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

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FEB 10 1994

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OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

**MEMORANDUM:**

**SUBJECT: FENBUCONAZOLE:** Registrant's Response to Agency Review of Studies Submitted to Fulfill Toxicology Data Requirements for Permanent Tolerances on Stone Fruit [PP1F3989] and Pecans [PP1F3995].

**FROM:** SanYvette Williams-Foy, D.V.M.
Review Section IV, Toxicology Branch II (H7509C)

**TO:** Cynthia Giles-Parker, PM 22/Dolphine Wilson
Registration Division

**THRU:** Jess Rowland, M.S., Acting Section Head
Section IV, Toxicology Branch II (H7509C) 2/9/94

and

Marcia van Gemert, Ph.D., Chief
Toxicology Branch II
Health Effects Division (H7509C) 2/10/94

**EPA IDENTIFICATION NUMBERS:**
PC Code: 129011
DP Barcode: D194777
MRID #: 428827-01 & -02
Submission #: S447325,

Registrant: Rohm and Haas Company

**Action Requested:** Toxicology Branch was requested to review registrant's response to Agency review of toxicology studies that had been classified as Core-supplementary.

**Response:** The Agency's review of the Registrant's responses and conclusions are attached. The information provided by the Registrant was satisfactory. Consequently, the Acute Inhalation Study [81-3]; the 21-Day Dermal Toxicity Study [82-2]; the Developmental Toxicity Study in rabbits [83-3b]; and the General Metabolism Study [85-1] are upgraded from Supplementary to Core Minimum. These studies satisfy the respective guideline requirements and are acceptable for regulatory purposes.

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I. **[84-3] Measurement of the Particle Size Distribution of kH-7592 2F Following Aerosol Generation** [MRID#: 418750-12]

Deficiency: This study does not meet requirements for guideline #81-3. Since it was performed to measure particle size distribution of the test material.

Registrant's Response: Because this study [MRID#: 418750-12] was intended as a formal confirmation of existing data already reviewed by the Agency [MRID#: 410312-25] and classified as Core Minimum, they submit that the two studies together fulfill data requirements when considered together.

Conclusion: The agency concurs that the two studies together [MRID#418750-12 and 410312-25] fulfill data requirements [#81-3] for an acute inhalation study in rats.

II. **[82-2] 21-Day Dermal Toxicity Study in Rat** [MRID#418750-13] and Report Amendment No. 1 to Final Report 90R-084 [MRID#: 428827-02]

Deficiency: This study was classified supplementary because neither test material stability [over the 4 week test period] nor a "flagging statement" were included in the study report.

Registrant's Response: The Registrant did not include stability because the dosing solutions were prepared fresh daily. The high-dose was applied undiluted and the low- and mid-dose groups were diluted with distilled water. Analysis of target concentrations were performed on the low- and mid-dose solutions [93% and 92% of target concentration, respectively], but results were inadvertently omitted from the original report and amended to this submission [MRID#: 428827-02].

It has been clarified that the Agency does not require a flagging statement for a 21-day dermal study.

Conclusion: This study is upgraded to Core-Minimum and satisfies the guideline requirements [#82-2] for a 21-day dermal toxicity study.

III. **[#83-3b] Rabbit Developmental Toxicity** [MRID#: 418750-14]

The following deficiencies were cited during the Agency's review of this study:

Deficiency 1: There were discrepancies in the calculations of mean corrected body weights and net weight changes from Day 0

in the control and high dose animals. Clarification of this discrepancy was requested.

Registrant's Response: The registrant explained the specific methodology used in calculating these parameters. Using this procedure, the data given was correct [See attachment page 5].

Deficiency 2: An explanation was requested for having more implantation sites than observed corpora lutea in the high-dose group which lead to the significant difference in preimplantation loss percentage rate when compared to controls.

Registrant's Response: Because only 1 high-dose female delivered a litter of viable fetuses, the number of corpora lutea (CL) and implantation sites were only from this animal. The registrant did not know the reason for the discrepancy between the CL and implantation sites, but did not rule out technical error. When all animals in the high-dose group were considered in terms of corpora lutea and implantation sites, group mean values were similar to other dose groups including controls [See attachment page 6].

Deficiency 3: A developmental toxicity LOEL could not be determined due to the very low number of fetuses available.

Registrant's Response: Using the high incidence of early resorptions in the high-dose group as indicative of embryo-fetal toxicity, the Registrant submitted that the 60 mg/kg dose should be used as the LOEL for developmental toxicity.

**Conclusion(s):** The maternal NOEL and LOEL are 30 mg/kg/day and 75 mg/kg/day, respectively. The developmental NOEL is 30 mg/kg/day and the LOEL is 60 mg/kg/day. Deficiencies have been adequately addressed and the Developmental Toxicity Study in rabbits [#83-3b] is upgraded to core-Minimum.

IV. **[85-1] Metabolism** [MRID#: 418750-17 and -18]

During the review of this study, the following deficiency was cited by the Agency:

Deficiency: Approximately 50% and 20% of the total radioactivity in the feces and urine, respectively, were not identified in the study, suggesting a lack of sensitivity of the analytical method used for metabolite analyses [MRID #'s 418750-17, and -18]. Since a low-dose oral group was not evaluated, a dose-related difference of metabolism could not be determined.

**Registrant's** submitted ad[illegible]MRID# 429008-01] was [illegible].

**Conclusion:** [illegible] Summary of the Data Evaluation Report of the [illegible] study is attached on page 7. The three studies [MRID#418750-17, -18 and 429008-01] together fulfill metabolism data requirements. They are upgraded to Core-Minimum.

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Pages 5 through 6 are not included.

The material not included contains the following type of information:

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ADDENDUM #3

EXECUTIVE SUMMARY: The absorption, distribution, metabolism, and excretion of RH-7592 were studied in groups of Crl:CD BR rats (3-5/sex/group) administered a single oral gavage dose of 1 or 100 mg/kg $^{14}$C-RH-7592 or administered 1 mg/kg/day unlabeled RH-7592 (in the diet) for 14 days followed by a single dose of 1 mg/kg $^{14}$C-hydrogen cyanamide on day 15. [MRID #: 429008-01]

The study demonstrated that radiolabeled RH-7592 is rapidly absorbed, distributed, and excreted following oral administration in rats. Total 3- or 4-day recoveries of the radioactivity were high for all groups [90.40-104.49% of the administered dose]. Biliary excretion data indicated that systemic absorption of RH-7592 was high for all dosing groups. The feces was the major route of excretion [78.74-94.43% of administered dose] after 4 days post-dosing, while recovery in the urine was low [<1% of the administered dose]. Tissue distribution and bioaccumulation of RH-7592 appeared to be minimal since <1% of the administered dose was recovered in tissues 4 dose after oral administration for all dosing groups. No sex- or dose-related differences in absorption, distribution, or elimination were found. Metabolism of RH-7592 was extensive as shown by the numerous metabolites characterized and isolated in the feces, bile, and urine. Furthermore, a dose-related difference in metabolism was evident. The higher amount of unmetabolized parent compound in the feces of the high-dose group compared to the low-dose and repeated-dose groups suggested that saturation of the metabolic pathway may be occurring at the high dose.

This study is classified as Core-Guideline. This study alone satisfies the guideline requirement for a metabolism study [#85-1] in rats. It fulfills the guideline requirement for oral low-dose, high-dose, and repeated-dose studies.

[illegible] study was submitted to upgrade a previously submitted metabolism study [MRID #: 418750-17 and -18]. The results were similar for the two studies. In the previous metabolism study, metabolite analysis data for the low-dose and repeated-dose groups were not provided; however, this study has addressed and satisfied this deficiency.