5-15-90

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

MAY 15 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: KATHON 287T - TECHNICAL GRADE OF ACTIVE INGREDIENT

TO: JOHN LEE
PRODUCT MANAGER (31)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 5/3/90
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL K. Clark Swentzel 5/4/90
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. Marcia van Gemert 5/7/90
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: ROHM ABD HAAS COMPANY
CHEMICAL: 4,5-DICHLORO-2-N-OCTYL-3(2H)-ISOTHIAZOLONE
SYNONYM: KATHON 287T
PROJECT NO.: 0-0921
CASWELL NO.: 314B
RECORD NO.: 257966
IDENTIFYING NO.: 707-EEU
MRID NO.: NOT APPLICABLE
ACTION REQUESTED: TECHNICAL FOR A NEW CHEMICAL; WILL DATA BASE SUPPORT USE?

COMMENT: THE COMPANY IS APPLYING FOR A PESTICIDE REGISTRATION FOR KATHON 287T. THE LABEL STATES THAT KATHON 287T IS FOR USE ONLY IN THE FORMULATION OF INDUSTRIAL MILDEWICIDES, THE ACTIVE INGREDIENT BEING 4,5-DICHLORO-2-N-OCTYL-3(2H)-ISOTHIAZOLONE (93.5%). INCLUDED ALSO IN THE PACKAGE IS THE CONFIDENTIAL STATEMENT OF FORMULA AND AN ATTACHMENT II, WHICH INCLUDES A LIST OF TOXICOLOGY DATA ON WHICH THE COMPANY IS RELYING.

KATHON 287T IS DESCRIBED IN ATTACHMENT I (TECHNICAL GRADE OF THE ACTIVE INGREDIENT - KATHON 287T) AS A TAN TO BROWN SOLID AT ROOM TEMPERATURE, WHICH IS COMPRISED OF APPROXIMATELY 97.6% ACTIVE INGREDIENT AND 2.4% MANUFACTURING BY-PRODUCTS AND PROCESS SOLVENT. THE REGISTRANT STATES THAT THERE ARE NO INTENTIONS AT THE PRESENT TIME TO COMMERCIALIZE KATHON 287T AS A FORMULATION USE PRODUCT, A STATEMENT THAT IS IN DISAGREEMENT WITH THE SUBMITTED LABEL. THE LABEL ALSO LISTS THE PERCENTAGE OF A.I. AS 93.5%.

THE TOXICOLOGICAL DATA AVAILABLE (PREVIOUSLY SUBMITTED TO THE AGENCY), WHICH ARE BEING RELIED ON ARE STUDIES PERFORMED ON FORMULATIONS CONTAINING VARIOUS AMOUNTS OF THE ACTIVE INGREDIENT WITH AND WITHOUT THE SOLVENT [redacted] THESE FORMULATIONS INCLUDE:

INERT INGREDIENT INFORMATION IS NOT INCLUDED

1

A) 32% A.I. BY WEIGHT [redacted] (CURRENT MANUFACTURING-USE PRODUCT AND END-USE PRODUCT FORMULATION)
B) 35%A.I. AND 5% 4-CHLORO-2-N-OCTYL-3(2H)-ISOTHIAZOLONE, 12-18% RELATED IMPURITIES, [redacted] THIS FORMULATION IS NO LONGER COMMERCIALLY PRODUCED.
C) FORMULATION B, ABOVE WITHOUT [redacted] 66% A.I.

THE TOXICITY DATA AVAILABLE INCLUDE:

ACUTE ORAL

1) ACUTE ORAL STUDY IN RATS USING (A) FORMULATION; LD_{50} MALES 4.4 G/KG (EQUIVALENT TO 1.4 G/KG A.I.); LD_{50} FEMALES 2.6 G/KG (EQUIVALENT TO 0.84 G/KG A.I.).

2) ACUTE ORAL STUDY IN MALE RATS USING (B) FORMULATION; LD_{50} 1.89 (1.46-2.61) G/KG.

THE REGISTRANT STATES THAT THE TOXICITY CATEGORY WOULD NOT BE EXPECTED TO CHANGE (FROM CATEGORY III TO II) IF THE ACTIVE INGREDIENT ITSELF WERE TESTED; THEREFORE, A WAIVER IS REQUESTED FOR THE ACUTE ORAL STUDY FOR KATHON 287T. TB II DOES NOT CONCUR. AN ACUTE ORAL STUDY IS REQUIRED ON THE TECHNICAL GRADE OF KATHON 287T.

ACUTE DERMAL

3) ACUTE DERMAL STUDY IN RABBITS USING (A); LD_{50} > 2.0 G/KG (EQUIVALENT TO >0.65 G/KG A.I.).

4) ACUTE DERMAL STUDY (MALES) 1.7 (1-4.5) G/KG OF (B).

THE REGISTRANT STATES THAT A 32.6% FORMULATION OF THE A.I. [redacted] WAS FOUND TO BE CORROSIVE IN A SKIN IRRITATION STUDY IN RABBITS; THEREFORE, BECAUSE OF THE CORROSIVITY OF THE A.I., THE REGISTRANT REQUESTS A WAIVER OF THE ACUTE DERMAL STUDY ON KATHON 287T.

TB II DOES NOT CONCUR. AN ACUTE DERMAL STUDY IS REQUIRED OF THE TECHNICAL GRADE OF KATHON 287T.

ACUTE INHALATION

5) ACUTE INHALATION STUDY IN RATS USING (B); 0.72 MG/L 4-HOUR WHOLE BODY EXPOSURE (EQUIVALENT TO 0.29 MG/L A.I).

THE REGISTRANT STATED THAT A 90-DAY INHALATION STUDY WAS INITIATED IN 1989 AND WILL BE SUBMITTED UPON COMPLETION; HOWEVER, THE TEST MATERIAL WAS NOT IDENTIFIED.

AN ACUTE INHALATION STUDY IS REQUIRED ON THE TECHNICAL GRADE OF KATHON 287T

INERT INGREDIENT INFORMATION IS NOT INCLUDED

PRIMARY EYE IRRITATION

6) PRIMARY EYE IRRITATION STUDY IN RABBITS USING (A) SHOWED MATERIAL TO BE SEVERELY IRRITATING TO THE EYES; OCULAR EFFECTS PERSISTED 21 DAYS AFTER EXPOSURE.

A WAIVER IS REQUESTED DUE TO THE SKIN CORROSIVITY NOTED ABOVE.

TB II CONCLUDES THAT DUE TO THE OCULAR EFFECTS OBSERVED FOLLOWING EXPOSURE TO A 32% FORMULATION OF KATHON 287T, THIS STUDY CAN BE WAIVED FOR THE TECHNICAL GRADE, PROVIDED THE LABEL BEARS THE APPROPRIATE SIGNAL WORD FOR A TOXICITY CATEGORY I COMPOUND.

PRIMARY DERMAL IRRITATION

7) PRIMARY DERMAL IRRITATION STUDY ON (A) - CORROSIVE.

8) TEST ON (B) SHOWED IT TO BE SEVERELY IRRITATING; PRIMARY IRRITATION SCORE BETWEEN 5 AND 8.

REGISTRANT REQUESTED A WAIVER. TB II CONCLUDES THAT A WAIVER CAN BE GRANTED, PROVIDED THE LABEL BEARS THE APPROPRIATE SIGNAL WORD FOR A CORROSIVE COMPOUND.

DERMAL SENSITIZATION

9) DERMAL SENSITIZATION STUDY ON (C) SHOWED IT TO BE A SENSITIZER.

ALTHOUGH THE REGISTRANT DID NOT REQUEST A WAIVER FOR THE TECHNICAL INGREDIENT, A STUDY NEED NOT BE PERFORMED ON KATHON 287T PROVIDED THE LABEL LISTS IT AS A SENSITIZER.

21-DAY DERMAL

10) 21-DAY DERMAL STUDY ON (B) RESULTED IN SKIN IRRITATION BUT NO DETECTABLE SYSTEMIC EFFECTS WERE NOTED.

TERATOLOGY

11) TERATOLOGY STUDY ON (B; ANTI-FOULANT C-9211M) IN THE RAT - NOT TERATOGENIC UNDER CONDITIONS OF STUDY AT DOSES UP TO 112.4 MG/KG/DAY; FETOTOXIC NOEL = 11.2 MG/KG, WITH INCREASED INCIDENCES OF BENT RIBS NOTED AT 33.7 MG/KG; MATERNAL NOEL = 11.2 MG/KG, THE LEL, 33.7 MG/KG (EFFECTS OBSERVED NOT STATED).

12) TERATOLOGY STUDY ON (B) IN RABBITS DEMONSTRATED NO EMBRYOTOXIC OR DEVELOPMENTAL TOXICITY EFFECTS IN FETUSES AT DOSES OF 5 AND 25 MG/KG; DUE TO COMPOUND-RELATED ABORTIONS, INSUFFICIENT NUMBERS OF LITTERS AVAILABLE TO ASSESS DEVELOPMENTAL TOXICITY AT THE HDT (70 MG/KG); TENTATIVE NOEL OF 25 MG/KG FOR DEVELOPMENTAL TOXICITY.

MUTAGENICITY

13) CHO/HGPRT GENE MUTATION STUDY ON (B); NO MUTATIONS INDUCED WITH OR WITHOUT METABOLIC ACTIVATION.

14) IN VITRO CYTOGENETIC ASSAY IN CHO CELLS ON (B); MATERIAL DID NOT INDUCE MUTATIONS WITH OR WITHOUT METABOLIC ACTIVATION.

15) MAMMALIAN CELL TRANSFORMATION ON (C) - DID NOT INDUCE ANY SIGNIFICANT LEVEL OF TRANSFORMING ACTIVITY IN C_3H 10T 1/2 MOUSE CELL SYSTEM UNDER CONDITIONS OF STUDY.

THESE STUDIES CANNOT BE USED TO SUPPORT THE REGISTRATION OF THE TECHNICAL GRADE OF KATHON 287T, EXCEPT AS NOTED UNDER 6, 7, 8, AND 9 ABOVE. STUDIES ON THE TECHNICAL GRADE OF THE TEST MATERIAL ARE REQUIRED FOR REGISTRATION. THIS COMPOUND IS CONSIDERED AN ANTIMICROBIAL, AND AS SUCH IS SUBJECT TO THE DATA REQUIREMENTS FOR THOSE COMPOUNDS. THE STUDIES REQUIRED FOR THE TECHNICAL GRADE OF THE A.I. (4,5-DICHLORO-2-N-OCTYL-3(2H)-ISOTHIAZOLONE), IN ADDITION TO ACUTE ORAL, DERMAL, AND INHALATION STUDIES, ARE:

1) 82-3 90-DAY DERMAL OR, IN THE CASE OF A DERMALLY CORROSIVE CHEMICAL, A 90-DAY FEEDING STUDY ALONG WITH DATA ON THE RELATIVE EFFICIENCY OF THE UPTAKE OF THE CHEMICAL VIA BOTH ROUTES OF EXPOSURE;

2) 82-4 90-DAY INHALATION, IF THE A.I. IS A GAS AT ROOM TEMPERATURE OR IF THE USE RESULTS IN RESPIRABLE DROPLETS;

3) 83-3 TERATOGENICITY (ONE SPECIES) - A HIGH EXPOSURE MAY TRIGGER A STUDY IN A SECOND SPECIES;

4) MUTAGENICITY BATTERY.

THE RESULTS OF THE FIRST-TIER STUDIES (IN ADDITION TO EXPOSURE INFORMATION) MAY INDICATE THE NEED FOR ADDITIONAL TESTING (TIERS 2/3, AS DESCRIBED IN THE ANTIMICROBIAL DATA CALL-IN, COPY ATTACHED). THE REGISTRANT SHOULD BE REQUESTED TO SUBMIT MORE DEFINITIVE USAGE INFORMATION (E.G., CONCENTRATIONS USED, CORRELATION OF THE CONCENTRATION OF THE ACTIVE INGREDIENT WITH A SPECIFIC USE, DEFINITION OF BUILDING MATERIALS AND CONSTRUCTION PRODUCTS), AND NDEB SHOULD BE CONTACTED FOR A DETERMINATION OF WHAT EXPOSURE INFORMATION IS REQUIRED.

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

OFFICE OF PESTICIDES AND TOXIC SUBST

DATA [illegible]-IN NOTICE FOR SUBCHRONIC AND CHRONIC TOXICOLOGICAL DATA FOR ANTIMICROBIAL PESTICIDE ACTIVE INGREDIENTS

Dear Registrant:

This Notice requires you and other registrants of pesticide products containing antimicrobial active ingredients (AIs) to submit certain data to the U.S. Environmental Protection Agency (EPA). Within 90 days after you receive this Notice you must inform EPA:

1. How you will comply with the data requirements set forth in this Notice; or

2. Why you believe you are exempt from the requirements of this Notice; or

3. Why you believe EPA should not require you to submit data in the manner specified by this Notice.

The registration of your product(s) subject to this Notice will be suspended if you do not respond to this Notice, or if you do not satisfactorily demonstrate to EPA that you will comply with its requirements or should be exempt or excused from doing so. We have provided a list of your products subject to this Notice (Attachment A), all AIs for which EPA is requiring data (Attachment A-1), and all registrants subject to this Notice (Attachment B).

The authority for this Notice is §3(c)(2)(B) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. §136a(c)(2)(B). The Administrator has determined that you must fulfill these data requirements to support your existing registrations of those products identified in Attachment A.

5

SECTION I. WHY YOU ARE RECEIVING THIS NOTICE

Under the authority of §3(c)(2)(B) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, EPA is requiring subchronic and chronic toxicology data on active ingredients (AIs) from registrants of antimicrobial pesticides.

40 CFR Part 158 (49 FR 42856, October 24, 1984) specifies the data that EPA generally requires to make regulatory judgments about the safety of each pesticide product. EPA will reregister a pesticide product only if EPA has sufficient information about the product to make the statutory risk and benefit determinations. In the past, EPA has assumed that exposure to most antimicrobial pesticides involved only short term exposure to low concentrations of the AI. Consequently, EPA generally has required acute toxicity data, but not subchronic or chronic toxicity data, to register most antimicrobial pesticides. However, in reviewing the data for registration standard development and other program activities, EPA has concluded that more data are needed to evaluate properly the potential hazards associated with the use of antimicrobial pesticides.

SECTION II. DATA REQUIRED

II-A. SUMMARY

EPA will permit registrants to select among several options for ways to comply with the data requirements of this Notice. This is because an EPA evaluation of the risks that may be posed by chronic exposure to an AI of an antimicrobial pesticide could be done in various ways. One way would be to obtain a full set of subchronic and chronic toxicology data on the AI and, if effects are noted from review of those data, then determine if exposure data are necessary to evaluate risk. This is the course that EPA ordinarily takes in evaluating risks of pesticides other than antimicrobials. This approach is presented below in more detail as Option 1.

EPA is concerned about the economic effects that imposition of full toxicology data requirements for antimicrobials would have on the industry and user community. EPA has concluded that for these pesticides it should be possible to evaluate risk by acquiring exposure data and by acquiring toxicity data under a tiered approach, in which low-tier (and less expensive) toxicity data (alone, or in combination with the exposure data) indicate the need for the higher-tier tests. Two variations of this approach are presented in detail below as Options 2 and 3. Registrants should select one of the options detailed below.

Option 1 -- A registrant who chooses this option must commit to develop the required subchronic and chronic toxicology data for each AI in his product. The data requirements for a given AI of a product are dependent upon likely exposure to the pesticide, as determined by EPA. EPA has examined the general pesticide use site groups that appear in Appendix A to 40 CFR Part 158, identified the groups that pertain to antimicrobial pesticides, and evaluated the type and estimated level of exposure experienced by users of those groups of pesticides. Subsequently, EPA placed each general use site into one of three exposure categories (high, medium, or low) based on evaluation of the frequency of use and the per-use exposure. The "high" group consists of those use sites where the estimated pesticide use frequency is high and the estimated per-use exposure is also high. The "medium" group consists of those use sites where either use frequency of exposure or per-use exposure is high. The "low" group consists of those use sites where both use frequency and per-use exposure is low. Table 1 shows the classification of general use sites, exposure routes of concern and exposure categories as determined by EPA. A registrant must assign each use authorized by his product's labeling to one of the general use sites and note the exposure category associated with that use site. The toxicity data requirements for that use site can be determined by consulting Table 2 (R = required; [illegible] = not required). For example, if a product has a use which falls into the "household sites" general use site, the exposure category is "high" and a 90-day feeding study is required, as indicated by the "R" in the "high" column for that study. This process must be repeated for each labeled use of the product in question. The studies required for the product are those required for each labeled use of the product.

A registrant who chooses to comply with this Notice by submitting the data required under Option 1 is not required by this Notice to submit any exposure data. The decision to require or not to require exposure data will be made by EPA after the review and evaluation of the toxicology data.

Options 2 and 3 -- Under these options, submission of both toxicology data and exposure data are required. The toxicology data requirements are the same under both options. However, the means for fulfilling the exposure requirements differ between the two options.

II-B. TOXICOLOGY DATA

In accordance with the time schedules in Table 2 of the Notice each registrant who chooses Option 2 or 3 as a means of satisfying his obligations under this Notice must submit the "first-tier" toxicity studies on each AI of his product.

Each such registrant also must agree to submit data from second-tier and/or third-tier toxicity studies to the extent that the results from the first-tier studies indicate a need for data from such higher-tier studies.

Tier 1 -- The first-tier studies (and corresponding Pesticide Guideline reference numbers) are:

90-day dermal (82-3)

This study is required for all AIs except for certain dermally corrosive antimicrobials. In these cases a 90-day feeding study will be more appropriate. However, if a 90-day feeding study is conducted, the relative efficiency of the uptake of the chemical by the animal via dermal and oral exposure must be determined in order that the oral doses can be converted to dermal exposure equivalents.

90-day inhalation (82-4)

The 90-day inhalation study is required only if the active ingredient is a gas at room temperature or if use of the product results in respicable droplets (15 microns or less in diameter).

Teratogenicity (1st species: rat or rabbit) (83-3)

Required of all AIs. High exposure may trigger the need for the second study.

Mutagenicity (84-2)

This battery of studies is required of all AIs.

Tier 2 -- The second-tier studies (with corresponding Pesticide Guideline reference numbers), and the conditions under which they are required, are:

Subchronic feeding, (82-1)

This study is required if the EPA notifies the registrant of its determination that (1) the no-observed-effect level in mg/kg/day from the 90-day dermal toxicity study or the dermal exposure equivalent level calculated from the 90-day oral study is less than 1000 times higher than the human dermal exposure to the active ingredient in mg/kg/day, using the dermal exposure data submitted under this Notice or (2) the no-observed-effect level from the 90-day inhalation toxicity study is less than 1000 times higher than the human inhalation exposure to the active ingredient, using the inhalation exposure data submitted under this Notice. The findings from the subchronic toxicity study will be used to establish the dose levels for the chronic feeding and oncogenicity studies.

Teratogenicity, second species (83-3)

This study is required if the EPA notifies the registrant of its determination that the data from the first-species teratogenicity study suggest embryo or developmental toxicity. High exposure may also trigger the need for the second study.

Dermal absorption (85-3)

This study is required if the Agency notifies the registrant of its determination that a significant teratogenic, reproductive or oncogenic risk is suggested based on the results of the exposure study and/or other data. For teratogenic and reproductive risks, the evaluation will be based on the effects seen in the first teratogenicity study; for oncogenic risk, the exposure data will be used to compare the AI with ethylene dibromide (EDB). (See Tier 3 oncogenicity below).

Tier 3 --The third-tier studies (with corresponding Pesticide Guideline reference numbers), and the conditions under which they are required, are:

Chronic feeding, 2 species (83-1)

These studies are required if the Agency notifies the registrant of its determination that the margin of safety is less than 1000 based on subchronic data, and exposure cannot be reduced.

Oncogenicity, 2 species (83-2)

These studies are required (1) if the Agency notifies the registrant of its determination that the overall results of the mutagenicity test battery strongly suggest that the AI may pose an oncogenic risk and/or (2) if, based on dermal exposure (as shown by lower tier studies or other data and not negated by the actual dermal absorption study) the calculated risk exceeds that of EDB. [EDB is used for comparison as a worst-cast example].

Reproduction (83-4)

This study is required if the Agency notifies the registrant of its determination that developmental toxicity and/or adverse effects on reproductive organs were observed in the 90-day dermal or inhalation study.

Metabolism (85-1)

This study is required only if the Agency notifies the registrant of its determination that additional information on the metabolism of the chemical is necessary to clarify unusual effects observed in chronic or reproduction studies or to clarify issues concerning structure activity relationships.

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A registrant who chooses to use Option 2 or 3 to satisfy this Notice's requirements also must arrange to conduct and submit to EPA data needed to determine the amount of dermal and inhalation exposure that results from the use of his product.

Protocol Approval -- All exposure studies required under Option 2 or 3 must be designed and conducted in accordance with Subdivision U of the Pesticide Assessment Guidelines. Before the studies are performed, the registrant (or group of registrants, in the case of Option 2) must prepare and submit to EPA a protocol for each of the studies, and obtain EPA approval of the protocols prior to study initiation.

Registrants who select Option 2 or Option 3 must work with EPA to develop approved protocol for developing exposure data. This protocol development and approval must be completed within 6 months after the date by which you are required to respond to this Notice. You must submit the exposure data to EPA within 1 year after protocol approval.

Sites and Application Methods for Which Testing is Required -- The principal factors that EPA considers germane to developing an adequate exposure data base matrix are application site and application method. Matrix elements are defined by grouping application sites and application methods (Table 3). Table 3 provides a sample data matrix of use patterns and corresponding application methods. Because Table 3 is only a sample, the elements may not be all inclusive and certain situations may require special treatment. EPA will require inhalation data only for those AIs which are gases at room temperature or if the product produces droplets or particles of respirable size (15 microns or less in diameter).

To ensure consistency in the design and results of the studies and to lessen the financial impact on industry, EPA is encouraging registrants to pursue joint agreements to develop and submit exposure studies. The designated agent(s) for this effort would work with EPA to develop protocols for obtaining the necessary data and select representative products for conducting exposure tests.

EPA believes the generic exposure data would best serve the pesticide industry, EPA, and the public interest if the contributors waive their FIFRA §3(c)(1)(D)(ii) data compensation rights. In addition to public interest benefits and cost savings to the pesticide industry, the benefits gained from this approach include:

1. The data on which decisions are based will be considerably expanded, thus strengthening the credibility, reliability and statistical power of EPA's exposure assessments.

2. The use of the database would be a more efficient way for the EPA to determine when an exposure study would be needed on a specific application method. When sufficient data have been compiled for a given use, no further studies will be required for that application method. This will result in lower overall costs to the pesticide industry.

3. The use of a mutually agreed upon database should reduce contention in one area of the overall risk assessment process.

Use Patterns Not Amenable to Passive Dosimetry Monitoring -- Some exposure situations are not amenable to monitoring via passive dosimetry (See Subdivision U of the proposed Pesticide Assessment Guidelines). These uses include, but are not limited to, swimming pools and metalworking fluids. In these uses part or all of the body often becomes saturated. Because these uses generally result in frequent exposure to relatively large amounts of AI, EPA has designated these as category 1 exposure. Therefore, EPA will require all subchronic and chronic toxicology data for the AIs for which generic exposure data is not applicable. If, however, a registrant does not believe that exposure for one of these uses ranks as category 1, the registrant must quantitatively demonstrate, by biological monitoring or other appropriate method, that exposure is of a lesser degree. The quantification must be on an AI, not generic, basis. If the registrant can develop suitable exposure data, then the toxicology data requirements will be imposed in the same manner as for Options 2 and 3. The protocol approval and data submission time requirements discussed under Protocol Approval also apply to these use patterns. Likewise, the toxicology data submission times listed in Table 2 also apply.

Option 2 -- EPA has determined that exposure to most antimicrobial pesticide products can be evaluated through the use of a set of studies on representative products. Such studies must be designed to measure exposure from all relevant combinations of use site groups and application methods.

Registrants who choose Option 2 must agree to jointly conduct and submit studies of dermal and inhalation exposure resulting from the use site group/application method combinations indicated with an "X" in Table 3. EPA will require a minimum of studies with 10 representative products for each matrix element, with 15 replicates each for dermal exposure and 5 for inhalation exposure, when inhalation monitoring is required.

Option 3 -- Instead of relying on the data generated by those who develop exposure data under Option 2, a registrant may elect to conduct and submit data from studies of dermal and respiratory exposure using the registrant's own product, for each combination of use site group and application method that is authorized by the registration of that product.

Registrants who choose Option 3 must agree to conduct and submit dermal and inhalation exposure studies on their products in compliance with Table 3. Each data point noted by an "X" in the table requires 15 dermal and 5 inhalation samples.

II-D. Testing Protocols

All studies submitted under Section II must be conducted in accordance with acceptable test standards such as those outlined in the Pesticide Assessment Guidelines. These guidelines are available from the National Technical Information Service, Att: Order Desk, 5285 Port Royal Rd., Springfield, VA 22161, 703-487-4650. The development of the exposure data must follow the protocols referenced and discussed in Subdivision U of the Pesticide Assessment Guidelines, Applicator Exposure Monitoring (NTIS Order No. PB 87-133286. Chronic toxicology data requirements are Subdivision F - Hazard Evaluation; Humans and Domestic Animals. (NTIS Order No. PB83-153916; (hard copy $16.00/microfiche $4.50). EPA will also accept protocols approved by the Organization for Economic Cooperation and Development (OECD) if the OECD test standards, such as test duration and selection of species requirements, conform to the standards specified in the Pesticide Data Requirements (40 CFR Part 158.70). When using the OECD protocols, care should be taken that the data generated by the study will satisfy the requirements of 40 CFR Part 158. The OECD protocols are available from OECD, 1750 Pennsylvania Ave., N.W., Washington, D.C. 20006.

SECTION III. COMPLIANCE WITH REQUIREMENTS OF THIS NOTICE

You must submit a completed copy of the "Data Call In Summary Sheet" (Attachment D), for each of your products containing an antimicrobial AI, within 90 days of receiving this Notice. On that sheet you must state which option(s) you have selected to comply with this Notice. At the same time, you must also submit any additional documents required to support the option(s) chosen. The Summary Sheet and other attachments are provided for use in responding to this Notice. Do not alter the printed material. If you believe you qualify for more than one of the available options provided by this Notice, you should choose each option for which you believe you may qualify when you respond to this Notice. In processing responses which specify more than one option for complying with this Notice, EPA will attempt to adopt the option which will impose the least burden on the registrant.

III-A. EXEMPTION FROM THE REQUIREMENTS OF THIS NOTICE

Generic Data Exemption -- Under FIFRA §3(c)(2)(D), an applicant for registration of a product is exempt from the requirement to submit or cite data concerning an AI if the AI in the product is derived exclusively from purchased registered pesticide products containing the AI. EPA has concluded that such a registrant also should normally be exempt from a §3(c)(2)(B) notice requiring data on the AI which they purchase. To qualify for this exemption all of the following requirements must be met:

1. The AI in your registered product must be present solely because of incorporation of another registered product which contains the same AI;

2. Each registrant who is the ultimate source of the AI in your product must be in compliance with the requirements of this Notice and must remain in compliance; and

3. You must have provided to EPA an accurate and current "Confidential Statement of Formula" for each of your products to which this Notice applies.

To apply for the generic data exemption you must submit a completed Generic Data Exemption Statement (Attachment E) and all supporting documentation for each of your products for which you claim the exemption.

Exemption for low volume minor use pesticides -- FIFRA §3(c)(2)(A) requires EPA to consider the appropriateness of requiring data for low volume minor use pesticides. EPA has considered the applicability of this required testing to product registrations and considers it unlikely that any waivers will be granted from Tier 1 testing.

EPA considers an AI to be a low volume chemical only if the total production by all manufacturers for all uses is small. In determining whether to grant a low volume minor use waiver, EPA will consider the volume of use, the economic incentive to conduct the testing, the economic importance of the AI, the public interest, and exposure and risk arising from use of the AI. If the AI is used for both high volume and low volume uses, EPA will not approve a request for a low volume exemption. If all uses of an AI are low volume and the combined volumes for all uses are also low, then EPA may grant an exemption, depending upon review of other relevant information as outlined below. EPA will not grant an exemption to a registrant if any registrant of the AI elects to conduct the testing. Any registrant receiving a low volume minor use waiver will be required to remain within the sales figures included in the forecast supporting the waiver request in order to remain qualified for such waiver. If granted a waiver, a registrant will be required, as a condition of the waiver, to submit annual sales reports.

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To apply for a low volume minor use data waiver, you must submit the following information, as applicable to your product(s), as part of the response required within 90 days of your receipt of this Data Call-In Notice.

1.(A) Total company sales (pounds and dollars) of all registered products containing the AI. If applicable to the AI, include foreign sales for only those products that are not registered in this country but are applied to sugar (cane or beet), coffee, bananas, and cocoa. Present the above information by year for each of the past five years.

(B) Provide an estimate of the sales (pounds and dollars) of the AI for each major use site. Present the above information by year for each of the past five years.

2. Total direct production cost of products containing the AI by year for the past five years. Include information on raw material cost, direct labor cost, advertising, sales and marketing, and any other significant costs listed separately.

3. Total indirect production cost charged to products (e.g. plant overhead, amortized plant and equipment) containing the AI by year for the past five years.

Exclude all non-recurring costs that were directly related to the AI, such as costs of initial registration and any data development.

4.(A) A list of each data requirement for which you seek a waiver. Indicate the type of waiver sought and the estimated cost to you (listed separately for each data requirement and associated test) of conducting the testing needed to fulfill each of these data requirements.

(B) A list of each data requirement for which you are not seeking any waiver and the estimated cost to you (listed separately for each data requirement and associated test) of conducting the testing needed to fulfill each of these data requirements.

5. For each of the next ten years, a year-by-year forecast of company sales (pounds and dollars) of the AI, direct production costs of products containing the AI (following the parameters in 2 above), indirect production costs of products containing the AI (following the parameters in 3 above).

6. A description of the importance and unique benefits of the AI to users. Discuss the use patterns and the effectiveness of the AI relative to the registered alternative chemicals and non-chemical control strategies. Focus on benefits unique to the AI, providing information that is as quantitative as possible. If you do not have quantitative data upon which to base your estimates, then present the reasoning used to derive your estimates. To assist EPA in determining the degree of importance of the AI in terms of the public interest, you should provide information on any of the following factors, as may be applicable to your product: (1) documentation of the usefulness of the AI in Integrated Pest Management, (2) description of the beneficial impacts on the environment of use of the AI, as opposed to its registered alternatives, (3) information on the breakdown of the AI after use and on its persistence in the environment, and (4) description of its usefulness against a pest or pests of public health significance.

EPA will deny your waiver if you do not provide sufficient information for EPA to adequately evaluate your waiver request.

III-B. PRODUCTION OF DATA REQUIRED BY THIS NOTICE

There are three alternative methods by which you can meet the data submission requirements of this Notice. First, you may commit to EPA that you will develop the data. Second, you may share the cost of developing the data. Third, you may submit existing data that satisfies the requirements of this Notice. If you choose to develop the required data yourself or to submit existing data, you must return a complete Data Cover Sheet (Attachment F) for each study within 90 days of receipt of this Notice.

Developing Data -- If you choose to develop the required data, your response to this Notice must indicate the protocols you will follow in conducting the study(s). If you wish to use a protocol that differs from the options provided by Section II of this Notice, you must submit a detailed description of the proposed protocol and your reasons for wishing to use it. EPA may choose not to accept a protocol not specified in Section II, and rejection of the proposed protocol normally will not be a basis for any extension of time for submission of data.

Sharing Cost to Develop Data -- If you choose to enter into an agreement to share in the cost of producing the required data but will not be submitting the data yourself, identify in your response to this Notice the name of the registrant who will be submitting the data. You must also provide EPA with documentary evidence that an agreement has

15

been formed. This evidence may be your letter offering to join in an agreement and the other registrant's acceptance of your offer, or a written statement by the parties that an agreement exists. The agreement to produce the data need not specify all of the terms of the final arrangement between the parties or the mechanism to resolve the terms. FIFRA §3(c)(2)(B) provides that if the parties cannot resolve the terms of the agreement they may resolve their differences through binding arbitration.

Submitting Existing Data -- If you choose to respond to this Notice by submitting existing but previously unsubmitted data, you must submit the data in the format required by PR Notice 86-5, effective November 1, 1986. This notice establishes required formats and procedures for data submission, and requirements for identifying and handling any confidential business information which may occur within submitted data. It also requires submission of three complete and identical copies of each study. In addition to the Title Page required for each study by PR Notice 86-5, you must also include a "Coversheet for Data Submitted in Response to Data Call In Notice" (Attachment F) for each study. Ensure that the data satisfy one or more of the specific requirements imposed by this Notice. If EPA determines that the data do not, you still will be required to comply with this Notice, normally without any extension of the submission deadline.

III-C. OTHER COURSES OF ACTION UNDER THIS NOTICE

There are additional options available in responding to this Notice. First, you may claim that one or more data requirements should not apply to your product. Second, you may amend your registration to delete the uses that apply to one or more data requirements. Third, you may ask for the voluntary cancellation of your registration. Fourth, you may request that EPA use its discretion and not suspend your registration because of your good faith yet unsuccessful efforts to enter into an agreement for a joint data development/cost sharing program.

Applicable Data Requirements -- EPA will not require you to supply the data pursuant to FIFRA §3(c)(2)(B) if EPA determines that the data requirements of this Notice do not apply to your product(s). If you claim that the data requirements do not apply to your product(s), you must submit an explanation of why you believe they do not apply. You must also submit the current label(s) and a copy of the Confidential Statement of Formula for the product(s). If EPA determines that the data are required for your product(s), you must choose another method to meet the requirements of this Notice. EPA will not normally extend the time for you to submit the required data.

Voluntary Cancellation or Amendment -- You may avoid the requirements of this Notice by eliminating the uses of your product to which the requirement applies. To do so, you may either request voluntary cancellation of your registration or seek amendment of the registration to delete the appropriate uses. If you want to amend your registration, you must submit a completed application for amendment, a copy of your proposed amended labeling, and all other information required for processing the application.

Discretionary Non-Suspension of your Registration(s) -- You may request that EPA exercise its discretion not to suspend your registration(s) although you do not comply with the data submission requirements of this Notice. EPA has determined that as a general policy, absent other relevant considerations, it will not suspend the registration of a product of a registrant who has in good faith sought and continues to seek to enter into a data development/cost sharing program if the other registrant(s) developing the data has not accepted his offer. To qualify for this option you must prove to EPA that you have made an offer to another registrant (who has an obligation to submit the same data) to share in the burden of developing that data. You must also provide us with a copy of that offer and proof (e.g., certified mail receipt) of the other registrant's receipt of that offer. Your offer must offer to share in the burden of producing the data upon terms to be agreed or, failing agreement, to be bound by binding arbitration as provided by FIFRA §3(c)(2)(B)(iii). Your offer must be without qualifications or restrictions. In addition you must also demonstrate that the other registrant to whom the offer was made has not accepted your offer to enter into a cost-sharing agreement. The other registrant must also inform us on a Summary Sheet that he will develop and submit the data required by this Notice.

In order for you to avoid suspension under this option, you may not withdraw your offer to share in the burdens of developing the data. In addition, the other registrant must fulfill its commitment to develop and submit the data required by this Notice.

III-D. EXISTING STOCKS OF SUSPENDED OR CANCELLED PRODUCTS

EPA has authority to permit continued sale and distribution of existing stocks of a suspended or cancelled pesticide product if doing so would be consistent with the purposes of FIFRA §6(a)(1). EPA has now determined that such disposition of existing stocks for a suspended registration when a FIFRA §3(c)(2)(B) data request is outstanding would generally be inconsistent with FIFRA's purposes. Accordingly, EPA anticipates granting permission to sell or distribute existing stocks of suspended products only in exceptional circumstances.

If you believe such disposition of existing stocks of your product(s) that may be cancelled or suspended because of this Notice should be permitted, you have the burden to clearly demonstrate to EPA that granting such permission would be consistent with FIFRA. Unless you meet this burden, EPA will not consider any request pertaining to your continued sale and distribution of your existing stocks after cancellation or suspension.

You must include the following information if you expect EPA will suspend your product or you intend to request a voluntary cancellation of your product(s) and wish to request an existing stocks provision:

1. Demonstration that such a provision would be consistent with the purposes of FIFRA, and

2. Explanation of why an "existing stocks" provision is necessary, including a statement of the quantity of existing stocks and your estimate of the time required for their sale and/or distribution.

SECTION IV. INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding the requirements and procedures established by this Notice, please contact:

Linda Lyon (703) 557-7470
or
James Wilson (703) 557-7470

All responses to this Notice must include a completed Data Call-In (DCI) Summary Sheet and the other documents required by Section III of this Notice, and should be submitted to:

PM 31 - Lyon
Disinfectants Branch
Registration Division (TS-767C)
U.S. Environmental Protection Agency
401 M Street, SW.
Washington, DC 20460

RE: [Specify the AI]

The Office of Compliance Monitoring (OCM) of the Office of Pesticides and Toxic Substances (OPTS), EPA will be monitoring the data being generated in response to this notice. Therefore, if you respond to this Notice by

1. committing to develop and/or submit data,
2. requesting a low volume minor use waiver,
3. stating that data requirements are not applicable, or
4. requesting extensions in due date for submitting final reports,

send a duplicate copy of the DCI Summary Sheets and cover-sheets with supporting information to:

Laboratory Data Integrity Program
Office of Compliance Monitoring (EN-342)
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, D.C. 20460.

Sincerely yours,

James W. Akerman

James W. Akerman, Deputy Director
Registration Division

007925

Attachments A = List of Registrant's Products Containing Antimicrobial AIs

A-1 = List of Antimicrobial AIs Requiring Subchronic and Chronic Toxicology Data

B = List of Registrants With Products Containing Antimicrobial AIs

C = Guidelines (pages X)

D = Data Call In Summary Sheet for Chronic Data

E = Generic Data Exemption Statement and Confidential Statement of Formula

F = Coversheet for Submitting Data

G = Federal Register Notice

19A

Table 1. Use Site Exposure Matrix. Use this table to clarify the exposure associated with the use site of your product if your select Option 1.

Use Site Exposure Matrix

Use Site	Routes of Exposure*	Exposure Category
Agricultural Premises and Equipment	I, D	High
Household Sites	I, D	High
Aquatic Sites		
- Industrial Processing Water Systems	I, D	Medium
- Air Washers and Cooling Towers	I, D	Medium
- Swimming Pools	D, Ig	High
- Human Drinking Water	D, Ig	High
- Lakes, Ponds, Rivers, Sewage Systems, Secondary Oil Recovery Systems	I, D	Low
Commercial, Industrial, Institutional Sites		
- Food and Non-Food Contact Surfaces	I, D, Ig	High
- Hospitals and Other Health Care Facilities	I, D,	High
- Adhesives Paperboards, Coatings, Paints	I, D	Low
- Metalworking Fluids	I, D	High
- Laundry, Dry Cleaning	I, D	High
- Leather, Textiles1/	D	Low-High

* D=Dermal; I=Inhalation; Ig=Ingestion.

1/ Textiles not used for clothing or furnishing (e.g. tarpaulins, awnings, fire hoses) may be considered in the low exposure category.

Table 2. Interpretation of 40 CFR Part 158.135. Data requirements for antimicrobial pesticides based on exposure categories. Registrants selecting Option 1 should use Table 1 to identity the exposure category for each product and then determine the studies required according to Table 2.

R = Required
N = Not Required

Data Requirements and Pesticide Guidelines Reference [1,2]		Exposure Category for Use Site: High	Medium [3]	Low	Deadline for Submission from the Date of Receipt of this Notice
Subchronic Testing					
90 day Feeding	82-1	R	R	N	15 months
21 day Dermal [4]	82-2	R	N	N	12 months
90 day Dermal [4]	82-3	N	R	R	15 months
90 day Inhalation	82-4	N	R	R	15 months
90 day Neurotoxicity	82-5	N	N	N	15 months
Chronic Testing					
Chronic Feeding	83-1	R	N	N	50 months
Oncogenicity	83-2	R	N	N	50 months
Teratogenicity	83-3	R	R	R	15 months
Reproduction	83-4	R	N	N	39 months
Mutagenicity [5]	84-2	R	R	R	12 months
General Metabolism	85-1	R	N	N	24 months

"conditionally required" ["CR"] in Part 158. In general, the [illegible] contained in this table apply to all antimicrobial pesticides. However, because of the wide range and diversity of products and associated circumstances, registrants should consult all of the footnotes contained in Part 158 concerning data requirements for their particular products.

2/ Registrants are reminded that EPA may require additional data when necessary to properly evaluate a product. Section 158.75 states "if information required under this part is not sufficient to evaluate the potential of the product to cause unreasonable adverse effects on man or the environment, additional requirements will be imposed".

3/ Registrants with products whose use patterns fall into the medium category of exposure must submit the full set of subchronic data, and teratology and mutagenicity studies. Dermal absorption, exposure, and chronic studies will be required for compounds having a serious toxic effect as identified by oral or inhalation studies, for which a significant route of human exposure is dermal and for which the assumption of 100% absorption does not produce an adequate margin of safety.

4/ The FIFRA Science Advisory Panel has recently advised EPA that the 21 day dermal study has significant shortcomings in elucidating toxicological concerns resulting from exposure to chemicals. As a result, EPA will now generally require 90 day dermal studies. However, for chemicals requiring a full chronic data base, the 21 day dermal study will be suffiqient. The justification for this lies in the expectation that any toxicological effects observed in the 90 day, but not 21 day study, will likely also be observed in the chronic studies.

5/ In vitro mutagenicity studies are normally preferred in satisfying data requirements because of their increased sensitivity. However, antimicrobial agents may produce excessive toxicity in the standard bacteria or mammalian cell lines used in the in vitro studies as recommended in the guidelines. If registrants find that the cellular toxicity is much greater than might be expected based on in vivo toxicity, it may be necessary to perform in vivo mutagenicity testing. This testing would preclude missing mutagenicity due to detoxification mechanisms or metabolites peculiar to intact mammalian systems.

Table 3. Generic Exposure Data Requirement Matrix.* Registrants when satisfying the exposure data requirements under Options 2 or 3 are to use this table.

Use Site Group 1/	Application Method										
	Spray	Brush	Mop	Pour	Pump	Wipe	Fumigate	Flood	Immerse	Impregnate	Post-application exposure
Agricultural Premises and Equipment	X	X	X			X		X			
Agriculture Premises 2/	X	X	X			X	X	X			
Aquatic Sites 3/				X	X						X
Household 4/	X	X	X	X		X					X
Antifouling Treatment 5/	X	X									X
Commercial, Industrial & Institutional Premises and Equipment	X	X	X			X	X	X	X		X
Preservatives and 6/ Protectants				X	X	X					X
Domestic, Human and Miscellaneous Indoor Uses 7/	X			X		X	X		X	X	X

*/ Each "X" denotes 10 products when Option 2 is selected; 15 dermal samples are required and at least 5 inhalation samples are required. Each "X" denotes 15 dermal samples and 5 inhalation samples if Option 3 is selected. Fifteen inhalation samples are required if spray or other use which produces droplets is used. This matrix is only a sample. A final matrix will be developed [illegible] stage.

Footnotes for Generic Exposure Data Requirements Matrix

1/ Specific use pattern listed according to use site groups in 40 CFR, Part 158, Appendix A where applicable:

- Animal Premises and Equipment (Animal Prem. and Equip.)
- Aquatic Sites - food processing water systems, pulp and paper mill systems, swimming pool water, hot tubs, spas, whirlpools, human drinking water, cooling water towers, evaporative condensers, air washer systems, sewage systems and drains, secondary oil recovery
- Household (Hshld) - premises and contents (food and nonfood contact surfaces)
- Antifouling treatments - boat bottoms and other submerged structures
- Commercial, Industrial and Institutional Premises and Equipment (Comm., Ind., and Inst. Prem. and Equip.) - food and feed processing plants (food and nonfood contact surfaces), eating establishments (food and nonfood contact surfaces)), food marketing storage and distribution, hospital and related institutions and facilities (environmental surfaces and medical equipment), commercial industria and institutional premises (bathroom, latrine, and toilet bowls), barber and beauty shop instruments and equipment, morgues, mortuaries, and funeral homes
- Preservatives and Protectants - adhesives, coatings, oil recovery drilling muds, paints and preservatives, fungicidal paints, metal working fluids, paper and paper products, plastic products, resin emulsions, rubber (nature) products, textiles (including carpets), leather products
- Domestic, Human and Miscellaneous Indoor Uses - carpets, dust control (mops, etc.), air sanitizers, laundry, dry cleaning

2/ Fumigation methods used primarily in hatcheries

3/ Post application exposure monitoring required for food processing water systems, swimming pools, hot tubs, spas, whirlpools, and human drinking water

4/ Post application exposure monitoring required on food contact surfaces

5/ Post application exposure if pesticide is incorporated into the paint during manufacture

6/ Post application exposure for metalworking fluids

7/ Post application exposure for air sanitizers, carpets, laundry and dry cleaning