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

MAR 19 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: KATHON 886 F MICROBICIDE (EPA REG. NO. 707-130)
LETTER IN RESPONSE TO AGENCY LETTER OF 1/8/91

TO: JOHN LEE/JIM WILSON
PRODUCT MANAGER (31)
REGISTRATION DIVISION (H7508C)

FROM: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 3/12/91
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL. K. Clark Swentzel 3/13/91
TOXICOLOGY BRANCH II, HEAD SECTION II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. Marcia van Gemert 3/14/91
CHIEF, HEALTH EFFECTS DIVISION (H7509C)

REGISTRANT: ROHM & HAAS COMPANY
CHEMICAL: 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE, 2 METHYL-4-ISOTHIAZOLIN-3-ONE
SYNONYMS: KATHON 886 F
PROJECT: 1-0660
CASWELL NO.: 195C
RECORD NO.: NOT PROVIDED; CASE # 022081; SUBMISSION: S390760
ACTION REQUESTED: REVIEW COVER LETTER AND COMMENT. NOTE: 2 "BEAN SHEETS" ATTACHED - ONE FROM JOHN LEE/ONE FROM JIM WILSON; ONE IS MARKED EXPEDITE.

COMMENT: IN RESPONSE TO A LETTER DATED 1/8/91, THE REGISTRANT HAS SUBMITTED INFORMATION ON THE FOLLOWING STUDIES, WITH RESPECT TO DATA REQUIREMENTS UNDER THE ANTIMICROBIAL DCI FOR KATHON 886F INDUSTRIAL MICROBICIDE.

SUBCHRONIC TOXICITY - 90 DAY ORAL
RABBIT DEVELOPMENTAL TOXICITY
RAT TERATOLOGY STUDY
MUTAGENICITY

SUBCHRONIC TOXICITY

THE REGISTRANT IS REQUESTING A WAIVER OF THE 90-DAY SUBCHRONIC TOXICITY STUDY IN LIGHT OF THE FACT THAT A 2-YEAR CHRONIC/CARCINOGENICITY STUDY IS CURRENTLY UNDERWAY. TB II DOES NOT OBJECT TO THE PERFORMANCE OF A LONG-TERM STUDY, BUT MUST AWAIT A REVIEW OF THE RESULTS OF THAT STUDY BEFORE A DECISION CAN BE MADE REGARDING THE NEED FOR A SUBCHRONIC STUDY. IF THE RESULTS OF THE CHRONIC/CARCINOGENICITY STUDY ARE ADEQUATE, THE SUBCHRONIC STUDY MAY BE WAIVED.

RABBIT DEVELOPMENTAL TOXICITY

WITH REGARD TO THE RABBIT DEVELOPMENTAL TOXICITY STUDY, TB II DOES NOT AGREE THAT A REPEAT OF THE STUDY IS UNNECESSARY, OR THAT IT WOULD ONLY PROVIDE CONFIRMATION OF DOSE-RELATED MATERNAL TOXICITY AND NO ADDITIONAL EVIDENCE FOR THE NON-TERATOGENIC EFFECTS OF THE TEST MATERIAL. TB II POINTS OUT THAT, ALTHOUGH THERE WERE NO TERATOGENIC EFFECTS OBSERVED AT THE LOW DOSE, WHICH WAS MATERNALLY-TOXIC DOSE (1.5 MG/KG), THE NUMBER OF AVAILABLE LITTERS IS INADEQUATE (7) TO MAKE A DEFINITIVE STATEMENT. ADDITIONALLY, THERE WAS NO NO-EFFECT DOSE OBSERVED FOR MATERNAL TOXICITY.

RAT TERATOGENICITY

WITH REGARD TO THE INFORMATION PROVIDED ON THE TEST MATERIAL USED IN THE RAT STUDY, THE DATA SHEET INDICATES THAT THE TEST MATERIAL IDENTIFIED AS USED IN THE STUDY (LOT #78/4435, TD NO. 79-15) WAS 14% ACTIVE INGREDIENTS, AND THE LETTER INDICATED THAT THIS WAS ALSO STATED ON PAGE 3 OF THE STUDY REPORT. THE STUDY REPORT (PAGE 3) AVAILABLE TO THIS REVIEWER (ACCESSION #'S 245555 AND 247625) INDICATES ONLY THAT THE PURITY WAS ASSUMED TO BE 100% BY THE AUTHOR OF THE REPORT (TESTING FACILITY). HOWEVER, IN THE ABSTRACT (ACCESSION #247017), LOT NO. 78/4435, TD NO. 79-15 IS $\approx$ 15.5% A.I. (COPY ATTACHED). THIS INCONSISTENCY IN REPORTING OF THE TEST MATERIAL PURITY REQUIRES CLARIFICATION BEFORE THE STUDY CAN BE UPGRADED. IT IS TO BE NOTED THAT THE THE REQUEST FOR TOXICITY STUDIES SHEET IS DATED WITH THREE DIFFERENT DATES: 1/19/78 AT THE BOTTOM; APPROVAL SIGNATURE IS DATED 10/12/78; AND 1/22/79 AT THE TOP OF THE PAGE. THE NEXT PAGE: DATA SHEET FOR TOXICITY STUDIES IS ALSO DATED 1/19/78, WHICH APPEARS TO INDICATE THAT THE ANALYSIS OF THE TEST MATERIAL WAS PERFORMED THEN, AND 1/22/79 ON THE LINE MARKED: SIZE OF SAMPLE SUBMITTED FOR TOXICITY TESTS. THE STUDY REPORT INDICATED THAT THE TEST MATERIAL WAS RECEIVED IN JULY, 1979 AT THE TESTING FACILITY.

MUTAGENICITY

THE REGISTRANT REITERATED THEIR PLAN TO PERFORM AN <u>IN VIVO</u> CYTOGENETIC ASSAY AND AN UNSCHEDULED DNA SYNTHESIS ASSAY TO COMPLETE THEIR TIER 1 MUTAGENICITY REQUIREMENTS, AS PREVIOUSLY INDICATED (SEE TB II MEMO DATED 10/1/90).

DISCUSSION

TB II POINTS OUT THAT THE PREVIOUS REQUEST FOR CLARIFICATION OF THE DISCREPANCIES NOTED IN THE % A.I. AND TOTAL STABLE % A.I. HAS NOT BEEN ADDRESSED BY THE REGISTRANT (TB II MEMO DATED 10/5/90). ADDITIONALLY, THE REGISTRANT HAS PROVIDED THE SAME INFORMATION ON THE TEST MATERIAL USED IN THE RAT TERATOLOGY STUDY AS PREVIOUSLY SUBMITTED, BUT HAS NOT ADDRESSED THE INCONSISTENCY IN REPORTING.

CONCLUSION

THE REGISTRANT HAS NOT ADDRESSED THE PREVIOUS REQUEST FOR CLARIFICATION OF THE DISCREPANCIES NOTED WITH REGARD TO THE COMPOSITION (% ACTIVE INGREDIENTS) OF THE VARIOUS KATHON 886 F TEST MATERIALS USED IN THE TOXICITY STUDIES SUBMITTED TO SUPPORT TIER I TESTING REQUIREMENTS.

I. A DETERMINATION OF WHETHER A SUBCHRONIC RODENT STUDY IS REQUIRED MUST AWAIT THE EVALUATION OF THE CHRONIC TOXICITY/CARCINOGENICITY STUDY.

II. A REPEAT OF THE RABBIT DEVELOPMENTAL TOXICITY STUDY IS REQUIRED. AT THE DOSE LEVELS TESTED, NO NO-EFFECT DOSE WAS OBTAINED FOR MATERNAL TOXICITY AND, ALTHOUGH NO TERATOGENIC EFFECTS WERE OBSERVED IN THE 47 PUPS FROM THE 7 LITTERS AT THE LOW-DOSE LEVEL, THE DATA ARE INSUFFICIENT TO MAKE ANY DEFINITIVE STATEMENT REGARDING DEVELOPMENTAL TOXICITY.

III. THE ABSTRACT AVAILABLE TO TB II INDICATES THE PERCENT ACTIVE INGREDIENT USED IN THE RAT TERATOLOGY STUDY WAS 15.5% AND THE DATA SHEET INDICATES 14%. BOTH SOURCES OF INFORMATION REFER TO THE SAME LOT # AND TD NO. THIS INCONSISTENCY IN REPORTING OF THE PURITY OF THE TEST MATERIAL MUST BE CLARIFIED BEFORE THE STUDY CAN BE UPGRADED.