4-9-90

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

007856

MEMORANDUM

SUBJECT: KATHON MICROBIOCIDES - MUTAGENICITY AND METABOLISM STUDIES SUBMITTED IN RESPONSE TO DATA CALL-IN

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: JAMES WILSON
PRODUCT MANAGER (32)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. 3/12/90
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL 3/16/90
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. 3/16/90
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: ROHM AND HAAS COMPANY
CHEMICAL: 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE (CODE 107103) AND 2-METHYL-4-ISOTHIAZOLIN-3-ONE (CODE 107104
SYNONYMS: KATHON® MICROBIOCIDES
PROJECT: 9-1564 & 9-1729
CASWELL NO.: 195C
RECORD NO.: 246046
IDENTIFYING NO.: 707-117
ACTION REQUESTED: NONE SPECIFIED.

COMMENT: IN RESPONSE TO THE MARCH 4, 1987 ANTIMICROBIAL DATA CALL-IN (AND SUBSEQUENT AGENCY LETTER DATED MARCH 22, 1989), THE REGISTRANT HAS SUBMITTED THE FOLLOWING METABOLISM AND MUTAGENICITY STUDIES TO FULFILL TIER I TOXICOLOGY REQUIREMENTS FOR THE ACTIVE INGREDIENTS AND REQUESTED THAT ALL OF THE STUDIES LISTED BELOW BE CROSS REFERENCED TO THE FORMULATION GRADE REGISTRATION, KATHON 886 F (707-130).

1) KATHON® BIOCIDE: COMPARISON OF ^{14}C-METABOLITE PROFILES FOLLOWING ORAL AND DERMAL DOSING IN MALE RATS. REPORT NO. 86R-232 (1988); MRID # 411014-02.

2) MICRONUCLEUS TEST ON KATHON 886. REPORT NO. 83RJ-25 (1983); MRID # 411477-01, SUBMITTED UNDER 707-130.

3) IN VITRO CHROMOSOMAL ABERRATION WITH KATHON CG. REPORT NO. 82RJ-4 (1982); MRID # 411014-03, SUBMITTED UNDER 707-130.

ADDITIONALLY, TWO PUBLICATIONS WERE SUBMITTED THAT DISCUSS THE MUTAGENICITY OF KATHON BIOCIDE. THE MUTAGENICITY STUDIES HAVE BEEN REVIEWED, AND THE DER'S ARE ATTACHED. AN OVERALL ASSESSMENT OF THE MUTAGENIC DATA ON KATHON® BIOCIDE HAS ALSO BEEN PERFORMED BY DR. J. CHEN AND IS PRESENTED BELOW.

THE SUBMITTED METABOLITE PROFILE COMPARISON STUDY HAS BEEN REVIEWED, BUT NO DER WAS PREPARED. A SUMMARY OF THE DATA IS PRESENTED BELOW.

BACKGROUND

FOUR ACTIVE INGREDIENTS WERE INCLUDED IN THE ANTIMICROBIAL DATA CALL-IN, BUT TWO OF THESE WERE RECENTLY CANCELLED. THE CURRENT VIABLE REGISTRATIONS WERE STATED TO CONTAIN THE ACTIVE INGREDIENTS IDENTIFIED BY EPA CHEMICAL CODES 107103 (5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE; RH-651) AND 107104 (2-METHYL-4-ISOTHIAZOLIN-3-ONE; RH-573). EACH REGISTERED PRODUCT CONTAINS BOTH ACTIVE INGREDIENTS. IT IS STATED THAT THE TWO ACTIVES ARE FORMED AS A RESULT OF A CHEMICAL REACTION AND ARE TYPICALLY PRESENT IN THE RATIO OF 3:1 CHLORINATED TO NON-CHLORINATED COMPONENT. KATHON® MICROCIDES CONTAINING THE TWO ACTIVE INGREDIENTS ARE CURRENTLY REGISTERED IN SEVERAL END-USE FORMULATIONS WITH MINIMUM A.I. LEVELS RANGING FROM 1.5 TO 11.2%, ACCORDING TO THE REGISTRANT.

NOTE: IT IS NOT CLEAR TO THIS REVIEWER WHAT IS CONSIDERED TO BE THE TECHNICAL FORM OF THE "ACTIVE INGREDIENT". SEVERAL TOXICITY STUDIES PREVIOUSLY SUBMITTED WERE PERFORMED ON A TEST MATERIAL IDENTIFIED AS KATHON 886, WHICH CONTAINED 9.7% RH-651 AND 3.4% RH-573; A MUTAGENICITY STUDY WAS PERFORMED ON KATHON 886, WHICH WAS STATED TO BE 17.2% A.I. (14.1% RH-651 AND 3.1% RH-573); OTHER MUTAGENICITY STUDIES USED KATHON 886 NAR PROCESS (15.5% A.I.); ACUTE STUDIES WERE PERFORMED ON KATHON 886T (14.5% RH-651 AND 4.68% RH-573); AND THE 3-MONTH DRINKING WATER STUDY REVIEWED FOR THIS ACTION WAS PERFORMED ON KATHON NAR (12.8% RH-651 AND 2.7% RH-573).

FOURTEEN PRODUCTS WERE LISTED IN THE SUBMISSION. THE MAJOR END-USE APPLICATIONS COVERED IN THE REGISTRATIONS INCLUDE METALWORKING FLUID PRESERVATION, COOLING TOWERS, OIL FIELDS, PAPERMILL SLIME CONTROL, POLYMER LATEX PRESERVATION, IN-CONTAINER PRESERVATION, AND FUEL PRESERVATION.

THE ORIGINAL RESPONSE TO THE DATA CALL-IN INDICATED THAT THE REGISTRANT WOULD DEVELOP ALL SUBCHRONIC AND CHRONIC TOXICOLOGY DATA (OPTION 1). THE AGENCY PROVIDED THE COMPANY WITH A LIST OF STUDIES THAT HAD BEEN REVIEWED AND FOUND ACCEPTABLE TO FULFILL VARIOUS DATA REQUIREMENTS. SUBSEQUENTLY THE REGISTRANT HAS OPTED TO PROVIDE THE AGENCY WITH QUANTITATIVE EXPOSURE DATA AND TOXICOLOGY DATA TO SUPPORT TIER 1 REQUIREMENTS (OPTION 2 OF THE ORIGINAL ANTIMICROBIAL DCI).

WITH REGARD TO THE DATA REQUIREMENT FOR A 90-DAY DERMAL STUDY, THE REGISTRANT STATES THAT THE ACTIVE INGREDIENTS ARE DERMALLY CORROSIVE AND REQUESTS A WAIVER OF THIS DATA REQUIREMENT, STATING THAT THE COMBINED RESULTS OF AN EXISTING 3-MONTH DRINKING WATER STUDY, A 30-MONTH CHRONIC SKIN-PAINTING STUDY, AND A METABOLISM STUDY SHOULD PROVIDE ADEQUATE DATA TO DETERMINE ANY ADVERSE EFFECTS FROM DERMAL EXPOSURE. AT THE TIME THIS HED PROJECT WAS RECEIVED IN TB II FOR REVIEW, THESE LATTER 3 STUDIES HAD YET TO BE SUBMITTED TO TB II FOR REVIEW. SUBSEQUENTLY, THESE WERE PROVIDED AND THEY (EXCEPTION-METABOLISM STUDY IS AN ENVIRONMENTAL FATE STUDY, WHICH IS NOT IN TB II PURVIEW) HAVE NOW BEEN REVIEWED. A DER WAS PREPARED ON THE 90-DAY DRINKING WATER STUDY ONLY AND IS ATTACHED. THE 30-MONTH CHRONIC SKIN-PAINTING STUDY WAS NOT REVIEWED IN DEPTH SINCE IT IS NOT AN ADEQUATE STUDY (ONLY ONE DOSE TESTED; ONLY MALES USED, TOO FEW ANIMALS TESTED; INADEQUATE HISTOPATH; ORGANS NOT WEIGHED; ETC.).

WITH REGARD TO THE DATA REQUIREMENT FOR A TERATOLOGY STUDY IN ONE SPECIES, THE REGISTRANT INDICATES THAT TWO PREVIOUSLY-SUBMITTED TERATOLOGY STUDIES WILL BE RELIED ON. ALTHOUGH THE REGISTRANT ACKNOWLEDGES THAT THE RABBIT STUDY IS CONSIDERED SUPPLEMENTARY, HE INDICATES THAT THE RAT STUDY IS "GRADED CORE MINIMUM". TB II POINTS OUT THAT THIS STUDY WAS RE-EVALUATED IN 1988 AND, AS COMMUNICATED TO ROHM AND HAAS (LETTER DATED 4/12/88), THIS STUDY WILL NOT SUPPORT THE TIER I DATA REQUIREMENT FOR A TERATOLOGY STUDY. AS STATED IN THE ORIGINAL REVIEW OF THIS STUDY, THE DOSE LEVELS WERE NOT SUFFICIENTLY HIGH, AND THE TEST MATERIAL WAS NOT ADEQUATELY IDENTIFIED.

DISCUSSION

1) METABOLITE PROFILE COMPARISON BETWEEN DERMAL AND ORAL EXPOSURES.

KATHON BIOCIDE WAS DEFINED AS AN AQUEOUS SOLUTION CONTAINING AN APPROXIMATE 75: 25 MIXTURE OF 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE (RH-651) AND 2-METHYL-4-ISOTHIAZOLIN-3-ONE (RH-573), [redacted]. FOLLOWING DERMAL AND ORAL EXPOSURES TO ^{14}C-KATHON (EITHER RH-651 OR RH-573 COMPONENT LABELED), THE METABOLITE PROFILES ARE QUALITATIVELY SIMILAR, BUT THE RATE OF ELIMINATION IS SLOWER FOLLOWING DERMAL EXPOSURE. IT IS TO BE NOTED THAT THE DOSES ADMINISTERED BY EACH ROUTE WERE NOT COMPARABLE. ADDITIONALLY, IT IS NOT EVIDENT THAT THE TECHNICAL FORM OF THE ACTIVE INGREDIENT(S) WAS UTILIZED, AND NO RAW DATA WERE PROVIDED.

2) OVERALL ASSESSMENT OF THE MUTAGENICITY DATA.

STUDIES PROVIDED IN CURRENT SUBMISSION

THE TWO NEW TESTS SUBMITTED ARE UNACCEPTABLE, SINCE NEITHER OF THESE WAS CONDUCTED IN ACCORDANCE WITH ACCEPTABLE PROCEDURES (DEFICIENCIES ARE LISTED IN THE ATTACHED DER'S). THE MICRONUCLEUS TEST WAS PERFORMED ON KATHON 886, WHICH WAS IDENTIFIED AS 16% ACTIVE ISOTHIAZOLONES (12.4% RH-651 AND 3.6% RH-573). THE IN VITRO CHROMOSOMAL ABERRATION ASSAY WAS PERFORMED ON KATHON CG, WHICH WAS IDENTIFIED AS 1.5% ACTIVE INGREDIENT (1.15% RH-651 AND 0.35% RH-573).

FROM THE PUBLISHED DATA, THE NEGATIVE RESPONSES OF THE ACTIVE COMPONENTS IN KATHON FROM THE MOUSE MICRONUCLEUS TEST (PUBLICATION: MUT. RES. 124, 241-246 (1983) AND THE NEGATIVE RESPONSE OF KATHON BIOCIDE FROM THE RAT HEPATOCYTE UDS ASSAY (PUBLICATION: MUT. RES. 118, 129-152 (1983) ARE UNACCEPTABLE BECAUSE NEITHER TEST WAS CONDUCTED IN ACCORDANCE WITH EPA TESTING GUIDELINES. IN THE FORMER STUDY, RH-651 WAS TESTED, WHILE THE LATTER STUDY UTILIZED BOTH COMPONENTS SEPARATELY AND TOGETHER (KATHON BIOCIDE: AN AQUEOUS SOLUTION CONTAINING A MIXTURE OF TWO ACTIVE INGREDIENTS, 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE (RH-651) AND 2-METHYL-4ISOTHIAZOLIN-3-ONE (RH-573) IN AN APPROXIMATE RATIO OF 3: 1.

PREVIOUSLY SUBMITTED DATA

CATEGORIES	ACCEPTABLE STUDIES	OVERALL ASSESSMENT
A. GENE MUTATION	1. SLRS ASSAY/DROSOPHILA NEGATIVE; EPA #003346 (KATHON 886; 17.2% AI)	NEGATIVE IN IN-VIVO TEST
	2. BACTERIAL ASSAY POSITIVE; EPA #003648 (KATHON MW886 BIOCIDE) 3. AMES TEST POSITIVE; EPA #002227 (KATHON 886 NAR PROCESS; 15.5% AI) 4. L5178Y ASSAY POSITIVE; EPA #002227 (KATHON 886 NAR PROCESS; 15.5%0	POSITIVE IN IN VITRO TEST
B. CHROMOSOMAL ABERRATIONS	NONE	UNKNOWN
C. OTHER GENOTOXIC EFFECTS	NONE	UNKNOWN

3) AT THE DOSE LEVELS TESTED IN THE 3-MONTH DRINKING WATER STUDY ON KATHON NAR (25, 75, AND 225 PPM), NO TOXICOLOGICALLY SIGNIFICANT EFFECTS WERE OBSERVED IN EITHER SEX OF RAT. EFFECTS OBSERVED FOLLOWING EXPOSURE WERE DECREASES IN BODY WEIGHT, BODY-WEIGHT GAIN, AND FOOD CONSUMPTION (ALL MINIMAL) AND SIGNIFICANT DECREASES IN WATER CONSUMPTION, WHICH WAS PROBABLY DUE TO PALATIBILITY. THE STUDY IS CLASSIFIED AS SUPPLEMENTARY, SINCE NO TOXICOLOGICALLY SIGNIFICANT EFFECTS WERE OBSERVED.

CONCLUSION

WITH RESPECT TO THE REQUEST FOR A WAIVER OF THE 90-DAY DERMAL STUDY DUE TO THE CORROSIVE NATURE OF THE ACTIVE INGREDIENTS AS SUPPLIED, TB II DOES NOT OBJECT TO THE WAIVER IF THE MATERIAL IS IN FACT CORROSIVE. THE ACUTE DATA AVAILABLE ON THE VARIOUS FORMULATIONS SUPPORT THIS CONTENTION SINCE THE FORMULATIONS FALL INTO A DERMAL TOXICITY CATEGORY OF 1 OR 2. HOWEVER, THE ORAL 3-MONTH DRINKING WATER STUDY DOES NOT FULFILL THE DATA REQUIREMENT FOR A 90-DAY ORAL STUDY, AS DISCUSSED ABOVE. ADDITIONALLY, THE 30-MONTH CHRONIC SKIN-PAINTING STUDY REFERENCED BY THE REGISTRANT IS NOT AN ADEQUATE STUDY.

AS POINTED OUT PREVIOUSLY (LETTER DATED APRIL 12, 1988), NEITHER OF THE PREVIOUSLY-SUBMITTED TERATOLOGY STUDIES WILL SUPPORT THE TIER I DATA REQUIREMENT FOR A TERATOLOGY STUDY.

THE MUTAGENICITY STUDIES SUBMITTED ARE NOT ADEQUATE AND DO NOT FULFILL THE DATA REQUIREMENTS FOR MUTAGENICITY. THE METABOLIC PROFILE DATA ARE NOT ADEQUATE SINCE NO RAW DATA WERE PROVIDED.

THE REGISTRANT SHOULD PROVIDE INFORMATION ON WHAT IS TO BE CONSIDERED THE TECHNICAL GRADE OF THE "ACTIVE INGREDIENT", SINCE THE ACTIVE INGREDIENT IS A COMBINATION OF TWO ACTIVE INGREDIENTS, AND THE VARIOUS STUDIES SUBMITTED IN SUPPORT OF KATHON HAVE BEEN ON DIFFERENT % OF BOTH THE COMBINED ACTIVE INGREDIENTS AND THE INDIVIDUAL ACTIVE INGREDIENTS. IT IS NOTED THAT KATHON 886F IS STATED TO BE THE "TECHNICAL GRADE FROM WHICH ALL THE KATHON 886 PESTICIDES ARE DERIVED" (ROHM AND HAAS LETTER DATED MAY 18, 1984). ADDITIONALLY, IN A LETTER DATED 8/26/87, IT IS STATED THAT "ANY TESTING OF KATHON 886 F IS DONE ON THE REACTION MIXTURE OF THE TWO ACTIVE INGREDIENTS (I.E., ON THE PRODUCT KATHON 886 F). THE COMPOSITION OF KATHON 886 F IS STATED TO CONTAIN 9.7% 5-CHLORO-2-METHYL 4-ISOTHIAZOLIN-3-ONE AND 3.4% 2-METHYL-4-ISOTHIAZOLIN-3-ONE (FROM A SUMMARY OF THE INGREDIENTS FOR ALL KATHON ISOTHIAZOLONE REGISTERED MICROBIOCIDES PROVIDED BY ROHM AND HAAS IN A LETTER DATED 10/23/86). IN LIGHT OF THIS CONFUSION REGARDING THE TEST MATERIAL, THE REGISTRANT SHOULD MEET WITH AGENCY PERSONNEL TO DECIDE THE MOST REPRESENTATIVE PRODUCT TO BE USED IN TESTING. ADDITIONALLY, THE REGISTRANT SHOULD DISCUSS POSSIBLE TEST OPTIONS TO FULFILL THE 90-DAY DERMAL DATA GAP WITH THE AGENCY BEFORE PROCEEDING WITH ACTUAL STUDIES. IT IS TO BE NOTED THAT THE DECISION REGARDING FURTHER TIER TESTING MUST AWAIT THE OUTCOME OF THE TIER 1 STUDIES.

TB II DEFERS TO NDEB REGARDING THE REGISTRANT'S DISCUSSION/CALCULATIONS OF THE "WORST CASE" EXPOSURE SCENARIO FOR AN END-USER EXPOSED TO KATHON® BIOCIDE ACTIVE INGREDIENTS AT THE MAXIMUM END-USE DILUTION LEVEL OF 15 PPM IN METALWORKING FLUIDS (SEE VOLUME 1, MRID #411014-01 OF SUBMISSION).

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