominant lethal studies over any given time period. However, this reviewer has seen two dominant lethal studies performed by this laboratory and agree they appear well conducted and hopes the laboratory continues their performance at such a level. Although they may be well conducted, quality assurance encompasses the use of positive control data to help assure proper performance of an assay. Any laboratory can state that they are excellent and should be relieved of such

assurances. If all laboratories were relieved of quality assurance, there is no telling what may happen to the quality of testing results. Laboratory personnel do change over time and new technicians and supervisors need to be "broken in" for proper performance of assays. The use of positive controls allows for assurance of quality throughout a laboratory's lifetime. This is a major reason why positive controls are part of an assay's standard protocol.

For the dominant lethal assay, the use of positive controls has been reevaluated. There is no longer the recommended requirement that a concurrent positive control be performed with every dominant lethal assay. This is due in part that once laboratories have established themselves in dominant lethal assays, the concurrent positive control is not as necessary, as Argus points out. Another consideration is the reduction of the number of animals that need to be sacrificed. However, to completely eliminate the need for periodic positive controls may compromise the continued quality of that laboratory's performance, as outlined above. Until the fields of genetic toxicology and reproduction/developmental toxicology comes to an agreement that positive controls are not necessary as part of quality assurance, OPP would like to see the periodic use of positive control data for submissions from laboratories performing the dominant lethal assay. It is recommended that Argus Research Laboratories, Inc. continue to perform periodic positive controls in support of future dominant lethal assay submissions to EPA.

Therefore, positive controls are not performed just to prove that TEM produces dominant lethal effects once again, nor to demonstrate that TEM produces dominant lethal effects in Sprague-Dawley rats once again. Positive controls are an integral part of quality assurance in the performance of assays in an atmosphere of changing personnel, possible alterations and problems in animal stocks and unexpected deviations in assay performance.