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

MAR 30 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

CERTIFIED MAIL

Dear Registrant:

Enclosed is a Reregistration Eligibility Document (RED) for the pesticide active ingredients hydroxytetracycline monohydrochloride and oxytetracycline calcium. Oxytetracycline *per se* is not included in the reregistration decision because there are no registered products containing oxytetracycline. However, much of the data supporting the reregistration was generated using oxytetracycline and tolerances are also expressed in terms of oxytetracycline. The three compounds are similar enough that data generated on oxytetracycline can be used to make regulatory decisions on the other two derivatives. The RED is the Agency's evaluation of hydroxytetracycline monohydrochloride and oxytetracycline calcium data bases, its conclusions regarding human and environmental risks associated with the current product uses, and its decisions and conditions under which uses and products will be eligible for reregistration. Also enclosed is the **EPA RED Facts** and the **Pesticide Reregistration Handbook** which provides instructions to registrants on how to respond to any labeling and data requirements specified in the RED and how to reregister products.

The RED identifies outstanding product specific data requirements for end-use products and manufacturing-use products. These requirements are listed on the Requirements Status and Registrant's Response Form, which along with the Data Call-In Response Form listing all of your company's products subject to the RED is included as an Attachment. Instructions for completing both forms are contained in the RED package. All product specific data must be submitted and found acceptable by the Agency before a product can be reregistered.

The Agency has determined that the generic data base supporting the reregistration of hydroxytetracycline monohydrochloride and oxytetracycline calcium products is substantially complete. However, some product chemistry information will be necessary in order to fulfill the generic data base.

The RED identifies any specific labeling requirements such as restricted use classification, groundwater hazard statements, endangered species precautions, etc., necessary for reregistration based on a review of the generic data for the active ingredient. In addition, in order to be reregistered, all product labeling must be in compliance with format and content labeling as described in 40 CFR §156.10 and all labeling changes imposed by Pesticide Regulation (PR) Notices, and any label changes imposed by this RED.

The Pesticide Reregistration Handbook contains detailed instructions for compliance with the RED and must be followed carefully. There are several key points to remember in preparing your response to the RED:

Within 90 Days of Your Receipt of this Letter

1. For each product which is subject to this RED, you must complete, sign and submit the data call-in (DCI) response forms attached to the RED [Appendix G, Attachments B and C, has forms for product specific data]. Follow the instructions in Attachments B and C for completing those forms and submit the forms to the appropriate address specified in the Data Call-In. The DCI forms for product specific data are to be sent to the Registration Division (use the mailing distribution code RED-RD-PM21 for your product specific response).

2. No time extensions will be granted for submitting the 90-day responses. If the Agency does not receive a response for a product, it may issue a Notice of Intent to Suspend (NOIS) for that product.

3. Any requests for data waivers or time extensions to the 8-month deadline must be submitted as part of your 90-day response. Such requests will generally not be considered if submitted later than the 90-day response.

Within 8 Months of the Date of this Letter

1. For each product, you must submit a completed Application for Reregistration (EPA Form 8570-1), five copies of the label and labeling revised as specified by the RED and in accordance

with current requirements, two completed copies of the Confidential Statement of Formula (CSF) (EPA Form 8570-4), a completed Certification with Respect to Citation of Data (EPA Form 8570-29), and data or references to data (see item 2 below).

2. You must submit or cite the required product specific data as part of your commitment for reregistration. For most products, you will probably be citing data which have already been submitted to the Agency. In these cases, you must submit a list of the studies and the corresponding EPA identifier numbers (i.e., ACCESSION or MRID numbers). Before citing these studies, you must make sure that they meet the Agency's current acceptance criteria (Appendix G, Attachment E). Be sure to follow data formatting requirements in P.R. Notice 86-5. Failure to adequately comply with the data requirements specified in this RED may result in the issuance of a Notice of Intent to Suspend for your product.

3. The labeling and CSF which you submit for each product must comply with P.R. Notice 91-2 (Appendix D). That Notice requires that the amount of active ingredient declared in the ingredient statement must be stated as the nominal concentration rather than the lower certified limit. You have two options for submitting a CSF: (1) accept the standard certified limits (see 40 CFR §158.175) or (2) provide certified limits that are supported by the analysis of five batches. If you choose the second option, you must submit or cite the data for the five batches along with a certification statement as described in 40 CFR §158.175(e).

4. Send your Application for Reregistration to the Registration Division Product Manager 21 (PM 21). Use the correct address shown on page 6 of the enclosed Product Reregistration Handbook (Appendix E). Note that the mailing distribution code for your response is RED-RD-PM21.

Questions on product specific data requirements and labeling (for both End-use and Manufacturing-use products) should be directed to the Registration Division Product Manager 21 Team member for hydroxytetracycline monohydrochloride and calcium oxytetracycline, Benjamin C. Chambliss at (703) 305 - 6900.

Any questions in regard to this RED should be addressed to Mario F. Fiol, Chemical Review Manager, Reregistration Branch, Special Review and Reregistration Division at (703) 308 - 8049.

The Agency is prepared to meet with any registrants who have questions about responding to the hydroxytetracycline monohydrochloride and calcium oxytetracycline RED. If you wish to

meet with the Agency, you must contact Mr. Chambliss within two weeks of your receipt of the RED. The Agency is willing to hold one combined meeting with interested registrants. If there are any requests for such a meeting, the Agency will notify all registrants who requested a meeting of the date, location and time. Requests for a meeting will not extend the 90-day or 8-month response deadlines.

Sincerely yours,

Peter Caulkins for

Daniel M. Barolo, Director
Special Review and
Reregistration Division

Enclosures

Oxytetracycline calcium is formulated as a wettable powder and is applied as a foliar application using ground or aircraft equipment. Hydroxytetracycline monohydrochloride is formulated as a soluble concentrate/solid and is applied either by tree injection or as an additive to paints.

Regulatory History

Oxytetracycline has been available in the United States as a drug for therapeutic use in humans since 1950. It also is used in veterinary medicine to prevent infections in fowl, cattle and swine.

Oxytetracycline first was registered as a pesticide in 1974. EPA issued a Registration Standard for oxytetracycline, hydroxytetracycline monohydrochloride and oxytetracycline calcium in December 1988 (NTIS PB89-138556). The Agency assessed the data submitted in response to the Registration Standard in developing this RED.

At present, five end-use products are registered containing hydroxytetracycline monohydrochloride or oxytetracycline calcium as active ingredients. There are no active registrations for products containing oxytetracycline, the third active ingredient covered in the 1988 Registration Standard. For this reason, the RED does not apply to oxytetracycline per se, but only to the two derivatives.

Human Health Assessment

Toxicity

EPA has waived all toxicological data requirements for hydroxytetracycline monohydrochloride and oxytetracycline calcium. The toxicity of all three oxytetracyclines is expected to be similar, and data generated on one compound can be used to assess exposure/risks of the other two. Sufficient information is available on their effects in humans, supplemented by the laboratory animal studies summarized below.

Hydroxytetracycline monohydrochloride and oxytetracycline calcium are of low acute toxicity through the oral route of exposure, and have been placed in Toxicity Category IV indicating the lowest degree of toxicity for this effect. Subchronic feeding studies in rats showed no adverse effects. In two-year chronic toxicity studies in rats and dogs, the No Observed Effect Level was the highest dose tested.

Carcinogenicity studies show some equivocal evidence of cancer in male and female rats administered extremely high doses. However, EPA has classified oxytetracycline as a "Group D" carcinogen--one that is "not classifiable as to human carcinogenicity."

One developmental toxicity study in rats showed a high incidence of maternal deaths and fetotoxicity; however, excessive dose levels were used. No adverse effects were demonstrated in another similar study.

United States
Environmental Protection
Agency

Office of Prevention, Pesticides
And Toxic Substances
(H-7508W)

EPA-738-F-93-001
March 1993

EPA R.E.D. FACTS

Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium

Pesticide Reregistration

All pesticides sold or used in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered years ago be reregistered to ensure that they meet today's more stringent standards.

In evaluating pesticides for reregistration, EPA obtains and reviews a complete set of studies from pesticide producers, describing the human health and environmental effects of each pesticide. The Agency imposes any regulatory controls that are needed to effectively manage each pesticide's risks. EPA then reregisters pesticides that can be used without posing undue hazards to human health or the environment.

When a pesticide is eligible for reregistration, EPA announces this and explains why in a Reregistration Eligibility Document, or RED. This fact sheet summarizes the information in the RED for hydroxytetracycline monohydrochloride and oxytetracycline calcium.

Use Profile

Oxytetracycline is an antibiotic drug produced by a micro-organism. Two related compounds, hydroxytetracycline monohydrochloride and oxytetracycline calcium, are registered as pesticides, for use in preventing the growth of or killing bacteria, fungi and mycoplasma-like organisms. These pesticides are used primarily to control fire blight of pears, pear decline, bacterial spot on peaches and nectarines, lethal yellowing of coconut palm, and lethal decline of pritchardia palm; and as an antifoulant added to marine paints to prevent the growth of barnacles.

During use and/or post-application, workers may be exposed to relatively greater amounts of these pesticides than the general public. However, label requirements will address concerns with potential allergic responses in oxytetracycline-sensitive people, as well as the potential development of resistance to oxytetracycline.

Environmental Assessment

Environmental Fate

EPA has waived all environmental fate data requirements for hydroxytetracycline monohydrochloride and oxytetracycline calcium because of their limited pesticidal use patterns and the availability of published literature.

Ecological Effects

Acute toxicity studies in the published literature indicate that oxytetracycline is practically non-toxic to birds, fish, aquatic invertebrates and non-target insects such as honey bees.

Ecological Effects Risk Assessment

Due to their low toxicity and the low estimated environmental concentration resulting from their use as pesticides, it is unlikely that hydroxytetracycline monohydrochloride and oxytetracycline calcium pose undue risks to avian or aquatic organisms or honey bees.

Additional Data Required

EPA is requiring product-specific acute toxicity and product chemistry studies for reregistration of these pesticides.

Product Labeling Changes Required

The labels of all registered pesticide products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium must comply with EPA's current pesticide labeling requirements. The Agency soon will issue a Pesticide Registration (PR) Notice providing instruction on changing labels of agricultural products in keeping with the Worker Protection Standard. That PR Notice also will apply to these products.

End-use products must bear the following additional or revised label statements in the Human Hazards section:

- Labels of products registered for use on agricultural crops by foliar application methods must include the restricted entry statement, "Entry into treated orchards (or "areas") is prohibited for 12 hours following application."

- Labels of products registered for use on agricultural crops by foliar applications must include the protective clothing statement, "Prolonged or frequently repeated exposure may cause allergic reactions in some individuals. Do not breathe dust or spray mist.

In humans administered oxytetracycline to treat infectious diseases caused by various microorganisms, a variety of adverse effects have been reported including toxic and irritative effects, hypersensitivity and other biological effects.

Dietary Exposure

Tolerances or maximum residue limits are established for residues of oxytetracycline in or on pears at 0.35 ppm and peaches (including nectarines) at 0.1 ppm. Please see 40 CFR 180.337. Tolerances of 0.1 ppm in or on tomatoes and cherries are pending. The 1988 Registration Standard concluded that EPA had adequate data to support the registered pear and peach uses, but also concluded that the tolerance for peaches should be raised to 0.35 ppm.

Because oxytetracycline is used in veterinary medicine, tolerances for residues in animals have been established by FDA. Please see 21 CFR 520, 522, 524 and 558. No Codex Maximum Residue Limits (MRLs) and no Canadian or Mexican tolerances are established or proposed for oxytetracycline.

Occupational and Residential Exposure

When oxytetracycline calcium is applied to pears, peaches and nectarines using foliar application methods, pesticide mixers, loaders, and applicators can be exposed; fieldworkers also can be exposed, post-application. Worker exposure from trunk injection of hydroxytetracycline monohydrochloride to agricultural and ornamental trees is expected to be negligible.

Because the toxicity data for oxytetracycline do not meet EPA criteria that would trigger requirements for these studies, no occupational or residential exposure monitoring data are required. However, oxytetracycline has produced allergic reactions in some patients, and resistance to the drug could result from human exposure. Therefore, EPA will require labeling on pesticide products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium to lessen these potential risks.

Human Risk Assessment

The risks to people from dietary and occupational exposure to pesticides containing hydroxytetracycline monohydrochloride and oxytetracycline calcium are considered negligible. Chronic dietary risks posed by all food uses of these pesticides are well below the level that would reasonably cause concern.

Wear a MSHA/NIOSH approved TC-21C dust/mist filtering respirator, long sleeved shirt, pants, shoes, and chemical-resistant gloves while handling or applying this product. Wash thoroughly after handling or applying."

Regulatory Conclusion

Use of the active ingredients hydroxytetracycline monohydrochloride and oxytetracycline calcium in accordance with approved labeling will not result in unreasonable adverse effects to human health or the environment, and all registered pesticide products containing these active ingredients are eligible for reregistration. These products will be reregistered once the required product-specific data and revised labeling are received and accepted by EPA.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Document (RED) for hydroxytetracycline monohydrochloride and oxytetracycline calcium during a 60-day time period, as announced in a Notice of Availability published in the Federal Register. To obtain a copy of the RED or to submit written comments, please contact the Pesticide Docket, Public Response and Program Resources Branch, Field Operations Division (H-7506C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Following the comment period, the hydroxytetracycline monohydrochloride and oxytetracycline calcium RED will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650.

For more information about hydroxytetracycline monohydrochloride and oxytetracycline calcium or about EPA's pesticide reregistration program, please contact the Special Review and Reregistration Division (H-7508W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8000. For information about reregistration of individual products containing these active ingredients, please contact Ben Chambliss, Product Manager, Registration Division (H-7505C), OPP, US EPA, Washington, DC 20460, telephone 703-305-6900.

For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, between 8:00 am and 6:00 pm Central Time, Monday through Friday.

REREGISTRATION ELIGIBILITY DOCUMENT

FOR

HYDROXYTETRACYCLINE MONOHYDROCHLORIDE and

OXYTETRACYCLINE CALCIUM

LIST A

CASE 0020

March, 1993

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS
SPECIAL REVIEW AND REREGISTRATION DIVISION
WASHINGTON, D.C.

TABLE OF CONTENTS

GLOSSARY OF TERMS AND ABBREVIATIONS

ADI	Acceptable Daily Intake. Also known as Reference Dose or RfD.
a.i.	Active Ingredient
ARC	Anticipated Residue Contribution
CAS	Chemical Abstracts Service
CSF	Confidential Statement of Formula
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
HDT	Highest Dose Tested
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death during inhalation exposure in 50% of test animals exposed for a specified time. The LC_{50} is expressed as weight or volume of test substance per volume of air, (e.g., mg/l or ppm).
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral or dermal). It is expressed as a weight of substance per unit weight of animal, (e.g., mg/kg).
LDT	Lowest Dose Tested
LEL	Lowest Effect Level
MP	Manufacturing-Use Product
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.

APPENDIX D - List of Available Related Documents

APPENDIX E - Pesticide Reregistration Handbook

APPENDIX F - Generic Data Call-In - NOT APPLICABLE
No generic data are being called-in for hydroxytetracycline monohydrochloride and oxytetracycline calcium

APPENDIX G - Product Specific Data Call-In

Attachment A - Product Specific DCI Chemical Status Sheet

Attachment B - Product Specific DCI Response Forms (Form A) plus Instructions

Attachment C - Product Specific DCI Requirements Status and Registrants' Response Forms (Form B) plus Instructions

Attachment D - EPA's Grouping of End-Use Products for Meeting Acute Toxicology Data Requirements

Attachment E - EPA Acceptance Criteria

Attachment F - List of Registrants sent this DCI

Attachment G - Product Specific Data Call-In Cost Share and Data Compensation Forms

EXECUTIVE SUMMARY

This Reregistration Eligibility Document (RED) will address the eligibility for reregistration of products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium.

Oxytetracycline is an antibiotic drug produced by the actinomycete Streptomyces rimosus. It is also registered to prevent the growth of, or control bacterial and fungi diseases and mycoplasmalike organisms in nectarines, peaches, pears, coconut and pritchardia palms and as an antifoulant added to paint to prevent the growth of barnacles. There are registered products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium, but none with oxytetracycline, per se. Therefore, this Reregistration Eligibility Document (RED) addresses only oxytetracycline calcium and hydroxytetracycline monohydrochloride, even though some of the studies supporting the RED decision were conducted with the oxytetracycline base.

The formulations of hydroxytetracycline monohydrochloride and calcium oxytetracycline are wettable powder and soluble concentrate/solid. The registered products are applied either by foliar spray, tree injection, or as an antifoulant additive to paints.

Oxytetracycline was initially registered as a pesticide in 1974. A Registration Standard was issued in December, 1988 (NTIS PB89-138556). This Registration Standard summarized the available data supporting the reregistration of products containing oxytetracycline, hydroxytetracycline monohydrochloride and, oxytetracycline calcium used for the control of bacteria, fungi, mycoplasmalike organisms and barnacles. The Registration Standard also required additional product chemistry, ecological effects, and environmental fate data. The Agency has now completed its review of the hydroxytetracycline monohydrochloride and calcium oxytetracycline data base including the data submitted in response to the 1988 Registration Standard.

The Agency has determined that the use of hydroxytetracycline monohydrochloride and oxytetracycline calcium to control bacteria, fungi, mycoplasmalike organisms and barnacles will not cause unreasonable risk to man or the environment and all uses are eligible for reregistration. The Agency has determined that the generic data base supporting the reregistration of oxytetracycline calcium and hydroxytetracycline monohydrochloride products is

N/A	Not Applicable
NPDES	National Pollutant Discharge Elimination System
NOEL	No Observed Effect Level
OPP	Office of Pesticide Programs
PADI	Provisional Acceptable Daily Intake
ppm	Parts Per Million
RfD	Reference Dose
RS	Registration Standard
TMRC	Theoretical Maximum Residue Contribution

substantially complete. However, some product chemistry information will be necessary in order to fulfill the generic data base. Reregistration of all products will proceed after these data are generated because end-use products cannot be reregistered until the Agency has received and reviewed the product chemistry for the technical or MPs.

Before reregistering the applicable products, the Agency is requiring that the product specific data, revised Confidential Statements of Formula (CSF) and labeling be submitted within eight (8) months of the issuance of this document. These data include product chemistry for each registration and acute toxicology testing. After reviewing these data and the revised labels, the Agency will reregister a product based on whether or not that product meets the requirements in Section 3(c)(5) of FIFRA. Those products which contain other active ingredients will be eligible for reregistration only when the other active ingredients are determined to be eligible for reregistration.

II. CASE OVERVIEW

A. Chemical Overview[2]

The following active ingredients are covered by this Reregistration Eligibility Document:

- **Common Name:** Hydroxytetracycline Monohydrochloride

  Chemical Name: 2-Naphthacenecarboxamide, 4-(dimethyl amino) -1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 6, 10, 12 dioxo-monohydrochloride, 12a pentahydroxy-6-methyl-1, 11-dioxo mono hydrochloride.

  Chemical Family: Antibiotic (produced by the actinomycete Streptomyces rimosus)

  CAS Registry Number: 2058-46-0

  OPP Chemical Code: 006308

  Empirical Formula: $C_{22}H_{24}N_2O_9$ HCL

  Trade and Other Names: Biosolvomycin, Hydrocyclin, Liquamycin, Otetryn, Oxlopar, 5-Hydroxytetracycline Hydrochloride, Terramycin Hydrochloride

  Basic Manufacturer: Pfizer, Inc.

- **Common Name:** Oxytetracycline Calcium

  Chemical Name: 4-(Dimethylamino)-1, 4, 4a, 5a, 6, 11, 12a-octahydro-3, 5, 6, 10, 12, 12a hexahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide calcium salt.

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[2] The 1988 Registration Standard reviewed the data requirements for registered products containing oxytetracycline, hydroxytetracycline monohydrochloride, and calcium oxytetracycline. Since there are no longer active products containing oxytetracycline, this document will only assess the requirements for the remaining two active ingredients.

I. INTRODUCTION

In 1988, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act provides a schedule for the reregistration process to be completed in nine years. There are five phases to the reregistration process. The first four phases of the process focus on identification of data requirements to support the reregistration of an active ingredient and the generation and submission of data to fulfill the requirements. The fifth phase is a review by the U.S. Environmental Protection Agency (hereafter referred to as "the Agency") of all data submitted to support reregistration.

FIFRA Section 4(g)(2)(A) states that in Phase 5 "the Administrator shall determine whether pesticides containing such active ingredient are eligible for reregistration" before calling in data on products and either reregistering products or taking "other appropriate regulatory action." Thus, reregistration involves a thorough review of the scientific data base underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether the pesticide meets the "no unreasonable adverse effects" criterion of FIFRA.

This document presents the Agency's decision regarding the reregistration of hydroxytetracycline monohydrochloride and oxytetracycline calcium. The document consists of the following six sections: Section I is the introduction; Section II describes the pesticide uses, data requirements and regulatory history; Section III discusses the human health and environmental assessment based on the data available to the Agency; Section IV discusses the reregistration decision for hydroxytetracycline monohydrochloride and oxytetracycline calcium; Section V discusses the actions required by registrants; and, Section VI is the Appendices which support this Reregistration Eligibility Document. Additional details concerning the Agency's review of applicable data are available on request.[1]

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[1] EPA's reviews of data on the set of registered uses considered for EPA's analysis may be obtained from the OPP Public Docket, Field Operations Division (H7506C), Office of Pesticide Programs, EPA, Washington, D.C. 20460

- **Formulation types registered:**

  - Oxytetracycline calcium - 31.5% oxytetracycline calcium complex wettable powder (equivalent to 17% oxytetracycline base).

  - Hydroxytetracycline monohydrochloride - 21.6% oxytetracycline hydrochloride soluble concentrate/solid (equivalent to 20% oxytetracycline base).

- **Methods and rates of application:**

  - Oxytetracycline calcium - foliar applications are made either by ground (airblast or pressure sprayer) or aircraft. Application rates vary depending on the site: pears - 0.085 lb ai/ac in 3 to 100 gallons/ac to 0.17 lb ai/ac in 20 to 100 gallons/ac and; peaches and nectarines - 0.05 lb ai/ac in 240 gallons/ac.

  - Hydroxytetracycline monohydrochloride - applications are made either by tree injection or as an additive to paints. The application rate varies depending on the site: pears - 100 ppm; coconut palm - 0.035 oz ai in 0.5 to 16 oz water/tree and 0.22 oz ai in 2 to 16 oz water/tree; pritchardia palm - 0.035 to 0.11 oz ai in 0.5 to 16 oz water/tree and; paints - 0.0706 oz ai/gal.

- **Use practice limitations:**

  - Oxytetracycline calcium - do not apply through any type of irrigation system. 21 day preharvest interval for peaches and nectarines, 60 day preharvest interval for pears.

  - Hydroxytetracycline monohydrochloride - applications on pears are limited to west coast states.

C. Estimated Usage of the Pesticides

This section summarizes the best estimates available for the pesticide uses of hydroxytetracycline monohydrochloride and oxytetracycline calcium. These estimates are derived from a variety of published and proprietary sources available to the Agency. The data, reported on an aggregate and site (crop) basis, reflect annual fluctuations in use patterns as well as the variability in using data from various information sources.

The table below summarizes the pesticides use by site. Most sites have a very small percentage of acreage treated with hydroxytetracycline monohydrochloride and oxytetracycline calcium, so small that these figures remain relatively consistent over time.

Chemical Family: Antibiotic (produced by the actinomycete Streptomyces rimosus)

CAS Registry Number: 15251-48-6

OPP Chemical Code: 006321

Empirical Formula: $C_{44}H_{46}CaN_4O_{18}$

Trade and Other Names: Agricultural Terramycin, Mycoshield

Basic Manufacturer: Pfizer, Inc.

B. Use Profile

The following information provides the active registered uses with specific use sites and application methods for calcium oxytetracycline and hydroxytetracycline monohydrochloride. A detailed table of eligible uses as well as the methods, application rates and limited use restrictions is included in Appendix A.

o Type of Pesticide:

Oxytetracycline calcium - bacteriocide/bacteriostat

Hydroxytetracycline monohydrochloride - bacteriostat, fungicide and antifoulant

o Use sites:

Oxytetracycline calcium -

- terrestrial food crops: nectarine, peach, and pear

Hydroxytetracycline monohydrochloride -

- terrestrial food crops: pear
- terrestrial non-food + outdoor residential: coconut palms, pritchardia palms
- aquatic non-food industrial: paints
- indoor non-food: paints

o Pests:

- Oxytetracycline calcium - fire blight on pears and bacterial spot on peaches and nectarines.

- Hydroxytetracycline monohydrochloride - pear decline, lethal yellowing on coconut palms, lethal decline on pritchardia palms, and barnacles.

and pear decline, bacterial spot of peaches and nectarines, lethal yellowing of coconut palm, lethal decline of pritchardia palm, and barnacles.

A Registration Standard for oxytetracycline, oxytetracycline calcium and hydroxytetracycline monohydrochloride was issued in December 1988. The Reregistration Eligibility Document reflects the reassessment of all data submitted in response to the 1988 Registration Standard.

There are currently five (5) end-use products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium registered in the United States. There are no technical or manufacturing-use products of oxytetracycline *per se* currently registered.

III. SCIENCE ASSESSMENT

The Agency has conducted a thorough review of the scientific data base for oxytetracycline calcium and hydroxytetracycline monohydrochloride for the purposes of determining the reregistration eligility of these pesticides.

A. Product Chemistry Assessment

The physical and chemical properties of oxytetracycline calcium and hydroxytetracycline monohydrochloride are as follows:

o	TGAI	Oxytetracycline calcium
	Color	dark brown
	Physical State	Solid
	Odor	earth-like
	pH	8.6 (1% aqueous solution)
	Molecular Weight	958.94
o	TGAI	Hydroxytetracycline Monohydrochloride
	Molecular weight	496.9
	Color	Bright Yellow
	Physical State	Solid (STP)
	Odor	Odorless
	Melting Point	Decomposes above 180 C
	Boiling Point	N/A (TGAI is a solid)
	pH	2.4 (1% aqueous solution)

There are several product chemistry requirements which are not fully satisfied for the calcium oxytetracycline and hydroxytetracycline monohydrochloride. Although data gaps exist these requirements are not critical to the reregistration eligibility decision. The Agency is requiring additional product chemistry data at this time to satisfy these data gaps. The requirements and data gaps are given in Appendix B.

It is important to note that their usage may vary greatly from year to year, depending on weather conditions.

Hydroxytetracycline monohydrochloride and oxytetracycline calcium are used primarily on pears. Reported resistance to streptomycin has increased their use in the Pacific Northwest since 1990. Based upon the available data, pears account for up to 36% of yearly use, peaches up to 25%, palms up to 21%, and marine antifouling paint up to 18%. The quantitative usage on palm trees and marine antifouling paints is uncertain.

DOMESTIC USAGE OF HYDROXYTETRACYCLINE MONOHYDROCHLORIDE AND CALCIUM OXYTETRACYCLINE AS PESTICIDES TYPICAL RECENT YEARS (1987 - 1991)

SITE	LBS. A.I. (1,000)	% OF TOTAL USE	% OF SITE TREATED	STATE USAGE
Pears[1]	25 - 50	25 -36	<60	OR, 1987; WA, CA 1990,
Peaches[1]	15 - 35	15 - 25	<30	MI, SC, CA 1990
Palms	<30	<21	NA	NA
Marine Uses	<25	<18	NA	NA
TOTAL	<100 - <140	100		

NA - Not Available

[1] Includes bearing and non-bearing acres.

No use is reported on nectarines.

D. Data Requirements

Data requested in the December 1988 Registration Standard for oxytetracycline, hydroxytetracycline monohydrochloride and oxytetracycline calcium included studies on product chemistry, ecological effects, and environmental fate. These data were required to support the uses listed in the Registration Standard. Appendix B includes all data requirements identified by the Agency for currently registered uses needed to support reregistration.

E. Regulatory History

Oxytetracycline has been available as a drug for therapeutic use in the United States since 1950 and was first registered as a pesticide in 1974. Oxytetracycline is also used in veterinary medicine to prevent infections in fowl, cattle and swine. As a pesticide, hydroxytetracycline monohydrochloride and oxytetracycline calcium are used to inhibit fire blight on pears

thyroid was observed in all dosed animals at necropsy. The NOEL was 10,000 ppm (approximately 250 mg/kg/day), the highest dose tested. In a second study, groups of mongrel dogs were fed diets containing 0, 5,000, or 10,000 ppm (approximately 0, 125, or 250 mg/kg/day) hydroxytetracycline monohydrochloride. The NOEL was 10,000 ppm (approximately 250 mg/kg/day), the highest dose tested.

These studies were judged to be supplementary because too few animals survived to study termination, too few tissues were examined histologically and/or specific details were not provided in the studies (e.g., individual animal data). However, the Agency waived this data requirement based upon availability of both animal and human data from oxytetracycline's drug uses.

d. Carcinogenicity

In an NTP study, hydroxytetracycline monohydrochloride was administered to groups of F344N rats fed 0, 25,000, or 50,000 ppm (approximately 0, 1,250, or 2,500 mg/kg/day), in their diet. Fatty metamorphosis of the liver was increased in rats in the 1,250 mg/kg/day group. The NTP's Peer Review Committee concluded that ".... there was equivocal evidence of carcinogenicity for the male rats as indicated by increased incidences of pheochromocytomas of the adrenal gland. There was equivocal evidence of carcinogenicity for the female rats as indicated by increased incidences of adenomas of the pituitary gland in the high dose group."

In a second NTP study, hydroxytetracycline monohydrochloride was administered to groups of B6C3F1 mice fed 0, 6,300, or 12,500 ppm (approximately 0, 945, or 1,875 mg/kg/day), in their diet. Body weights were decreased in mice in the 1,875 mg/kg/day group when compared to controls. The NTP's Peer Review Committee concluded that ".... there was no evidence of carcinogenicity for male or female mice fed diets containing the higher doses of hydroxytetracycline monohydrochloride."

The Agency's Peer Review Committee has classified oxytetracycline as a "Group D" carcinogen ("Not Classifiable as to Human Carcinogenicity").

This classification is in agreement with the conclusion made by the National Toxicological Program's (NTP) Peer Review Committee. In their report, the NTP Peer Review Committe concluded that "...there was equivocal evidence of carcinogenicity for male rats (of the high dose group) as indicated by increased incidences of pheochromocytomas of the adrenal gland (with a statistically significant positive trend, not significant in pairwise comparison with concurrent controls, and was outside the historical control range). There was equivocal evidence of carcinogenicity for females rats as indicated by increased incidences of adenomas of the pituitary gland (known to have a high background rate) in the high dose group." With respect to the mouse study, the NTP report concluded that "...there was no evidence of carcinogenicity for male or female mice fed hydroxytetracycline monohydrochloride for two years."

B. Human Health Assessment

1. Toxicology Assessment

The oxytetracyclines include oxytetracycline, oxytetracycline calcium, and hydroxytetracycline monohydrochloride. The toxicity of all 3 oxytetracyclines would be expected to be similar. At the time of the Registration Standard, no toxicological studies were required based on the data available at the time. The information available on the effects of oxytetracycline, oxytetracycline calcium, and hydroxytetracycline monohydrochloride in humans, supplemented with the data available on the toxicity of oxytetracycline in laboratory animals, is sufficient to evaluate the toxicity of oxytetracycline and related compounds. The laboratory animal data consist of the following:

a. Acute Toxicity

The acute oral LD_{50} value of hydroxytetracycline monohydrochloride in Swiss mice has been reported to be 7,200 mg/kg. Based on this, oxytetracycline is classified as Toxicity Category IV (the lowest category).

b. Subchronic Toxicity

The National Toxicology Program (NTP) conducted a 13-week study in B6C3F1 mice administered hydroxytetracycline monohydrochloride at concentration of 3,100, 6,300, 12,500, 25,000, or 50,000 ppm (approximate doses of 465, 945, 1875, 3750 or 7,500 mg/kg/day) in the diet. The NOEL was approximately 25,000 ppm (approximately 3,750 mg/kg/day). The LOEL was 50,000 ppm (approximately 7,500 mg/kg/day), based on decreases in body weight.

The NTP also conducted a 13-week study in F344N rats at concentrations of 3,100, 6,300, 12,500, 25,000, or 50,000 ppm (approximate doses of 155, 315, 625, 1,250, or 2,500 mg/kg/day) in the diet. No adverse effects were observed.

c. Chronic Toxicity

Two, 2-year chronic toxicity studies were conducted in rats. In one study, Osborne Mendel rats were fed diets containing 0, 100, 1,000, or 3,000 ppm (approximately 0, 5, 50, or 150 mg/kg/day) hydroxytetracycline monohydrochloride in the diet. The NOEL was 3,000 ppm (approximately 150 mg/kg/day), the highest dose tested. In a second study, groups of Sprague-Dawley rats were fed diets containing 0, 100, or 1,000 ppm (approximately 0, 5, or 50 mg/kg/day) hydroxytetracycline monohydrocholoride. The NOEL was 1,000 ppm (approximately 50 mg/kg/day), the highest dose tested.

In addition, two chronic toxicity studies were conducted in dogs. In the first study, beagle and mongrel dogs were fed diets containing 0, 100, 3,000 or 10,000 ppm (approximately 0, 2.5, 75, or 250 mg/kg/day) hydroxytetracycline monohydrochloride. A yellow discoloration of the long bones and brownish discoloration of the

mg/kg/day. Although not tested, the same potential may exist for the development of chemical resistance in respiratory flora.

h. Human Data

In humans, oxytetracycline is administered orally and intravenously to treat infectious diseases caused by a wide variety of microorganisms such as rickettsiae, mycoplasma pneumoniae, spirochetes, gram-negative bacteria (Bartonella bacilliformis, Pasteurella pestis, Brucella sp.), and gram-positive bacteria (Streptococcus sp., Staphylococcus aureus, Neisseria gonorrhea).

The dose for adults ranges from 1 to 2 grams per day (orally or intravenously). The usual daily dose for children is 25 to 50 mg/kg.

A variety of adverse effects in humans have been reported from the therapeutic use of oxytetracycline. The major adverse effects are described below:

1) Toxic and Irritative Effect -

The antibiotic may cause gastrointestinal irritation, mostly after oral administration, in some but not in all individuals. Epigastric burning and distress, abdominal discomfort, nausea, vomiting and diarrhea may occur which may be lessened by administering oxytetracycline with a meal and/or at more frequent intervals and smaller doses. Intravenous administration may produce thrombophlebitis. Long-term therapy may produce changes in the peripheral blood; leucocytosis, atypical lymphocytes, toxic granulation of granulocytes and thrombopenia purpura may occur. A phytotoxic reaction, which is rare, may occur, sometimes accompanied by onycholysis and pigmentation of the nails. Large doses administered orally or parenterally (situated or occurring outside of the intestine) may produce liver injury; this effect is more pronounced in pregnant women. Children under 7 years of age may develop a brown discoloration of the teeth. Treatment of pregnant women also may produce discoloration of the teeth of infants. Oxytetracycline deposited in the skeleton of fetuses and children can produce depression of bone growth. However, this is readily reversible if the period of exposure to the drug is short.

2) Hypersensitivity -

Various skin reactions such as morbilliform rashes, urticaria, and generalized dermatitis may occur but they are rare. Angioedema and anaphylaxis may develop. Other effects such as burning sensation of the eyes, cheilosis (the condition marked by fissuring and dry scaling of the vermillion surface of the lips and angles of the mouth; it is characteristic of riboflavin deficiency), brown or black coating of the tongue,

Given the equivocal nature of the carcinogenic response in the rat study at an extremely high dose level (especially when the actual dietary exposure to the human is taken into consideration), and the fact that mutagenicity data were inconclusive, the Agency's Peer Review Committee believes that the "Group D" classification is appropriate. It should be emphasized, however, that this classification is based on adequate studies in two animal species. Therefore, new carcinogenicity studies are not needed at this time. However, the Agency notes that the carcinogenicity issue may be revisited if the exposure is significantly increased.

e. Developmental Toxicity

Groups of female Charles River CD (COBS) rats were dosed by gavage during gestation days 6 through 15 with 1,200, 1,350, or 1,500 mg/kg/day of hydroxytetracycline monohydrochloride. There were dose-related decreases in maternal survival and body weight gain, and increases in incidence of breathing difficulties and rough coat. In addition, there were significant dose-related decreases in the percent of pregnant dams. There was also a dose-related decrease in fetal body weight. The high incidence of maternal deaths and the fetotoxicity noted at all dose levels tested did not allow for an establishment of a NOEL. The LEL was 1,200 mg/kg/day. The significant findings discussed in this study can be attributed to the excessive dose levels used, thereby overly stressing the treated dams.

Groups of female CD-1 mice were dosed by gavage during gestation days 6 through 15 with 0, 1,350, 1,670, or 2,100 mg/kg/day of hydroxytetracycline monohydrochloride. No adverse effects were demonstrated. The NOEL for maternal and developmental toxicity in this study was 2,100 mg/kg/day (highest dose tested).

f. Mutagenicity

In studies conducted for the NTP, hydroxytetracycline monohydrochloride at concentrations up to 1 mg/plate was not mutagenic to Salmonella typhimurium strains TA100, TA1535, TA1537, OR TA98, with or without metabolic activation. Concentrations of 100 and 200 mg/ml were mutagenic to L5178Y/TK+/- mouse lymphoma cells, only with metabolic activation. In cultured Chinese hamster ovary cells, hydroxytetracycline monohydrochloride was weakly positive in inducing sister chromatic exchanges, with and without metabolic activation, but did not induce structural chromosomal aberrations.

g. Antibiotic Microbial Resistance

Mature beagle dogs were fed a diet containing 0, 2, or 10 ppm (approximately 0, 0.05, or 0.25 mg/kg/day) oxytetracycline for 44 days. There was a shift from a predominantly drug-susceptible population of enteric (pertaining to the intestinal tract) lactose-fermenting organisms to a multiple antibiotic-resistant population at 0.25 mg/kg/day but not at 0.05 mg/kg/day. The NOEL was 0.05

The overall human and animal toxicological data on oxytetracycline indicate that this pesticide does not meet the Agency's toxicity criteria that would trigger the requirement of occupational or residential exposure monitoring data. Although there is a potential for exposure to workers from foliar application of oxytetracycline, this potential exposure may be reduced by label statements restricting entry into treated fields and specifying the use of certain protective clothing and equipment (PPE) while handling or applying end-use products registered for foliar application to agricultural crops.

There are no proposed or established CODEX MRL's for oxytetracycline. Therefore, there are no harmonization issues to be resolved.

a. Dietary Exposure Assessment

A chronic dietary exposure assessment has been conducted using the following parameters:

1) RfD of 0.005 mg/kg/day

2) Residue Evaluation based on all published and pending tolerances for oxytetracycline, including peaches at 0.35 ppm, and assuming 100% crop treatment.

3) Chronic Exposure Estimates based on a Theoretical Maximum Residue Contribution (TMRC). Exposure estimates for the overall U.S. population and the most highly exposed subgroups are as follows:

Group/Subgroup	TMRC (mg/kg/day)	% RfD
U.S. Population	0.000268	5.35
Non-Nursing infants (less than 1 yr old)	0.001391	27.81
Nursing Infants (less than 1 yr old)	0.000970	19.41
Children (1 to 6 yrs old)	0.000549	10.97
Children (7 to 12 yrs old)	0.000405	8.11

b. Occupational and Residential Exposure

The 1988 Registration Standard for oxytetracycline, hydroxytetracycline monohydrochloride and calcium oxytetracycline did not require occupational or residential exposure data. Hydroxytetracycline monohydrochloride and calcium oxytetracycline are applied by foliar application methods to agricultural crops, including pears, peaches, and nectarines, and also is applied by tree trunk injection to agricultural and ornamental trees. Foliar application can be expected to result in exposure to both mixer/loader/applicators and fieldworkers (post-application); worker exposure resulting from tree injection application is expected to be negligible.

atrophic or hypertrophic glossitis, pruritus ani or vulvae or vaginitis, fever and eosinophilia may persist for weeks after cessation of therapy.

3) Other Biological Effects -

Administration of oxytetracycline to undernourished adults results in weight loss, increased urinary (but not fecal) nitrogen excretion, negative nitrogen balance, and elevated serum nonprotein nitrogen concentrations. Administration of oxytetracycline, like most antibiotics, may lead to development of super infections by strains of bacteria or yeasts resistant to the agent. There is limited evidence of microbial resistance occurring in humans. A NOEL was estimated to be 0.033 mg/kg/day based on the absence of microbial resistance in a 60 kg person receiving a dose of 2 mg/day administered for 7 consecutive days.

i. Reference dose (RfD)

A Reference Dose (RfD) for oxytetracycline was established by the Agency's RfD Peer Review Committee at 0.005 mg/kg/day. The RfD was based on 1) a NOEL of 0.05 mg/kg/day from the 44-day feeding study in dogs, and 2) an uncertainty factor of 10 to account for intraspecies variability. An additional uncertainty factor of 10 to account for interspecies extrapolation was deemed unnecessary since human data clearly demonstrate that humans are not significantly more sensitive to the toxic effects of oxytetracycline than experimental animals.

2. Exposure Assessment

Tolerances of 0.35 and 0.1 ppm currently are established for the bactericide/fungicide oxytetracycline in or on pears and peaches, respectively, from foliar treatments or injection [40 CFR §180.337]. Tolerances of 0.1 ppm in or on tomatoes and cherries are pending. The 1988 Registration Standard concluded that the Agency had adequate data to support registered uses on pears and peaches. However, the Registration Standard also concluded that the tolerance for peaches should be raised from 0.1 to 0.35 ppm.

Because oxytetracycline is used in veterinary medicine, tolerances for oxytetracycline residues in animals have been established by FDA under 21 CFR 520, 522, 524, and 558.

The nature of the residue in plants was addressed in the 1988 Registration Standard; due to the widespread use of oxytetracycline as a drug, and to the low residue levels expected in or on pears and peaches, no metabolism data are required for plants. Also, since there are no animal feed items involved for pears and peaches, no animal metabolism studies are required. Adequate analytical methods and residue and storage stability data are available to support the tolerances on peaches and pears.

C. Environmental Assessment

1. Environmental Fate

All environmental fate requirements are waived. All data requirements were waived by the Agency based on the limited use pattern and the information found in a literature search. References in the literature indicate that oxytetracycline was adsorbed and inactivated by clays, but the adsorption was not commensurate with inactivation. The degree of adsorption and inactivation can depend upon the specific clay and mineralogy and quantity in the soil. Different types of soil have different bonding capacities to oxytetracycline. A study concluded that oxytetracycline has a higher bonding capacity to clayish soil and sandy clayish soil than if it were sandy soil (c. 100 fold), as demonstrated by the oxytetracycline resistance of soil bacillus species. Assuming that the solubility of oxytetracycline exceeds 100 ppm, 5% runoff would be used in calculating the estimated environmental concentration.

2. Ecological Effects

a. Effects on Birds

An avian acute oral toxicity test on the bobwhite quail (Colinus virginianus) revealed that calcium oxytetracycline has an LD_{50} > 2000 mg ai/kg and is practically non-toxic. In dietary studies performed on the bobwhite quail (Colinus virginianus) and the mallard duck (Anas platyrhynchos), calcium oxytetracycline was found to be practically non-toxic with LC_{50} > 5620 ppm ai.

b. Effects on Fish

Freshwater fish toxicity tests revealed that hydroxytetracycline monohydrochloride has an LC_{50} value > 116 ppm for the rainbow trout (Oncorhynchus mykiss) and a LC_{50} value > 95 ppm for the bluegill sunfish (Lepomis macrochirus). These LC_{50} values are classified as practically non-toxic.

Currently in Europe, furunculosis, a major disease of salmonid fish caused by Aeromonas salmonicida, is treated with the use of oxytetracycline.

c. Effects on Aquatic Invertebrates

A 48-hour Daphnia magna toxicity test showed a 48-hour EC_{50} of > 102 ppm and this classifies hydroxytetracycline monohydrochloride as practically non-toxic to Daphnia magna.

d. Effects on Non-target Insects

An acute contact honey bee study showed that the LD_{50} for worker honeybees exposed to calcium oxytetracycline is greater than 100 µg per bee and therefore practically non-toxic.

Because oxytetracycline also is used as an antibiotic drug used in humans to treat infectious diseases caused by a variety of microorganisms, there is a body of toxicological data on the chemical. The review of these data indicates that oxytetracycline does not meet the Agency's toxicity criteria that would trigger the requirement for occupational and residential exposure monitoring data. However, oxytetracycline has produced various allergic reactions in some patients, and there is a potential for the development of oxytetracycline-resistance from exposure. Because the Agency is concerned about allergic reactions to workers and possible development of oxytetracycline resistance from exposure, the Agency has decided to require label statements to lessen some of these risks.

3. Human Health Risk Assessment

The Agency is aware of data showing a relationship between the use of oxytetracycline and development of oxytetracycline-resistant microflora in the canine intestine. Although there is limited evidence in humans, the estimated NOEL for this toxicological effect, 0.033 mg/kg /day, is well above the estimated TMRCs for all U.S. population subgroups.

The potential roles that oxytetracycline residues and/or oxytetracycline-resistant microorganisms already present in ingested food may play in a putative development of an oxytetracycline-resistant microflora in mammalian intestines have yet to be experimentally determined.

The chronic dietary exposure analysis used the assumption of tolerance-level residues and 100% crop treatment values to estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. The TMRC for the overall population based on registered and pending uses of oxytetracycline is 0.000268 mg/kg/day, which represents 5.35% of the RfD. The most highly exposed subgroup (Non-Nursing infants less than 1 year old) has a TMRC of 0.001391 mg/kg/day, or 27.81% of the RfD. Because of the assumptions of tolerance-level residues and 100% crop treatment, it is likely that these values overestimate the exposure and risk. Even then, the chronic dietary risk posed by all food uses of oxytetracycline are well below the level at which the Agency would have concern.

Workers may be exposed to oxytetracycline during use and/or in the post-application period. There is a potential for an allergic response from individuals that are oxytetracycline sensitive. Specific label requirements limiting inhalation exposure would mitigate this potential risk. These label requirements would address concerns for the potential development of oxytetracycline resistant microorganisms in the respiratory tract.

The Agency made its reregistration eligibility determination based upon the target data base required for reregistration, the current guidelines for conducting acceptable studies to generate such data and the data identified in Appendix B. Although the Agency has found that all uses of hydroxytetracycline monohydrochloride and oxytetracycline calcium are eligible for reregistration, it should be understood that the Agency may take appropriate regulatory action, and/or require the submission of additional data to support the registration of products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium, if new information comes to the Agency's attention or if the data requirements for reregistration (or the guidelines for generating such data) change.

1. Eligibility Decision

Based on the reviews of the generic data for the active ingredients hydroxytetracycline monohydrochloride and oxytetracycline calcium, the Agency has sufficient information on the health effects of hydroxytetracycline monohydrochloride and oxytetracycline calcium and on its potential for causing adverse effects in fish and wildlife and the environment. Therefore, the Agency concludes that products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium for all uses (pears, peaches, nectarines, pritchardia and coconut palms and antifoulant uses) are eligible for reregistration. The Agency furthermore, has determined that some product chemistry information will only be necessary to complete the data bases. Reregistration of all products will proceed after these data are generated because end-use products cannot be reregistered until the Agency has received and reviewed the product chemistry for the technical or MPs.

The Agency has determined that hydroxytetracycline monohydrochloride and oxytetracycline calcium products, labeled and used as specified in this Reregistration Eligibility Document, will not pose unreasonable risks or adverse effects to humans or the environment.

B. Regulatory Position

The following is a summary of the regulatory positions and rationales for hydroxytetracycline monohydrochloride and calcium oxytetracycline. Where labeling revisions are imposed, specific language is set forth in Section V of this document.

1. Tolerance Reassessment

Existing tolerances of 0.35 and 0.1 ppm are currently established for the bactericide/fungicide oxytetracycline in or on pears and peaches, respectively, from foliar treatments or injection [40 CFR §180.337]. The 1988 Registration Standard concluded that the Agency had adequate data to support registered uses on pears and peaches (including nectarines). However, the

3. Ecological Effects Risk Assessment

The Agency has sufficient data to perform an ecological hazard assessment based on current use rates and patterns. In laboratory studies, calcium oxytetracycline has demonstrated low toxicity to birds and hydroxytetracycline monohydrochloride has demonstrated low toxicity to fish. Of the tested species, the bluegill sunfish (Lepomis macrochirus) was the most sensitive with a LC_{50} > 95 ppm.

In a worse case scenario, using the highest aerial application rate and assuming a 5% runoff to a 1-acre, 6 inch-deep pond, the estimated environmental concentration would be 0.31 ppm in shallow water. The amount of hydroxytetracycline monohydrochloride used in tree injection formulations and aquatic paints is nominal in comparison to aerial applications and therefore, these uses are not expected to cause exposure concerns. Due to the low toxicity of both pesticides (hydroxytetracycline monohydrochloride and oxytetracycline calcium) and their low estimated environmental concentration, it is unlikely that either pesticide would be available in amounts toxic to avian or aquatic organisms or honey bees.

IV. RISK MANAGEMENT AND REREGISTRATION DECISION

A. Determination of Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether products containing the active ingredients are eligible for reregistration. The Agency has previously identified and required the submission of the generic (i.e. active ingredient specific) data required to support reregistration of products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium as active ingredients. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of hydroxytetracycline monohydrochloride and oxytetracycline calcium, and lists the submitted studies that the Agency found acceptable.

The data identified in Appendix B were sufficient to allow the Agency to assess the registered uses of hydroxytetracycline monohydrochloride and calcium oxytetracycline and to determine that hydroxytetracycline monohydrochloride and calcium oxytetracycline can be used without resulting in unreasonable adverse effects to man and the environment. The Agency therefore finds that all products containing hydroxytetracycline monohydrochloride and calcium oxytetracycline as the active ingredients are eligible for reregistration. The reregistration of particular products is addressed in Section V of this document.

to meet the requirements of 40 CFR 156.10, this RED, and other current policies.

B. End-Use Products

1. Additional Product-Specific Data Requirements

Section 4(g)(2)B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The product specific data requirements are listed in Appendix G, the Product Specific Data Call-In Notice.

Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria (Appendix F; Attachment E) and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

2. Labeling Requirements for End-Use Products

The labels and labeling of all products must comply with EPA's current regulations and requirements as specified in 40 CFR §156.10. Please follow the instructions in the Pesticide Reregistration Handbook with respect to labels and labeling.

The Agency has determined that the current label precautions are still applicable and are required for product reregistration.

The Agency will issue in the near future a Pesticide Regulation Notice providing instructions on changing labels of agricultural products in keeping with the Worker Protection Standard. Products for agricultural use as a foliar application must comply with all requirements of the Worker Protection Standard as of April 21, 1994.

The following additional (or revised) label statements are required in the human hazards section:

A. The labels of products registered for use on agricultural crops by foliar application methods must include the following restricted entry statement: "Entry into treated orchards (or "areas") is prohibited for 12 hours following application."

B. The labels of products registered for use on agricultural crops by foliar application must include the following protective clothing statement: "Prolonged or frequently repeated exposure may cause allergic reactions in some individuals. Do not breathe dust or spray mist. Wear a MSHA/NIOSH approved TC-21C dust/mist filtering respirator, long sleeved shirt, pants, shoes, and chemical-resistant gloves while handling or applying this product. Wash thoroughly after handling or applying."

Agency has concluded that the available data indicate that the tolerance for peaches should be raised from 0.1 to 0.35 ppm.

There are no proposed or established CODEX (international), Canadian or Mexican tolerances for oxytetracycline. Therefore, there are no harmonization issues to be resolved. Furthermore, because oxytetracycline also is used in veterinary medicine, tolerances for oxytetracycline residues have been established by FDA.

2. Labeling Rationale

Because oxytetracycline can produce various adverse effects (previously described) on human patients and because foliar application can be expected to result in exposure to both mixer/loader/applicators and fieldworkers (post application), the Agency is requiring label statements restricting the reentry into treated fields. It also is specifying the use of certain protective clothing and equipment (PPE) while handling and applying end-use products for use on agricultural crops and ornamentals. The specific label language is in Section V, Labeling Requirements.

V. ACTIONS REQUIRED BY REGISTRANTS

This section specifies the data requirements and responses necessary for the reregistration of both manufacturing-use and end-use products.

A. Manufacturing-Use Products

1. Additional Generic Data Requirements

The generic data base supporting the reregistration of hydroxytetracycline monohydrochloride and oxytetracycline calcium products for the above eligible uses has been reviewed and determined to be substantially complete. However, some of the product chemistry guidelines have not been completely fulfilled.

All of the product chemistry data for both pesticides were originally required in the Registration Standard and are therefore not included in a generic Data Call-In for the RED. Further, registrants are reminded that any changes, since the Registration Standard was issued in 1988, in the manufacturing process for the technical grade of hydroxytetracycline monohydrochloride and/or oxytetracycline calcium, and any detection of new impurities since that time, must be reported to the Agency.

There are no new generic data being called-in for either hydroxytetracycline monohydrochloride or oxytetracycline calcium.

2. Labeling Requirements for Manufacturing-Use Products

No technical or manufacturing-use products currently are registered. However, if any are registered, they will be required

APPENDIX A

Table of Use Patterns
Subject to Reregistration

APPENDIX A for Hydroxytetracycline Monohydrochloride - Case number 655 Chemical number 6308

	USE GROUP	SITE	Application timing	Form	Application type and Application Equipment	Minimum Application Rate (ppm refers to Oxytetracycline Base content)	Maximum Application Rate	Max. # Appl.	Max. # Appl. @ Max. Rate	Min. Interval Between Appl. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations		Use Limitations
												Allowed	Disallowed	
USES ELIGIBLE FOR REREG														
FOOD/ FEED USES														
	A	Pear	After harvest but before leaf fall	Soluble concentrate/ solid	Tree injection equipment	100 ppm	100 ppm	1 per year	1 per year	1 per year	NA	West coast states only	N/A	West coast states only

The following table shows the eligible uses of hydroxytetracycline monohydrochloride and oxytetracycline calcium. It does not show any changes resulting from the RED review itself. Changes that result from the RED review, e.g. PHI, application rates, etc. are specified in Section IV.

APPENDIX A for Oxytetracycline Calcium - Case number 655 Chemical number 6321

	USE GROUP	SITE	Application timing	Form	Application type and Application Equipment	Minimum Application Rate	Maximum Application Rate	Max. # Appl.	Max. # Appl. @ Max. Rate	Min. Interval Between Appl. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations: Allowed	Geographic Limitations: Disallowed	Use Limitations
USES ELIGIBLE FOR REREG														
FOOD/ FEED USES														
	A	Nectarine	Applications begin at shuck split and continue on a weekly basis	Wettable powder	Foliar spray by either airblast or pressure sprayer equipment	0.05 lb ai/ac in 240 gallons/ac	0.05 lb ai/ac in 240 gallons/ac	9	9	7	N/A	N/A	N/A	Do not apply through any type of irrigation system. 21 day preharvest interval.
	A	Peach	Applications begin at shuck split and continue on a weekly basis	Wettable powder	Foliar spray by either airblast or pressure sprayer equipment	0.05 lb ai/ac in 240 gallons/ac	0.05 lb ai/ac in 240 gallons/ac	9	9	7	N/A	N/A	N/A	Do not apply through any type of irrigation system. 21 day preharvest interval.
	A	Pear	Applications begin at 10 percent bloom and continue through the growing season.	Wettable powder	Foliar spray (aircraft equipment in CA and WA; ground equipment in WA)	0.085 lb ai/ac in 20 gallons/ac in CA; 0.085 lb ai/ac in 3-100 gallons in WA	0.17 lb ai/ac in 100 gallons/ac (0.17 lb ai/ac in 20 gallons/ac in CA)	10	10	4	N/A	CA and WA are identified	N/A	Do not apply through any type of irrigation system. 60 day preharvest interval.

APPENDIX A for Hydroxytetracycline Monohydrochloride - Case number 655 Chemical number 6308

	USE GROUP	SITE	Application timing	Form	Application type and Application Equipment	Minimum Application Rate (Upon refers to Oxytetracycline free content)	Maximum Application Rate	Max. # Appls.	Max. # Appls. @ Max. Rate	Min. Interval Between Appls. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations: Allowed	Geographic Limitations: Disallowed	Use Limitations
	C+K	Pritchardia palm	Applications begin at first sign of disease and are repeated at 3 month intervals	Soluble concentrate/ solid	Tree injection equipment	0.035 oz ai in 0.5 to 16 oz water/ tree	0.11 oz ai in 0.5 to 16 oz water/ tree	4	4	90 days	N/A	N/A	N/A	Do not make up more solution at one time than can be used in one day.
NONFOOD/ NONFEED USES														
	F	Paints, latex/oil/ varnish (applied film). Applied in paints to boats.	Applied to paints prior to application	Soluble concentrate/ solid	Used as a paint additive. Equipment not on label	0.0706 oz ai/gal	0.0706 oz ai/gal	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	M	Paints, latex/oil/ varnish (applied film)	Applied to paints prior to application	Soluble concentrate/ solid	Used as a paint additive. Equipment not on label	0.0706 oz ai/gal	0.0706 oz ai/gal	N/A	N/A	N/A	N/A	N/A	N/A	N/A

INELIGIBLE USES = **NONE**

KEY FOR "USE GROUP" COLUMN

- A = Terrestrial Food
- C = Terrestrial Non-food
- F = Aquatic Non-food Industrial
- K = Residential Outdoor
- M = Indoor Non-food

APPENDIX A for Hydroxytetracycline Monohydrochloride - Case number 655 Chemical number 6308

	USE GROUP	SITE	Application timing	Form	Application type and Application Equipment	Minimum Application Rate (ppm refers to Oxytetracycline free content)	Maximum Application Rate	Max. # Appl.	Max. # Appl. @ Max. Rate	Min. Interval Between Appl. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations: Allowed	Geographic Limitations: Disallowed	Use Limitations
	C+K	Coconut palm	Preventive: after initial application, repeat at 4 month intervals. Curative: pre-yellowing phase - apply at nutfall or browning of young flower stalks. Repeat at 4 month intervals. If after 90 days, yellowing of fronds continues, a second application is suggested. Early yellowing phase - begin applications when 5 yellow fronds or less are apparent. Repeat applications at four month intervals.	Soluble concentrate/ solid	Tree injection equipment	0.035 oz ai in 0.5 to 16 oz water/ tree	0.22 oz ai in 2 to 16 oz water/ tree	4	4	90 days	N/A	N/A	N/A	Do not make up more solution at one time than can be used in one day.

APPENDIX B

Table of the Generic Data Requirements and Studies Used to Make the Reregistration Decision

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
PRODUCT CHEMISTRY			
61-2	Start. Mat. & Mnfg. Process	All	41602201 - DATA GAP
61-3	Formation of Impurities	All	41602001 - DATA GAP
62-1	Preliminary Analysis	All	41602001 - DATA GAP
63-2	Color	All	41602001
63-3	Physical State	All	41602001
63-4	Odor	All	41602001
63-5	Melting Point	All	41602001
63-7	Density	All	41602001 - DATA GAP
63-8	Solubility	All	41602001 - DATA GAP
63-9	Vapor Pressure	All	41602001 - DATA GAP
63-10	Dissociation Constant	All	41602001 - DATA GAP
63-11	Octanol/Water Partition	All	41602001 - DATA GAP
63-12	pH	All	41602001
63-13	Stability	All	41602001 - DATA GAP

GUIDE TO APPENDIX B

Appendix B contains listings of data requirements which support the reregistration for the pesticide hydroxytetracycline monohydrochloride and oxytetracycline calcium covered by this Reregistration Eligibility Document. It contains generic data requirements that apply to hydroxytetracycline monohydrochloride and oxytetracycline calcium in all products, including data requirements for which a "typical formulation" is the test substance.

The data table is organized in the following format:

1. Data Requirement (Column 1). The data requirements are listed in the order in which they appear in 40 CFR, Part 158. The reference numbers accompanying each test refer to the test protocols set in the Pesticide Assessment Guidelines, which are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161 (703) 487 - 4650.

2. Use Pattern (Column 2). This column indicates the use patterns for which the data requirements apply. The following letter designations are used for the given use patterns:

   A Terrestrial food
   B Terrestrial feed
   C Terrestrial non-food
   D Aquatic food
   E Aquatic non-food outdoor
   F Aquatic non-food industrial
   G Aquatic non-food residential
   H Greenhouse food
   I Greenhouse non-food
   J Forestry
   K Residential
   L Indoor food
   M Indoor non-food
   N Indoor medical
   O Indoor residential

3. Bibliographic citation (Column 3). If the Agency has acceptable data in its files, this column lists the identifying number of each study. This normally is the Master Record Identification (MRID) number, but may be a "GS" number if no MRID number has been assigned. Refer to the Bibliography appendix for a complete citation of the study.

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
RESIDUE CHEMISTRY			
	Nature of the Residue (Metabolism)		
171-4(c)	Residue Analytical Methods	A	00058254
171-4(3)	Storage Stability Data	A	00081151
171-4(k)	Magnitude of the Residue in Plants		
	Pome Fruits		
	- Pears	A	00039917, 00049096, 00081266, 00162260
	Stone Fruits		
	- Peaches (includes peaches and nectarines)	A	00064602, 00081153, 00096305, 00135300

APPENDIX B

Generic Data Requirements for Reregistration of Oxytetracycline Calcium and Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
PRODUCT CHEMISTRY			
61-2	Start. Mat. & Mnfg. Process	All	41602001 - DATA GAP
61-3	Formation of Impurities	All	41602001 - DATA GAP
62-1	Preliminary Analysis	All	41602001 - DATA GAP
63-2	Color	All	41602001
63-3	Physical State	All	41602001
63-4	Odor	All	41602001
63-5	Melting Point	All	41602001 - DATA GAP
63-7	Density	All	41602001 - DATA GAP
63-8	Solubility	All	41602001 - DATA GAP
63-9	Vapor Pressure	All	41602001 - DATA GAP
63-10	Dissociation Constant	All	41602001 - DATA GAP
63-11	Octanol/Water Partition	All	41602001 - DATA GAP
63-12	pH	All	41602001
63-13	Stability	All	41602001 - DATA GAP

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
TOXICOLOGY			
* NOTE:	Certain toxicological data requirements were waived based on existing animal and human data. Toxicological references are listed in the Bibliography (Appendix C).		
81-1	Acute Oral Toxicity - Rat	All	*
81-2	Acute Dermal Toxicity - Rabbit/Rat	All	*
81-3	Acute Inhalation Toxicity - Rat	All	*
82-1A	90-Day Feeding - Rodent	All	*
82-1B	90-Day Feeding - Non-rodent	All	*
82-2	21-Day Dermal - Rabbit/Rat	All	*
83-1(a)	Chronic Feeding Toxicity - Rodent	All	* and 00132394
83-1(b)	Chronic Feeding Toxicity - Non-Rodent	All	* and 00132394, 00132395
83-2(a)	Oncogenicity - Rat	All	00159856
83-2(b)	Oncogenicity - Mouse	All	00159856
83-3(a)	Developmental Toxicity - Rat	All	00132391
83-3(b)	Developmental Toxicity - Mouse	All	00132392
83-4	2-Generation Reproduction - Rat	All	*

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
ECOLOGICAL EFFECTS			
71-1A	Acute Avian Oral - Quail/Duck	ACFK	41777801
71-2A	Avian Dietary (LC_{50}) - Quail	ACFK	41777802
71-2B	Avian Dietary (LC_{50}) - Duck	ACFK	41777803
72-1A	Fish Acute (LC_{50}) - Bluegill	ACFK	41783201
72-1C	Fish Acute (LC_{50}) - Trout	ACFK	41783202
72-2A	Aquatic Invertebrate (EC_{50})	ACFK	41783203
141-1	Honey Bee Acute Contact	ACJF	41777804

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
ENVIRONMENTAL FATE			
* NOTE:	Environmental Fate Requirements were waived based on the limited use pattern and the information found in a literature search. References are found in the Bibliography (Appendix C).		
161-1	Hydrolysis	ACFK	*
161-2	Photodegradation - Water	ACFK	*
161-3	Photodegradation - Soil	ACFK	*
162-1	Aerobic Soil Metabolism	ACFK	*
162-2	Anaerobic Soil Metabolism	ACFK	*
163-1	Leaching/Adsorp/Desorption	ACFK	*
165-4	Bioaccumulation in Fish	ACFK	*

APPENDIX B

Generic Data Requirements for Reregistration of Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Data Citations Supporting Reregistration

Guideline Citation	Title of Study	Use Patterns	Bibliographic Citation
84-2(a)	Gene Mutation (Ames Test)	All	*
84-2(b)	Structural Chromosomal Aberration	All	*
84-4	Other Genotoxic Effects	All	*
85-1	General Metabolism	All	
	Antibiotic Resistance	All	40840101

APPENDIX C

BIBLIOGRAPHY

Citations Considered to be Part of the Data Base Supporting Reregistration

b. **Document Date.** The date of the study is taken directly from the document. When the date is followed by a question mark, the bibliographer has deduced the date from the evidence contained in the document. When the date appears as (19??), the Agency was unable to determine or estimate the date of the document.

c. **Title.** In some cases, it has been necessary for the Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. **Trailing Parentheses.** For studies submitted to the Agency in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

(1) Submission Date. The date of the earliest known submission appears immediately following the word "received".

(2) Administrative Number. The next element immediately following the word "under" is the registration number, experimental use permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter. When authorship is de-faulted to the submitter, this element is omitted.

(4) Volume Identification (Accession Numbers). The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol "CDL", which stands for "Company Data Library". This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume.

GUIDE TO APPENDIX C

1. **CONTENTS OF BIBLIOGRAPHY.** This bibliography contains citations of all studies considered relevant by EPA in arriving at the positions and conclusions stated elsewhere in the Reregistration Eligibility Document. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions. Selections from other sources including published literature, in those instances where they have been considered, are included.

2. **UNITS OF ENTRY.** The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review and can be described with a conventional bibliographic citation. The Agency has also attempted to unite basic documents and commentaries upon them, treating them as a single study.

3. **IDENTIFICATION OF ENTRIES.** The entries in this bibliography are sorted numerically by Master Record Identifier, or "MRID Number". This number is unique to the citation, and should be uses whenever a specific reference is required. It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted studies (see paragraph 4(d)(4) below for further explanation). In a few cases, entries added to the bibliography late in the review may be preceded by a nine character temporary identifying number is also to be used whenever specific reference is needed.

4. **FORM OF ENTRY.** In addition to the Master Record Identifier (MRID), each entry consists of a citation containing standard elements followed, in the case of material submitted to EPA, by a description of the earliest known submission. Bibliographic conventions used reflect the standard of the American National Standards Institute (ANSI), expanded to provide for certain special needs.

   a. **Author.** Whenever the author could confidently be identified, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown a identifiable laboratory or testing facility as the author. When no author or laboratory could be identified, the Agency has shown the first submitter as the author.

MRID	Citation
00132392	Wolkowski-Tyl, R.; Jones-Price, C.; Ledoux, T.; et al. (1982) Teratologic Evaluation of Oxytetracyline Hydrochloride(CAS 2058-46-0) in CD-1 mice: By RTP and NCI for Toxicological Research, Perinatal and Postnatal Evaluation Branch. Jefferson, AK: NCTR. (Contract No. 222-80-2031 (C); study code no. Mi81-OX; available from NTIS, Springfield, VA 22151; also in unpublished submission received October 26, 1983 under 1007-79; submitted by Pfipharmecs Div., Pfizer, Inc., New York, NY; CDL:251603-F)
00132394	Deichmann, W.; Radomski, J.; et al. (1959): The Chronic Toxicity of the Arquad-C Salt of Oxytetracycline and Oxytetracycline Hydrochloride. Final Report. (Unpublished study received 10/26/83 under 1007-79; prepared by University of Miami School of Medicine; submitted by Pfipharmecs Division, Pfizer Inc., New York, N.Y. (CDL:251603-F).
00132395	Deichmann, W.; Bernal E.; et al. (1962): Final Report on Oxytetracycline - Chronic Feeding Studies in Rats and Dogs. (Unpublished study received 10/26/83 under 1007-79; prepared by University of Miami School of Medicine; submitted by Pfipharmecs Division, Pfizer Inc., New York, N.Y.
00135300	Interregional Research Project No. 4 (1977) The Results of Tests on the Amount of Terramycin Remaining in or on Peaches Including Description of the Analytical Method Used. (Compilation; unpublished study received Dec 3, 1976 under 7E1894; CDL:097772-A)
00159856	US Public Health Service (1986) Toxicology and Carcinogenesis Studies of Oxytetracycline Hydrochloride (CAS No. 2058-46-0) in F344/N Rats and B6C3F1 Mice: (Feed Studies): Technical Report Series No. 315:NIH Publication No. 86-2571:: Draft. Unpublished study prepared in cooperation with Physiological Research Laboratories and MidwestResearch Institute and others. 194 p.
00162260	Beutel, J. (1980) Letter sent to V. Carroll dated Nov 3, 1980: :Summary of procedure used to secure the Terramycin residue samples from 12 year old Bartlett pear trees in the University of California orchards at Davis, California, during the 1980 season:. Prepared by Univ. of California, Pomology Dept. 11 p.

BIBLIOGRAPHY

MRID	Citation
00039917	California, Department of Food and Agriculture (1972) Residue Results: [Terramycin. (Unpublished study; CDL:093760-D)
00049096	Pfipharmecs (1973) [Residue Study of Terramycin in Pears]. (Compilation; unpublished study received Mar 25, 1974 under unknown admin. no.; CDL:223547-G)
00058254	Pfizer, Incorporated (19??) Microbiological Agar Diffusion Assay for Oxytetracycline in Fruit Extract: Report No. 0 12.14. Undated method. (Unpublished study received Apr 1, 1975 under 5E1611: submitted by California, Dept. of Food & Agriculture, Sacramento, Calif.; CDL:095168-G)
00064602	Bly, B. (1980) Letter sent to Eugene Wilson dated Aug 27, 1980 [Residues of terramycin in peaches]. (California, Dept. of Food and Agriculture; unpublished study; CDL:243793-A)
00081151	Wood, R. T. (1977) Letter sent to V. J. Carroll dated Sep 13, 1977: Oxytetracycline stability in fresh peach and pear extracts (QCSA 71886). (Unpublished study received on unknown date under 6E1700; prepared by Biological Control Laboratories, submitted by Interregional Research Project No. 4, New Brunswick, N.J.; CDL:097771-A)
00081153	Carroll, V. J. (1975) Determination of Terramycin (Oxytetracycline) Residues in Peaches. Includes undated standard test procedure no. 0 12.4. (Unpublished study received Oct 31, 1975 under 6E1700; prepared by Pfizer, Inc., submitted by Interregional Research Project No. 4, New Brunswick, N.J.; CDL:097771-G)
00081266	Carroll, V. J. (1974) Determination of Terramycin (Oxytetracycline) Residues in Pears. (California, Dept. of Food & Agriculture; unpublished study; CDL:095187-D)
00093605	Chas. Pfizer & Company (1966) [Determination of Terramycin Residues in Peaches]. (Compilation; unpublished study received Mar 20, 1967 under 7G0584; CDL:090748-D)
00132391	Wolkowski-Tyl, R.; Jones-Price, C.; Ledoux, T.; et al. (1983) Teratologic Evaluation of Oxytetracycline Hydrochloride(CAS 2058-46-0) in CD Rats: RTI Project No. 31U-2077. (Unpublished study received Oct 26, 1983 under 1007-79; prepared by Research Triangle Institute, submitted by Pfipharmecs Div., Pfizer, Inc., New York, NY; CDL:251603-A)

MRID Citation

Modern Drug Encyclopedia and Therapeutic Index - A Compendium (1977): Yorke Medical Books. Donelly Publishing Co., New York.

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Oxytetracycline Hydrochloride (CAS No. 2058-46-0) in F344/N Rats and B6C3F1 Mice (Feed studies): NIH Publication No. 87-2571. U.S. DHHS, Public Health Service. January 1987.

P'an, S.; Reilly, J.; Halley, T.; Richard, G.; Pekich, A.; Pallets. (1950) Pharmacology of Terramycin. J. Pharmacol. Exp. Ther. 99: 234-244.

Memo R. B. Perfetti (CBRS) to CCB (10/13/92). Subject: Oxytetracycline - List A Reregistration Case No. 0655., CBRS Input to the Reregistration Eligibility Document (RED). CBRS Nos. 10,575 and 10,583, DP Barcode Nos. D182571 and 182601.

Put, H. M. C. and C. C. Conway. 1974. The limitations of oxytetracycline as a selective agent in media for the enumeration of fungi in soil, feeds and foods in comparison with the electivity obtained by globenicol (chloramphenicol). Arbiv Fur Lebensmittelhygiene 25 (4): 73-83.

Memo P. Perreault (OREB) to CCB (11/92). Subject: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Document for Oxytetracycline.

Physician Desk Reference (1980). Medical Economics Company. pp. 1372-1373.

Sande, M. A. and Mandell, G. L. (1990): Antimicrobial Agents. In Goodman and Gilman The Pharmacological Basis of Therapeutics. Editors Gilman, A., Rall, T. W., Nies, A. S., and Taylor, P. Eight edition. Pergammon Press. pp. 1117-1145.

Shulman, J. A. and Sellers, T. F., Jr. (1971): Chemotherapy of Bacterial Infection VII - Other Important Antibiotics. In Drill's Pharmacology in medicine. Editor J. R. Dipalma. Fourth edition. McGraw-Hill Books Co. Inc., New York. pp. 1729-1754.

Weinstein, L. (1970): The Tetracyclines. In The Pharmacological Basis of Therapeutics. Editors Goodman, L. and Gilman, A. Fourth edition. Macmillan Publishing Company. pp. 1240-1244.

MRID	Citation
40840101	Rollins, L.; Gaines, S.; et al. (1975) Animal Model for Determining the No-Effect Level of Antimicrobial Drug on Drug Resistance in the Loctose-Fermenting Enteric Flora. Antimicrobial Agents and Chemotherapy. p. 661-665.
	Barnes, A. C., C. S. Lewin, T. S. Hastings, and S. G. B. Amyes. 1990. Cross resistance between oxytetracycline and oxolinic acid in Aeromonas salmonicida associated with alterations in outer membrane proteins. FEMS Microbiology Letters 72: 337-340.
	Batchelder, A. R. 1982. Chlortetracycline and oxytetracycline effects on plant growth and development in soil systems. J. Environ. Qual. 11: 675-678.
	Memo J. Bazuin (DRES) to CCB (12/14/92). Subject: Oxytetracycline Dietary Exposure Analysis for Reregistration - Increase in the Tolerance for Peaches and Change in the reference Dose.
	Deichmann, W. B., Bernal, E., Anderson, W. A., et al. (1974). Chronic oral toxicity of oxytetracycline-HCl and tetracycline-HCl in the rat, dog and pig. Industrial Medicine and Surgery 33(11):787-806.
	Deichmann, W. B., (1959) The chronic toxicity of the Arquad C salt of oxytetracycline and oxytetracycline-hydrochloride. (Unpublished final report prepared by the University of Miami, School of Medicine, Coral Gables, FL for Charles Pfizer & Co., Inc. New York, NY, dated June 1, 1959).
	Memo G. Ghali to RD and SRRD (12/09/92). Subject: RfD Report on Oxytetracycline - Expedite Review.
	Memo B. Greear (TB) to SRRD (12/09/92). Subject: Reregistration Eligibility Document on Oxytetracycline (Case No. 0655/Chemical No. 6304) - Expedite Review.
	Grollman, A. and Grollman, E. F. (1970): Pharmacology and Therapeutics. Seventh Edition. Lea and Febiger, Philadelphia, PA.
	Martin, N. and D. Gottlieb. 1952. The production and role of antibiotics in soil. III. Terramycin and aureomycin. Phytopathology 42: 294-296.
	Guidance for the Reregistration of Pesticides Products Containing Oxytetracycline, Oxytetracycline Hydrochloride, and Oxytetracycline Calcium Complex as the Active Ingredient: EPA 540/RS-89-018. December 1988.

MRID	Citation
	World Health Organization (1990): Evaluation on Certain Veterinary Drug Residues in Food. Technical Report Series 799. Geneva, Switzerland.

APPENDIX D

List of Available Related Documents

APPENDIX D

The following is a list of available documents related to hydroxytetracycline monohydrochloride and oxytetracycline calcium. Its purpose is to provide a path to more detailed information if it is required. These accompanying documents are part of the Administrative Record for hydroxytetracycline monohydrochloride and oxytetracycline calcium and are included in the EPA's Office of Pesticide Programs Public Docket.

1. Health and Environmental Effects Science Chapters

2. Detailed Label Usage Information System (LUIS) Report

3. Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium RED Fact Sheet (included in this RED)

4. PR Notice 91-2 (Included in this RED) Pertains to the Label Ingredient Statement

5. Summary of the Residue Data Used in the DRES Analysis and the DRES Analysis Tables

Federal publications on hydroxytetracycline monohydrochloride and oxytetracycline calcium are available and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161.

1. Pesticide Fact Sheet (No. 188) for Oxytetracycline: NTIS Stock No. PB89-139026.

2. Guidance for the Reregistration of Pesticide Products Containing Oxytetracycline, Oxytetracycline Hydrochloride and Oxytetracycline Calcium Complex as the Active Ingredient (The 1988 Registration Standard): NTIS Stock No. PB89-138556.

APPENDIX E

Pesticide Reregistration Handbook

United States Environmental Protection Agency
Office of Pesticide Programs
October 1991

EPA

Pesticide Reregistration Handbook

How to Respond to the Reregistration Eligibility Document (RED)

PRODUCT REREGISTRATION HANDBOOK

TABLE OF CONTENTS

PESTICIDE REREGISTRATION HANDBOOK

HOW TO RESPOND TO THE

REREGISTRATION ELIGIBILITY DOCUMENT (RED)

OFFICE OF PESTICIDE PROGRAMS

ENVIRONMENTAL PROTECTION AGENCY

OCTOBER 1991

If the RED declares that some or all uses of the chemical are eligible for reregistration, affected registrants must first respond within 90 days of receipt to the data call-in portion of the RED. Within 8 months of receiving the RED, registrants must submit or cite any data and labels/labeling required for each product. EPA has until 14 months after the RED is issued (i.e., 6 months after the registrants' 8 month deadline) to review the submission for each product and decide whether to reregister it based on the following criteria:

--whether all of the product specific data and labels/labeling are acceptable,

--whether all of the uses on the label/labeling are eligible,

--whether all of the active ingredients in the product are eligible, and

--if no List 1 toxic inert ingredient is contained in the product (a List 1 inert is permitted only if all data for it have been submitted and EPA determines that the inert does not pose any unreasonable adverse effects in that product).

Products which meet all of these criteria will be reregistered. Products which do not meet all of these criteria, but which have acceptable product specific data and labeling, will be processed as amendments in order to implement label changes required by the RED.

II. INSTRUCTIONS FOR RESPONDING

A. How and When to Respond

This section provides directions for submitting timely and adequate responses necessary to reregister products containing the active ingredient covered by the RED. Registrants must follow these steps exactly to avoid suspension of their products. All products containing the active ingredient in the RED [i.e., manufacturing use products, end use products and special local need (SLN or Section 24c) registrations] are subject to the requirements of the RED. Figure 1 summarizes how and when to respond to the RED. A step-by-step explanation follows.

Step 1. Are Expedited Label Changes Required? In some instances, EPA may conclude that certain changes to product labels/labeling must be implemented rapidly. If the RED requires expedited label/labeling changes, registrants must submit the items below by the deadline specified in the RED. If expedited label changes are not required, go to Step 2.

a. Application for Registration (EPA Form 8570-1). Complete

PESTICIDE REREGISTRATION HANDBOOK

I. INTRODUCTION

A. Purpose and Content of this Handbook

This Handbook provides instructions to registrants on how to respond to the Reregistration Eligibility Document (hereafter referred to as the "RED") and how to reregister products.

Section I is this introduction.

Section II contains step-by-step instructions which must be followed by registrants responding to the RED.

Section III provides additional instructions on the format, content and other aspects of generic data, product specific data and labels/labeling which may be required to be submitted.

Detailed instructions are in the Appendix.

B. The Reregistration Eligibility Document (RED)

Under Section 4 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended in 1988, EPA is required to reregister pesticides that were first registered before November 1, 1984. The RED describes in detail the subject chemical, its uses and its regulatory history; describes EPA's decision concerning the eligibility of the uses of the chemical for reregistration; and explains the scientific and regulatory bases for this decision. EPA's reviews of the data by scientific discipline are available upon request.[1] Appendices to the RED contain: (1) a Data Dall-In Notice which requires submission of generic and product specific data and which gives directions for responding, (2) a listing of existing studies that satisfy generic data requirements and (3) a bibliography of the generic studies EPA has reviewed.

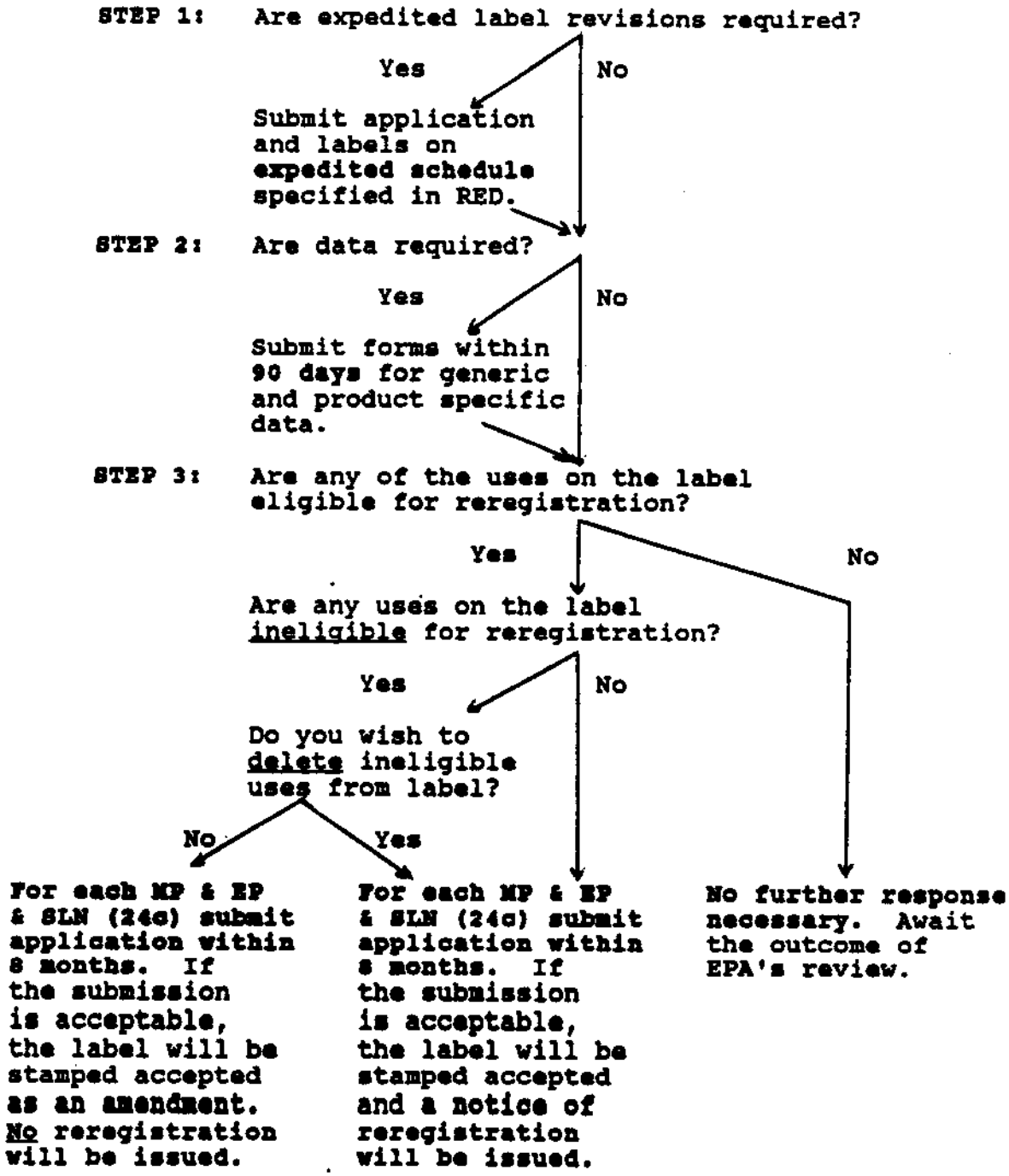
C. The Reregistration Process

Reregistration involves a thorough review of the scientific data base underlying a pesticide's registration. The purpose of EPA's review is to reassess the potential hazards arising from the currently registered uses of the pesticide, to determine whether the data base is substantially complete or there is need for additional generic data, and to determine whether the pesticide is eligible for reregistration. This decision is issued as the RED.

---

[1] EPA's science reviews and information on the registered uses considered for EPA's analyses may be obtained from: EPA, Freedom of Information, 401 M St., S.W., Washington, D.C. 20460.

FIGURE 1. HOW AND WHEN TO RESPOND TO THE REREGISTRATION ELIGIBILITY DOCUMENT (RED) FOR MANUFACTURING USE PRODUCTS (MPs), END-USE PRODUCTS (EPs) and SPECIAL LOCAL NEEDS REGISTRATIONS (SLNs).



and sign the form. In Section II, insert the phrase "**Expedited Amendment in Response to the Reregistration Eligibility Document for (insert case name for chemical).**" Applications for expedited label changes will be processed as applications for amended registration. **Use only an original application form with a red identifier number in the upper right-hand corner.**

b. **Five (5) copies of revised draft label and labeling.** Refer to the RED for label/labeling changes and follow the instructions in Section III.C. and the Appendix of this Handbook for revising the label and labeling for each product.

Step 2. Are data required? If the RED requires generic or product specific data, you must follow the directions in the data call-in notice in the RED. All registrants must respond for all products within 90 days of receipt; products for which an adequate response is not received on time will be subject to suspension. No time extensions will be given for responding within 90 days.

Step 3. Are Uses of a Pesticide Eligible for Reregistration? If any uses of the active ingredient(s) covered by the RED are eligible for reregistration, follow these instructions. If no uses are eligible, no further response may be needed (see page 5).

EPA's decision on the eligibility of each of the uses of the active ingredient(s) is presented in the RED. **If any uses of a chemical are eligible for reregistration, registrants for manufacturing-use products (MPs), end-use products (EPs) and special local needs registrations (SLNs), must submit the items below for each product within 8 months of the date of issuance of the RED:**

a. **Application for Reregistration (use EPA Form 8570-1).** Complete and sign the form. In Section II of that form, check the box "Other" and insert the phrase "**Application for Reregistration.**" **Use only an original application form with a red identifier number in the upper right-hand corner.**

b. **Five (5) copies of revised draft label and labeling.** Refer to the RED for labeling changes specific to the active ingredient, follow the instructions in Section III.C. of this Handbook and refer to the Appendix of this Handbook for guidance on current requirements for labels and labeling. If there are ineligible uses on the label or labeling, you may delete such uses and avoid all requirements and consequences which may be associated with ineligible uses (e.g, generic data requirements, cancellation, suspension, etc.). If you delete certain uses now and those uses become eligible for reregistration later, you must submit an amendment application to add those uses back to the label.

C. Where to Respond

By U.S. Mail:

Document Processing Desk (insert distribution code)
Office of Pesticide Programs (H7504C)
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460-0001

By express mail or by hand delivery:

Document Processing Desk (insert distribution code)
Office of Pesticide Programs (H7504C)
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

These mailing addresses and the following distribution codes must be used to assure the timely receipt and processing of your submissions. Not using them may significantly delay the handling of your submissions:

RED-SRRD-xxx (where xxx is the case code given on the front of the RED)--use this distribution code for all responses pertaining to or containing generic data. Such responses include the 90-day response forms for generic data or hard copies of generic data.

RED-RD-PMxx (where xx is the Product Manager team number)--use this distribution code for all responses pertaining to or containing product specific data or labeling. Such responses would include expedited labeling amendments, 90-day responses to product specific data requirements, hard copies of product specific data and applications for reregistration.

III. SUBMISSION OF DATA AND LABELS/LABELING

This section provides additional instructions concerning responses required for generic data, product specific data and labels/labeling.

A. Generic Data

During EPA's evaluation of an active ingredient for reregistration, additional generic data requirements may be identified that registrants must fulfill. In some instances these data requirements would have to be satisfied before an active ingredient or some of its uses could be declared eligible for reregistration. In other cases, these new data requirements would not affect the eligibility of the active ingredient, but would be necessary to confirm EPA's assessment of that chemical.

c. **Product Specific Data.** You must follow the instructions in the Data Call-In Notice in the RED and in Section III of this Handbook. Responses to the data call in are due within 90 days of receipt of the RED and submission or citation of data is due within 8 months of the issuance of the RED.

d. **Two (2) copies of the current Confidential Statement of Formula (EPA Form 8570-4, revised February 85).** Two completed and signed CSF forms must be submitted for the basic formulation and for each alternate formulation. If CSFs are not provided for the alternate formulas, they will not be reregistered and will no longer be acceptable. The Appendix of this Handbook has specific instructions for completing the CSF form.

e. **Certification With Respect to Citation of Data (EPA Form 8570-31).** This form must be completed, signed and submitted for each product to assure that the data compensation provisions of FIFRA are met.

B. When No Response is Needed

If no uses of a pesticide are eligible for reregistration, it is unlikely that you will be required to submit product specific data or labeling. Uses of an active ingredient may be declared ineligible for reregistration for two possible reasons:

--Available data indicate that one or more of the criteria for an in-depth special review have been met;

--Additional generic data are required.

In the first instance, if the active ingredient is placed into special review, reregistration activities associated with those uses of the chemical are stopped until EPA makes a final determination. At that time, EPA will indicate which uses may be eligible for reregistration and which uses are to be cancelled. If some or all of the previously ineligible uses become eligible for reregistration, EPA will start the reregistration process for products containing only eligible uses.

In the second instance, based upon the review of studies for an active ingredient during reregistration, additional generic data (e.g., second- or third-tier studies) may be needed (see the RED). In such cases, the chemical's uses will not be eligible for reregistration until the additional generic data have been submitted to and reviewed and found acceptable by EPA. If the data are reviewed and found to be acceptable, EPA will indicate which uses will be eligible for reregistration and will initiate reregistration of products containing previously ineligible uses. If the data are not submitted, products containing the active ingredient may be suspended.

--Potentially toxic inerts (List 2) for which only limited data are available, but such data or the chemical structure suggest the potential for toxicity (includes about 60 chemicals).

--Inerts of unknown toxicity (List 3) for which no data or bases for suspecting toxic effects are available (includes up to 2,000 chemicals).

--Inerts of minimal concern (List 4) which are generally regarded as innocuous (includes about 290 chemicals).

When a RED is issued and any uses of an active ingredient are declared eligible for reregistration, all products containing that active ingredient will be subject to reregistration. EPA will, as part of the reregistration review, examine the inert ingredients of each product prior to reregistration to ensure that they do not present unreasonable risks. In reviewing the product chemistry data, EPA will identify List 1 inerts. EPA will continue to encourage registrants to eliminate any List 1 inerts present. Reregistration of products containing only List 2, 3 or 4 inerts will be unaffected by the inerts strategy.

Consistent with the strategy on inerts, a product containing a List 1 inert ingredient will <u>not</u> be reregistered until a full risk assessment of the product has been conducted, based on the data called in for that inert ingredient. However, the existing registration of a product containing a List 1 inert will remain valid as long as the product bears the required label warning and is in compliance with any outstanding DCI, or other activity under the inerts strategy.

Any product containing a List 2, 3 or 4 inert <u>may</u> be reregistered <u>if</u> it meets all other requirements for reregistration. As the inerts strategy is implemented and data for the List 2 and 3 inerts are reviewed, EPA may move these inerts to the other Lists. If an inert were moved to List 1, products containing that inert would become ineligible for reregistration. Inert ingredients must also meet normal registration and tolerance requirements, as applicable.

2. <u>Acute Toxicity</u>

The data call-in notice in the RED specifies the acute toxicity data required for reregistration of each MP or EP. It indicates whether any of the standard tests have been waived and, if so, why.

If feasible, EPA will "batch" products that are similar with respect to their acute toxicity so that one set of tests can support reregistration of each baatch of products. This approach will impose the least amount of testing necessary to adequately support the registration and labeling for pesticide products. The

Any new data requirements and how they affect reregistration eligibility of a chemical are discussed in the RED. If new generic data requirements are imposed in a Data Dall-In Notice in the RED, registrants must respond as described in that Notice. The RED also contains instructions for completing these forms, a citation of EPA's legal authority for requiring the new data, a listing of options available to registrants for satisfying the data requirements and the name of the contact person for inquiries.

B. Product Specific Data

Product specific data may be required for the reregistration of each pesticide product in three areas--product chemistry, acute toxicity and efficacy.

1. Product Chemistry

Following are instructions for submitting product-specific data and a discussion of EPA's policy on inert ingredients.

a. Data

All data requirements for MPs, EPs and SLNs (24c's) are specified in the Data Call-In Notice in the RED. In addition:

--If you cite data from another identical, registered product, you must identify the EPA registration number of that product.

--If the product-specific data submitted or cited do not pertain to an identical formulation to the product submitted for reregistration, then new product-specific data are required to be submitted by the deadline specified in the Data Call-In Notice. The only exception is for products which EPA "groups" together a being similar enough to depend on the same data. Such groupings are discussed in the appendix to the RED (for acute toxicity purposes, for example), if it was feasible to do so.

b. Inert Ingredients

EPA has implemented a strategy for regulating inert ingredients which affects the reregistration of pesticide products. This strategy, issued on April 22, 1987 (52 FR 13305-13309) and updated on November 22, 1989 (54 FR 48314-48316), adopted certain policies designed to reduce the potential for adverse effects from pesticide products containing intentionally added inert ingredients. EPA divided the known inert ingredients into four categories:

--Inerts of toxicological concern (List 1) for which available data demonstrate toxic effects of concern (includes about 50 chemicals).

b. Claims and Products for Which Efficacy Data Generally Are Required

Submission of efficacy data at reregistration typically is required for the following types of products:

1. products claimed to control microorganisms that pose potential threats to public health;

2. products claimed to control vertebrate pests that may directly or indirectly transmit diseases to humans;

3. potentially very hazardous products for which EPA determines that it is necessary to conduct a "risk-benefits" analysis;

4. products of types for which EPA has reasons (e.g., consumer complaints, unlikely claims, unusual use patterns, etc.) to question claims; and

C. Labels and Labeling

To remain in compliance with FIFRA, the label and labeling of each product must be revised to meet the requirements for reregistration as described below. "Labeling" includes the container label and any written, printed or graphic matter that accompanies the pesticide in U.S. commerce at any time (such as technical bulletins, collateral labeling, etc.). Applications for new uses or labeling changes that do not pertain to reregistration must be filed separately from the application for reregistration described in Step 3 earlier. Changes to labeling which must be made for reregistration include, but are not limited to:

1. Labeling changes specified in the RED. Such changes may include statements on RESTRICTED USE, groundwater hazards, protective clothing/equipment, endangered species, environmental hazards, etc.

2. The format and content of labeling as described in 40 CFR 156.10. When further acute testing is needed, the currently accepted precautionary statements will usually be retained until testing is completed and the data are reviewed.

3. Labeling changes required by Pesticide Regulatory (PR) Notices, regulations, regulatory decisions and policies issued by EPA which are relevant to the pesticide. Your product's labeling must reflect any applicable requirements which are in effect at the time the RED is issued. Some existing notices are referred to in Section B. of the Appendix.

main benefits of this approach are to minimize the need for animal testing, reduce the expense to registrants to generate the tests and decrease the resources EPA must spend on reviewing data. Registrants may contact other registrants with products in the same "batch" to decide whether to provide or depend on one set of data; alternatively, registrants may choose to conduct their own studies.

3. Product Performance

Consult the Data Call-In section of the RED to determine whether Product Performance data are required for your product.

Product performance (efficacy) data are generated in studies designed to document how candidate pesticide formulations perform as pest control agents. These data include tests run to determine whether a formulation is lethal to certain pest species, to document the effectiveness of the formulation in controlling pest species in actual use situations, and to determine whether certain claims beyond mere control of a pest (e.g., "six-month residual effect," "kills Warfarin resistant house mice," etc.) are justified.

EPA has standard protocols for certain efficacy tests. In general, standard methods have been developed for tests needed to substantiate claims that have been made frequently for pesticide products. As the scope of potential pesticidal claims is extremely broad, the Agency does not have standard methods for tests needed to substantiate many pesticide claims, especially those that are uncommon. The Product Performance Guidelines, Subdivision G, offer general guidance for developing protocols for efficacy testing. Proposed protocols should be submitted to EPA for review before tests are initiated.

a. Efficacy Data Submission Waiver Policy

FIFRA gives the Administrator of EPA authority "to waive data requirements pertaining to efficacy" but does not require that efficacy data requirements be waived for any class of pesticide product registered under Section 3 of the Act. As a matter of policy, EPA does not require submission of efficacy data to support many types of pesticidal claims but does require submission of such data for certain types of claims. As noted in 40 CFR 158.640, this waiver applies to the submission of efficacy data rather than to the generation of efficacy data. EPA expects each registrant to "ensure through testing that his products are efficacious when used in accordance with commonly accepted pest control practices."

This general policy notwithstanding, EPA may, at any time, require a registrant to submit efficacy data to support any claim made for a product. EPA also may require that certain claims of effectiveness be established before a Section 3 registration is granted.

Confidential Business Information: Does Not Contain National Security Information (E.O. 12065)

Form Approved. OMB No. 2070-0060. Approval expires 9-30-90

EPA

United States Environmental Protection Agency
Office of Pesticide Programs (TS-767)
Washington, DC 20460

Confidential Statement of Formula

A. ☐ Basic Formulation ☐ Alternate Formulation

B. Page of

See Instructions on Back

1. Name and Address of Applicant/Registrant *(Include ZIP Code)*

2. Name and Address of Producer *(Include ZIP Code)*

3. Product Name

4. Registration No./File Symbol

5. EPA Product Mgr/Team No.

6. Country Where Formulated

7. Pounds/Gal or Bulk Density

8. pH

9. Flash Point/Flame Extension

EPA USE ONLY	10. Components in Formulation *(List as actually introduced into the formulation. Give commonly accepted chemical name, trade name, and CAS number.)*	11. Supplier Name & Address	12. EPA Reg. No.	13. Each Component in Formulation a. Amount	b. % by Weight	14. Certified Limits % by Weight a. Upper Limit	b. Lower Limit	15. Purpose in Formulation

16. Typed Name of Approving Official

17. Total Weight 100%

18. Signature of Approving Official

19. Title

20. Phone No *(Include Area Code)*

21. Date

APPENDIX

A. Confidential Statement of Formula and Instructions

B. Instructions for Label Contents

C. Sample Label Formats--General Use & Restricted Use

D. Label Regulations (40 CFR 156.10)

B. INSTRUCTIONS FOR LABEL CONTENTS

40 CFR 156.10 and Pesticide Regulatory (P.R.) Notices require that specific labeling statements appear at certain locations on the label. The sample label formats in Appendix C show where these statements are to be placed.

Item 1. PRODUCT NAME - The name, brand or trademark is required to be located on the front panel, preferably centered in the upper part of the panel. The name of a product will not be accepted if it is false or misleading. [40 CFR 156.10(b)]

Item 2. COMPANY NAME AND ADDRESS - The name and address of the producer, registrant or person for whom the product is produced are required on the label and should be located at the bottom of the front panel or at the end of the label text. [40 CFR 156.10(c)]

Item 3. NET CONTENTS - A net contents statement is required on all labels or on the container of the pesticide. The preferred location is the bottom of the front panel immediately above the company name and address, or at the end of the label text. The net contents must be expressed in the largest suitable unit, e.g., "1 pound 10 ounces" rather than "26 ounces." In addition to English units, net contents may be expressed in metric units. [40 CFR 156.10(d)]

Item 4. EPA REGISTRATION NUMBER - The registration number assigned to the pesticide product must appear on the label, preceded by the phrase "EPA Registration No.," or "EPA Reg. No." The registration number must be set in type of a size and style similar to other print on that part of the label on which it appears and must run parallel to it. The registration number and the required identifying phrase must not appear in such a manner as to suggest or imply recommendation or endorsement of the product by the Agency. [40 CFR 156.10(e)]

Item 5. EPA ESTABLISHMENT NUMBER - The EPA establishment number, preceded by the phrase "EPA Est." is the final establishment at which the product was produced, and may appear in any suitable location on the label or immediate container. It must also appear on the wrapper or outside container of the package if the EPA establishment number on the immediate container cannot be clearly read through such wrapper or container. [40 CFR 156.10(f)]

Item 6A. INGREDIENTS STATEMENT - An ingredients statement is normally required on the front panel. The ingredients statement must contain the name and percentage by weight of each active ingredient and the total percentage by weight of all inert ingredients. The preferred location is immediately below the product name. The ingredients statement must run parallel with, and be clearly distinguished from, other text on the panel. It must not be placed in the body of other text. [40 CFR 156.10(g)]

Item 6B. POUNDS PER GALLON STATEMENT - For liquid agricultural

Instructions for Completing the Confidential Statement of Formula

The Confidential Statement of Formula (CSF) Form 8570-4 must be used. Two legible, signed copies of the form are required. Following are basic instructions:

a. All the blocks on the form must be filled in and answered completely.

b. If any block is not applicable, mark it N/A.

c. The CSF must be signed, dated and the telephone number of the responsible party must be provided.

d. All applicable information which is on the product-specific data submission must also be reported on the CSF.

e. All weights reported under item 7 must be in pounds per gallon for liquids and pounds per cubic feet for solids.

f. Flashpoint must be in degrees Fahrenheit and flame extension in inches.

g. For all active ingredients, the EPA Registration Numbers for the currently registered source products must be reported under column 12.

h. The Chemical Abstracts Service (CAS) Numbers for all actives and inerts and all common names for the trade names must be reported.

i. For the active ingredients, the percent purity of the source products must be reported under column 10 and must be exactly the same as on the source product's label.

j. All the weights in columns 13.a. and 13.b. must be in pounds, kilograms, or grams. In no case will volumes be accepted. Do not mix English and metric system units (i.e., pounds and kilograms).

k. All the items under column 13.b. must total 100 percent.

l. All items under columns 14.a. and 14.b. for the active ingredients must represent pure active form.

m. The upper and lower certified limits for all active and inert ingredients must follow the 40 CFR 158.175 instructions. An explanation must be provided if the proposed limits are different than standard certified limits.

n. When new CSFs are submitted and approved, all previously submitted CSFs become obsolete for that specific formulation.

Item 7C. SKULL & CROSSBONES AND WORD "POISON" - On products assigned a toxicity Category I on the basis of oral, dermal, or inhalation toxicity, the word "Poison" shall appear on the label in red on a background of distinctly contrasting color and the skull and crossbones shall appear in immediate proximity to the word POISON. [40 CFR 156.10(h)(1)(i)].

Item 7D. STATEMENT OF PRACTICAL TREATMENT - A statement of practical treatment (first aid or other) shall appear on the label of pesticide products in toxicity Categories I, II, and III. [40 CFR 156.10(h)(1)(iii)]

Item 7E. REFERRAL STATEMENT - The statement "see Side (or Back) Panel for Additional Precautionary Statements" is required on the front panel for all products, unless all required precautionary statements appear on the front panel. [40 CFR 156.10(h)(1)(iii)].

Item 8. SIDE/BACK PANEL PRECAUTIONARY LABELING - The precautionary statements listed below must appear together on the label under the heading "PRECAUTIONARY STATEMENTS." The preferred location is at the top of the side or back panel preceding the directions for use, and it is preferred that these statements be surrounded by a block outline. Each of the three hazard warning statements must be headed by the appropriate hazard title. [40 CFR 156.10(h)(2)]

Item 8A. HAZARD TO HUMANS AND DOMESTIC ANIMALS - Where a hazard exists to humans or domestic animals, precautionary statements are required indicating the particular hazard, the route(s) of exposure and the precautions to be taken to avoid accident, injury or damage. [40 CFR 156.10(h)(2)(i)]

Item 8B. ENVIRONMENTAL HAZARD - Where a hazard exists to non-target organisms excluding humans and domestic animals, precautionary statements are required stating the nature of the hazard and the appropriate precautions to avoid potential accident, injury, or damage. [40 CFR 156.10(h)(2)(ii)]

Item 8C. PHYSICAL OR CHEMICAL HAZARD - FLAMMABILITY Precautionary statements relating to flammability of a product are required to appear on the label if it meets the criteria in the PHYS/CHEM Labeling Appendix. The requirement is based on the results of the flashpoint determinations and flame extension tests required to be submitted for all products. These statements are to be located in the side/back panel precautionary statements section, preceded by the heading "Physical/Chemical Hazards." Note that no signal word is used in conjunction with the flammability statements.

Item 9A. RESTRICTED USE CLASSIFICATION - FIFRA sec. 3(d) requires that all pesticide formulations/uses be classified for either general or restricted use. Products classified for restricted use may be limited to use by certified applicators or persons under their direct supervision (or may be subject to other restrictions that may be imposed by regulation). If your product has been classified for restricted use, then these requirements apply:

formulations, the pounds per gallon of active ingredient must be indicated on the label. [40 CFR 156.10(h)(iv)]

Item 6C. NAMES TO BE USED IN INGREDIENT STATEMENT - The acceptable common name, if there is one, shall be used, followed by the chemical name. If no common name has been established, the chemical name alone shall be used. Chemicals related to the active ingredient are allowed to be listed only if efficacy data supporting such claims are submitted or referenced. If such data are provided, the related chemicals must be listed separately and not as a portion of the active ingredient.

Item 6D. INERT INGREDIENTS RECLASSIFIED AS ACTIVE INGREDIENTS - If EPA has reclassified chemicals from inert ingredient status to active ingredient status, registrants of affected products must change the ingredient statement accordingly (See 52 FR 13307-8, April 22, 1987). If such pesticides have food uses, tolerances must either be established for such uses, or an exemption from the requirement for tolerances must be obtained.

Item 6E. NOMINAL CONCENTRATION - The amount of active ingredient declared in the ingredient statement must be the nominal concentration of the product as defined in 40 CFR 158.153(i) and described in P.R. Notice 91-2.

Item 7. WARNINGS AND PRECAUTIONARY STATEMENTS - Front panel precautionary statements must be grouped together, preferably within a block outline. The table below shows the minimum type size requirements for various size labels.

Size of Label on Front Panel in Square Inches	Signal Word Minimum Type Size All Capitals	"Keep Out of Reach of Children" Minimum Type Size
5 and under	6 point	6 point
above 5 to 10	10 point	6 point
above 10 to 15	12 point	8 point
above 15 to 30	14 point	10 point
over 30	18 point	12 point

Item 7A. CHILD HAZARD WARNING STATEMENT - The statement "Keep Out of Reach of Children" must be located on the front panel above the signal word except where contact with children during distribution or use is unlikely. [40 CFR 156.10(h)(1)(ii)]

Item 7B. SIGNAL WORD - The signal word (DANGER, WARNING, or CAUTION) is required on the front panel immediately below the child hazard warning statement. [40 CFR 156.10(h)(1)(i)].

accordance with PR Notice 83-2, March 29, 1983.

Item 10B. STORAGE AND DISPOSAL BLOCK - All labels are required to bear storage and disposal statements. These statements are developed for specific containers, sizes, and chemical content. These instructions must be grouped and appear under the heading "Storage and Disposal" in the directions for use. This heading must be set in the same type sizes as required for the child hazard warning. Refer to P.R. Notices 83-3 and 84-1 to determine the storage and disposal instructions appropriate for your products.

Item 10C. DIRECTIONS FOR USE - Directions for use must be stated in terms which can be easily read and understood by the average person likely to use or to supervise the use of the pesticide. When followed, directions must be adequate to protect the public from fraud and from personal injury and to prevent unreasonable adverse effects on the environment. [40 CFR 156.10(i)(2)]

COLLATERAL LABELING .

Bulletins, leaflets, circulars, brochures, data sheets, flyers, or other written or graphic printed matter which is referred to on the label or which is to accompany the product are termed collateral labeling. Such labeling may not bear claims or representations that differ in substance from those accepted in connection with registration of the product. Collateral labeling must be made part of the response to the RED and submitted for review.

1. **All uses restricted.** The following statements must be placed in a black box at the top of the front panel of the label and labeling:

   a. The statement "Restricted Use Pesticide" must appear at the top of the front panel of the label. The statement must be set in type of the same minimum size as required for human hazard signal word [see table in 40 CFR 156.10(h)(1)(iv)]. No statements of any kind may appear above this RUP statement.

   b. The reason for the the restricted use classification must appear below the RUP statement. The RED will prescribe this statement.

   c. A summary statement of the terms of restriction must appear directly below this reason statement on the front panel. If use is restricted to certified applicators, the following statement is required: "For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's Certification." The RED will specify what statement must be used.

2. **Some but not all uses restricted.** If the RED states that some uses are classified for restricted use, and some are unclassified, several courses of action are available:

   a. You may label the product for Restricted use. If you do so, you may include on the label uses that are unrestricted, but you may not distinguish them on the label as being unrestricted.

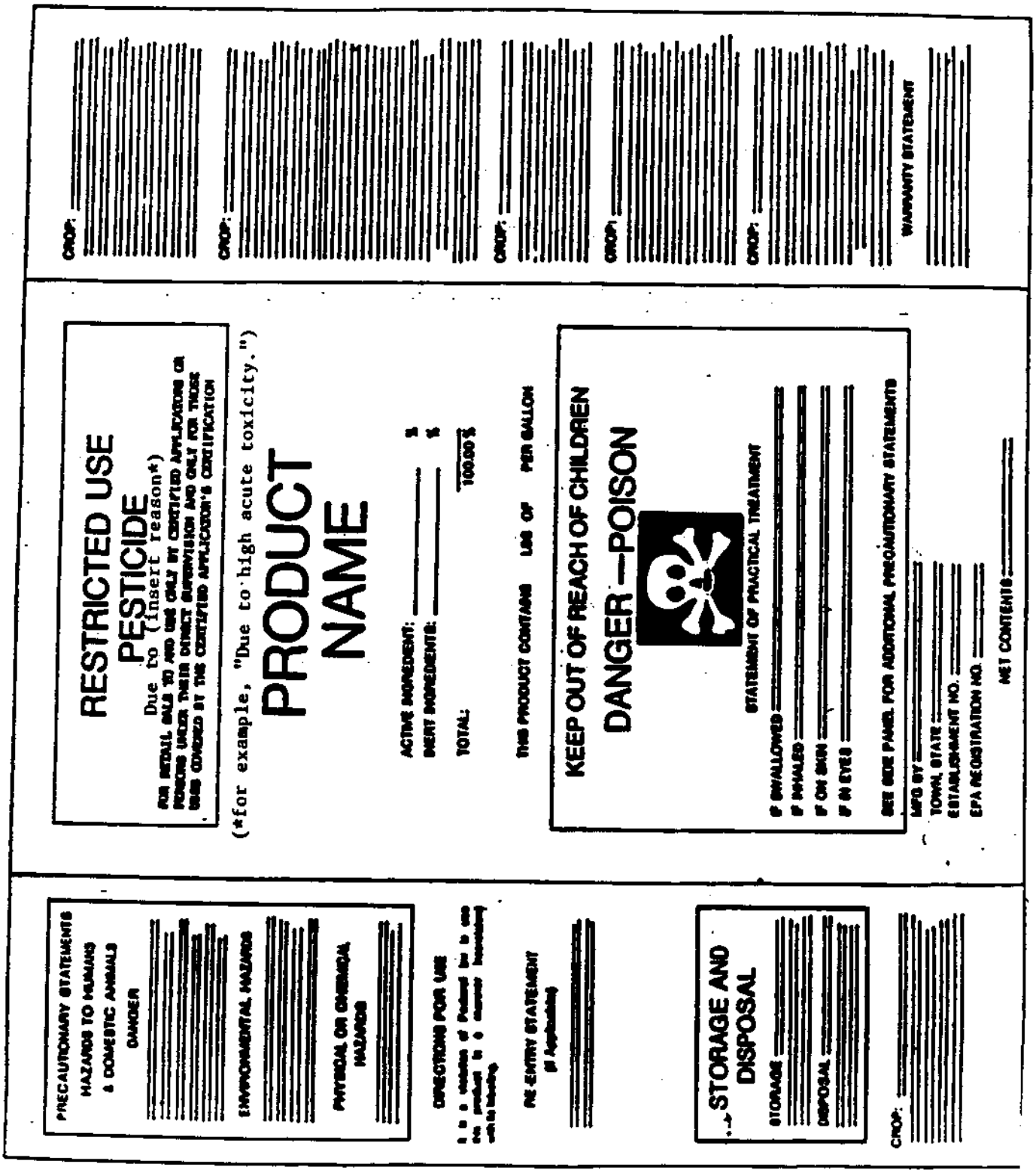
   b. You may delete all restricted uses from your label and submit draft labeling bearing only unrestricted uses.

   c. You may "split" your registration, i.e., register two separate products with identical formulations, one bearing only unrestricted uses, and the other bearing restricted uses. To do so, submit two applications for reregistration, each containing all forms and necessary labels. Both applications should be submitted simultaneously. Note that the products will be assigned separate registration numbers.

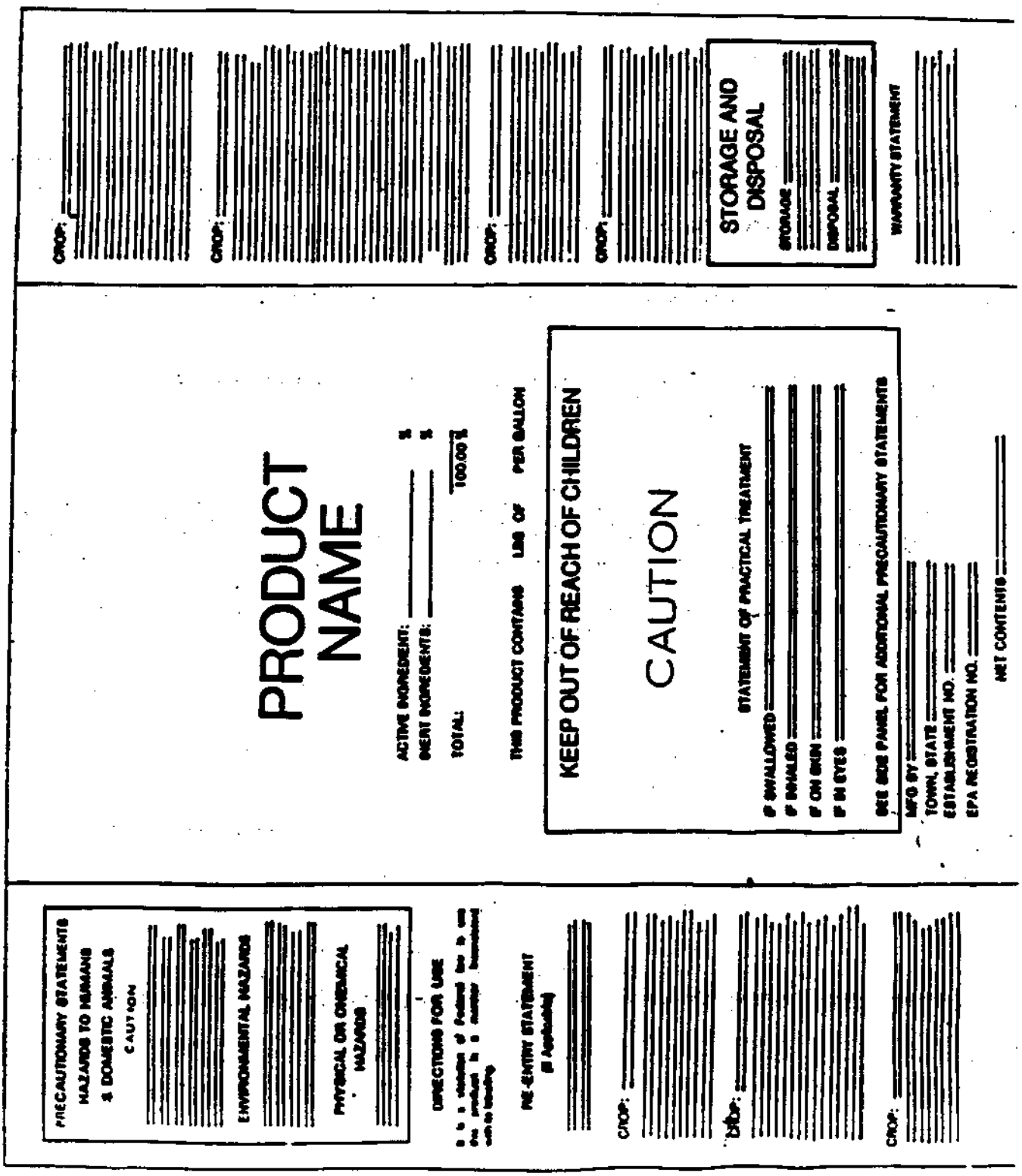
Item 9B. MISUSE STATEMENT - All products must bear the misuse statement, "It is a violation of Federal law to use this product in a manner inconsistent with its labeling." This statement appears at the beginning of the directions for use, directly beneath the heading of that section.

Item 10A. REENTRY STATEMENT - If a restricted entry interval (REI) has been established by the Agency, it must be included on the label. Additional worker protection statements may be required in

LABEL FORMAT FOR PRODUCTS CLASSIFIED FOR RESTRICTED USE



LABEL FORMAT FOR UNCLASSIFIED PRODUCTS



lations in this Part. The contents of a label must show clearly and prominently the following:

(i) The name, brand, or trademark under which the product is sold as prescribed in paragraph (b) of this section;

(ii) The name and address of the producer, registrant, or person for whom produced as prescribed in paragraph (c) of this section;

(iii) The net contents as prescribed in paragraph (d) of this section;

(iv) The product registration number as prescribed in paragraph (e) of this section;

(v) The producing establishment number as prescribed in paragraph (f) of this section;

(vi) An ingredient statement as prescribed in paragraph (g) of this section;

(vii) Warning or precautionary statements as prescribed in paragraph (h) of this section;

(viii) The directions for use as prescribed in paragraph (i) of this section; and

(ix) The use classification(s) as prescribed in paragraph (j) of this section.

(2) *Prominence and legibility.* (i) All words, statements, graphic representations, designs or other information required on the labeling by the Act or the regulations in this part must be clearly legible to a person with normal vision, and must be placed with such conspicuousness (as compared with other words, statements, designs, or graphic matter on the labeling) and expressed in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(ii) All required label text must:

(A) Be set in 6-point or larger type;

(B) Appear on a clear contrasting background; and

(C) Not be obscured or crowded.

(3) *Language to be used.* All required label or labeling text shall appear in the English language. However, the Agency may require or the applicant may propose additional text in other languages as is considered necessary to protect the public. When additional text in another language is necessary, all labeling requirements will be applied equally to both the English and other-language versions of the labeling.

(4) *Placement of Label*—(i) *General.* The label shall appear on or be securely attached to the immediate container of the pesticide product. For purposes of this Section, and the misbranding provisions of the Act, "securely attached" shall mean that a label can reasonably be expected to remain affixed during the foreseeable conditions and period of use. If the immediate container is enclosed within a wrapper or outside container through which the label cannot be clearly read, the label must also be securely attached to such outside wrapper or container, if it is a part of the package as customarily distributed or sold.

(ii) *Tank cars and other bulk containers*—(A) *Transportation.* While a pesticide product is in transit, the appropriate provisions of 49 CFR Parts 170-189, concerning the transportation of hazardous materials, and specifically those provisions concerning the labeling, marking and placarding of hazardous materials and the vehicles carrying them, define the basic Federal requirements. In addition, when any registered pesticide product is transported in a tank car, tank truck or other mobile or portable bulk container, a copy of the accepted label must be attached to the shipping papers, and left with the consignee at the time of delivery.

(B) *Storage.* When pesticide products are stored in bulk containers, whether mobile or stationary, which remain in the custody of the user, a copy of the label of labeling, including all appropriate directions for use, shall be securely attached to the container in the immediate vicinity of the discharge control valve.

(5) *False or misleading statements.* Pursuant to section 2(q)(1)(A) of the Act, a pesticide or a device declared subject to the Act pursuant to § 153.240, is misbranded if its labeling is false or misleading in any particular including both pesticidal and non-pesticidal claims. Examples of statements or representations in the labeling which constitute misbranding include:

(i) A false or misleading statement concerning the composition of the product;

submitter has asserted a confidential business information claim concerning the material).

(5) A copy of each document, proposal, or other item of written material concerning the Registration Standard provided by the Agency to any person or party outside of government (within 15 working days after the item is made available to such person or party).

(6) A copy of the Registration Standard;

(7) With respect to a Registration Standard for which the Agency has determined that a substantially complete chronic health and teratology data base exists, a copy of the FEDERAL REGISTER notice concerning availability of a proposed Registration Standard, and a copy of each comment received in response to that notice (within 10 working days after receipt by the Agency, or 15 working days if the submitter has asserted a confidential business information claim concerning the material).

(8) A copy of the FEDERAL REGISTER notice announcing the issuance of the Registration Standard (within 10 working days after the publication of the notice).

(c) *Index of the docket.* The Agency will establish and keep current an index to the docket for each Registration Standard. The index will include, but is not limited to:

(1) A list of each meeting between the Agency and any person or party outside of government, containing the date and subject of the meeting, the names of participants and the name of the person requesting the meeting.

(2) A list of each document in the docket by title, source or recipient(s), and the date the document was received or provided by the Agency.

(d) *Availability of docket and indices.* (1) The Agency will make available to the public for inspection and copying the docket and index for any Registration Standard.

(2) The Agency will establish and maintain a mailing list of persons who have specifically requested that they receive indices for Registration Standard dockets. On a quarterly basis, EPA will distribute the indices of new materials placed in the public docket to these persons. Annually, EPA will require that persons on the list renew their requests for inclusion on the list.

(3) The Agency will issue annually in the FEDERAL REGISTER (in conjunction with the annual schedule notice specified in § 155.25) a notice announcing the availability of docket indices.

(4) Each FEDERAL REGISTER notice of availability of a Registration Standard will announce the availability of the docket index for that Standard.

§ 155.34 Notice of availability.

(a) The Agency will issue in the FEDERAL REGISTER a notice announcing the issuance and availability of Registration Standard which:

(1) Concerns a previously unregistered active ingredient; or

(2) Concerns a previously registered active ingredient, and the Registration Standard states that registrants will be required (under FIFRA section 3(c)(2)(B)) to submit chronic health (including, but not limited to, chronic feeding, oncogenicity and reproduction) or teratology studies.

(b) Interested persons may submit comments concerning any Registration Standard described by paragraph (a) of this section at any time.

(c) The Agency will issue in the FEDERAL REGISTER a notice announcing the availability of, and providing opportunity for comment on, each proposed Registration Standard which concerns a previously registered active ingredient for which the Agency has determined that a substantially complete chronic health and teratology data base exists. Following the comment period and issuance of the Registration Standard, the Agency will issue in the FEDERAL REGISTER a notice of availability of the Registration Standard.

PART 156—LABELING REQUIREMENTS FOR PESTICIDES AND DEVICES

AUTHORITY: 7 U.S.C. 136-136y.

§ 156.10 Labeling requirements.

(a) *General*—(1) *Contents of the label.* Every pesticide products shall bear a label containing the information specified by the Act and the regu-

tent of the packages in a shipment fall below the stated average content.

(e) *Product registration number.* The registration number assigned to the pesticide product at the time of registration shall appear on the label, preceded by the phrase "EPA Registration No.," or the phrase "EPA Reg. No." The registration number shall be set in type of a size and style similar to other print on that part of the label on which it appears and shall run parallel to it. The registration number and the required identifying phrase shall not appear in such a manner as to suggest or imply recommendation or endorsement of the product by the Agency.

(f) *Producing establishments registration number.* The producing establishment registration number preceded by the phrase "EPA Est.", of the final establishment at which the product was produced may appear in any suitable location on the label or immediate container. It must appear on the wrapper or outside container of the package if the EPA establishment registration number on the immediate container cannot be clearly read through such wrapper or container.

(g) *Ingredient statement*—(1) *General.* The label of each pesticide product must bear a statement which contains the name and percentage by weight of each active ingredient, the total percentage by weight of all inert ingredients; and if the pesticide contains arsenic in any form, a statement of the percentages of total and water-soluble arsenic calculated as elemental arsenic. The active ingredients must be designated by the term "active ingredients" and the inert ingredients by the term "inert ingredients," or the singular forms of these terms when appropriate. Both terms shall be in the same type size, be aligned to the same margin and be equally prominent. The statement "Inert Ingredients, none" is not required for pesticides which contain 100 percent active ingredients. Unless the ingredient statement is a complete analysis of the pesticide, the term "analysis" shall not be used as a heading for the ingredient statement.

(2) *Position of ingredient statement.* (i) The ingredient statement is normally required on the front panel of the label. If there is an outside container or wrapper through which the ingredient statement cannot be clearly read, the ingredient statement must also appear on such outside container or wrapper. If the size or form of the package makes it impracticable to place the ingredient statement on the front panel of the label, permission may be granted for the ingredient statement to appear elsewhere.

(ii) The text of the ingredient statement must run parallel with other text on the panel on which it appears, and must be clearly distinguishable from and must not be placed in the body of other text.

(3) *Names to be used in ingredient statement.* The name used for each ingredient shall be the accepted common name, if there is one, followed by the chemical name. The common name may be used alone only if it is well known. If no common name has been established, the chemical name alone shall be used. In no case will the use of a trademark or proprietary name be permitted unless such name has been accepted as a common name by the Administrator under the authority of section 25(c)(6).

(4) *Statements of percentages.* The percentages of ingredients shall be stated in terms of weight-to-weight. The sum of percentages of the active and the inert ingredients shall be 100. Percentages shall not be expressed by a range of values such as "22-25%." If the uses of the pesticide product are expressed as weight of active ingredient per unit area, a statement of the weight of active ingredient per unit volume of the pesticide formulation shall also appear in the ingredient statement.

(5) *Accuracy of stated percentages.* The percentages given shall be as precise as possible reflecting good manufacturing practice. If there may be unavoidable variation between manufacturing batches, the value stated for each active ingredient shall be the lowest percentage which may be present.

(6) *Deterioration.* Pesticides which change in chemical composition significantly must meet the following labeling requirements:

(ii) A false or misleading statement concerning the effectiveness of the product as a pesticide or device;

(iii) A false or misleading statement about the value of the product for purposes other than as a pesticide or device;

(iv) A false or misleading comparison with other pesticides or devices;

(v) Any statement directly or indirectly implying that the pesticide or device is recommended or endorsed by any agency of the Federal Government;

(vi) The name of a pesticide which contains two or more principal active ingredients if the name suggests one or more but not all such principal active ingredients even though the names of the other ingredients are stated elsewhere in the labeling;

(vii) A true statement used in such a way as to give a false or misleading impression to the purchaser;

(viii) Label disclaimers which negate or detract from labeling statements required under the Act and these regulations;

(ix) Claims as to the safety of the pesticide or its ingredients, including statements such as "safe," "nonpoisonous," "noninjurious," "harmless" or "nontoxic to humans and pets" with or without such a qualifying phrase as "when used as directed"; and

(x) Non-numerical and/or comparative statements on the safety of the product, including but not limited to:

(A) "Contains all natural ingredients";

(B) "Among the least toxic chemicals known"

(C) "Pollution approved"

(6) *Final printed labeling.* (i) Except as provided in paragraph (a)(6)(ii) of this section, final printed labeling must be submitted and accepted prior to registration. However, final printed labeling need not be submitted until draft label texts have been provisionally accepted by the Agency.

(ii) Clearly legible reproductions or photo reductions will be accepted for unusual labels such as those silk-screened directly onto glass or metal containers or large bag or drum labels. Such reproductions must be of microfilm reproduction quality.

(b) *Name, brand, or trademark.* (1) The name, brand, or trademark under which the pesticide product is sold shall appear on the front panel of the label.

(2) No name, brand, or trademark may appear on the label which:

(i) Is false or misleading, or

(ii) Has not been approved by the Administrator through registration or supplemental registration as an additional name pursuant to § 152.132.

(c) Name and address of producer, registrant, or person for whom produced. An unqualified name and address given on the label shall be considered as the name and address of the producer. If the registrant's name appears on the label and the registrant is not the producer, or if the name of the person for whom the pesticide was produced appears on the label, it must be qualified by appropriate wording such as "Packed for * * *," "Distributed by * * *," or "Sold by * * *" to show that the name is not that of the producer.

(d) *Net weight or measure of contents.* (1) The net weight or measure of content shall be exclusive of wrappers or other materials and shall be the average content unless explicitly stated as a minimum quantity.

(2) If the pesticide is a liquid, the net content statement shall be in terms of liquid measure at 68° F (20°C) and shall be expressed in conventional American units of fluid ounces, pints, quarts, and gallons.

(3) If the pesticide is solid or semi-solid, viscous or pressurized, or is a mixture of liquid and solid, the net content statement shall be in terms of weight expressed as avoirdupois pounds and ounces.

(4) In all cases, net content shall be stated in terms of the largest suitable units, i.e., "1 pound 10 ounces" rather than "26 ounces."

(5) In addition to the required units specified, net content may be expressed in metric units.

(6) Variation above minimum content or around an average is permissible only to the extent that it represents deviation unavoidable in good manufacturing practice. Variation below a stated minimum is not permitted. In no case shall the average con-

that it is approved for use on infants or small children, may the Administrator waive this requirement.

(iii) *Statement of practical treatment*—(A) *Toxicity Category I.* A statement of practical treatment (first aid or other) shall appear on the front panel of the label of all pesticides falling into Toxicity Category I on the basis of oral, inhalation or dermal toxicity. The Agency may, however, permit reasonable variations in the placement of the statement of practical treatment is some reference such as "See statement of practical treatment on back panel" appears on the front panel near the word "Poison" and the skull and crossbones.

(B) *Other toxicity categories.* The statement of practical treatment is not required on the front panel except as described in paragraph (h)(1)(iii)(A) of this section. The applicant may, however, include such a front panel statement at his option. Statements of practical treatment are, however, required elsewhere on the label in accord with paragraph (h)(2) of this section if they do not appear on the front panel.

(iv) *Placement and prominence.* All the require front panel warning statements shall be grouped together on the label, and shall appear with sufficient prominence relative to other front panel text and graphic material to make them unlikely to be overlooked under customary conditions of purchase and use. The following table shows the minimum type size requirements for the front panel warning statements on various sizes of labels:

Size of label front panel in square inches	Points	
	Required signal word, all capitals	"Keep out of reach of children"
5 and under	6	8
Above 5 to 10	10	6
Above 10 to 15	12	8
Above 15 to 30	14	10
Over 30	18	12

(2) *Other required warnings and precautionary statements.* The warnings and precautionary statements as required below shall appear together on the label under the general heading "Precautionary Statements" and under appropriate subheadings of "Hazard to Humans and Domestic Animals," "Environmental Hazard" and "Physical or Chemical Hazard."

(i) *Hazard to humans and domestic animals.* (A) Where a hazard exists to humans or domestic animals, precautionary statements are required indicating the particular hazard, the route(s) of exposure and the precautions to be taken to avoid accident, injury or damage. The precautionary paragraph shall be immediately preceded by the appropriate hazard signal word.

(B) The following table depicts typical precautionary statements. These statements must be modified or expanded to reflect specific hazards.

Toxicity category	Precautionary statements by toxicity category	
	Oral, inhalation, or dermal toxicity	Skin and eye local effects
I	Fatal (poisonous) if swallowed [inhaled or absorbed through skin]. Do not breathe vapor [dust or spray mist]. Do not get in eyes, on skin, or on clothing [Front panel statement of practical treatment required.].	Corrosive, causes eye and skin damage [or skin irritation]. Do not get in eyes, on skin, or on clothing. Wear goggles or face shield and rubber gloves when handling. Harmful or fatal if swallowed. [Appropriate first aid statement required.]
II	May be fatal if swallowed [inhaled or absorbed through the skin]. Do not breathe vapors [dust or spray mist]. Do not get in eyes, on skin, or on clothing. [Appropriate first aid statements required.].	Causes eye [and skin] irritation. Do not get in eyes, on skin, or on clothing. Harmful if swallowed. [Appropriate first aid statement required.]
III	Harmful if swallowed [inhaled or absorbed through the skin]. Avoid breathing vapors [dust or spray mist]. Avoid contact with skin [eyes or clothing]. [Appropriate first aid statement required.].	Avoid contact with skin, eyes or clothing. In case of contact immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists.
IV	[No precautionary statements required.]	[No precautionary statements required.]

(i) In cases where it is determined that a pesticide formulation changes chemical composition significantly, the product must bear the following statement in a prominent position on the label: "Not for sale or use after [date]."

(ii) The product must meet all label claims up to the expiration time indicated on the label.

(7) *Inert ingredients.* The Administrator may require the name of any inert ingredient(s) to be listed in the ingredient statement if he determines that such ingredient(s) may pose a hazard to man or the environment.

(h) *Warnings and precautionary statements.* Required warnings and precautionary statements concerning the general areas of toxicological hazard including hazard to children, environmental hazard, and physical or chemical hazard fall into two groups; those required on the front panel of the labeling and those which may appear elsewhere. Specific requirements concerning content, placement, type size, and prominence are given below.

(1) *Required front panel statements.* With the exception of the child hazard warning statement, the text required on the front panel of the label is determined by the Toxicity Category of the pesticide. The category is assigned on the basis of the highest hazard shown by any of the indicators in the table below:

Hazard indicators	Toxicity categories			
	I	II	III	IV
Oral LD_{50}	Up to and including 50 mg/kg.	From 50 thru 500 mg/kg.	From 500 thru 5000 mg/kg.	Greater than 5000 mg/kg.
Inhalation LC_{50}	Up to and including .2 mg/liter.	From .2 thru 2 mg/liter	From 2. thru 20 mg/liter	Greater than 20 mg/liter.
Dermal LD_{50}	Up to and including 200 mg/kg.	From 200 thru 2000	From 2,000 thru 20,000	Greater than 20,000.
Eye effects	Corrosive; corneal opacity not reversible within 7 days.	Corneal opacity reversible within 7 days; irritation persisting for 7 days.	No corneal opacity; irritation reversible within 7 days.	No irritation.
Skin effects	Corrosive	Severe irritation at 72 hours.	Moderate irritation at 72 hours.	Mild or slight irritation at 72 hours.

(i) *Human hazard signal word*—(A) *Toxicity Category I.* All pesticide products meeting the criteria of Toxicity Category I shall bear on the front panel the signal word "Danger." In addition if the product was assigned to Toxicity Category I on the basis of its oral, inhalation or dermal toxicity (as distinct from skin and eye local effects) the word "Poison" shall appear in red on a background of distinctly contrasting color and the skull and crossbones shall appear in immediate proximity to the word "poison."

(B) *Toxicity Category II.* All pesticide products meeting the criteria of Toxicity Category II shall bear on the front panel the signal word "Warning."

(C) *Toxicity Category III.* All pesticide products meeting the criteria of Toxicity Category III shall bear on the front panel the signal word "Caution."

(D) *Toxicity Category IV.* All pesticide products meeting the criteria of Toxicity Category IV shall bear on the front panel the signal word "Caution."

(E) *Use of signal words.* Use of any signal word(s) associated with a higher Toxicity Category is not permitted except when the Agency determines that such labeling is necessary to prevent unreasonable adverse effects on man or the environment. In no case shall more than one human hazard signal word appear on the front panel of a label.

(ii) *Child hazard warning.* Every pesticide product label shall bear on the front panel the statement "keep out of reach of children." Only in cases where the likelihood of contact with children during distribution, marketing, storage or use is demonstrated by the applicant to be extremely remote, or if the nature of the pesticide is such

(B) The label bears a reference to the directions for use in accompanying leaflets or circulars, such as "See directions in the enclosed circular:" and

(C) The Administrator determines that it is not necessary for such directions to appear on the label.

(iii) *Exceptions to requirement for direction for use*—(A) Detailed directions for use may be omitted from labeling of pesticides which are intended for use only by manufacturers of products other than pesticide products in their regular manufacturing processes, provided that:

(*1*) The label clearly shows that the product is intended for use only in manufacturing processes and specifies the type(s) of products involved.

(*2*) Adequate information such as technical data sheets or bulletins, is available to the trade specifying the type of product involved and its proper use in manufacturing processes;

(*3*) The product will not come into the hands of the general public except after incorporation into finished products; and

(*4*) The Administrator determines that such directions are not necessary to prevent unreasonable adverse effects on man or the environment.

(B) Detailed directions for use may be omitted from the labeling of pesticide products for which sale is limited to physicians, veterinarians, or druggists, provided that:

(*1*) The label clearly states that the product is for use only by physicians or veterinarians;

(*2*) The Administrator determines that such directions are not necessary to prevent unreasonable adverse effects on man or the environment; and

(*3*) The product is also a drug and regulated under the provisions of the Federal Food, Drug and Cosmetic Act.

(C) Detailed directions for use may be omitted from the labeling of pesticide products which are intended for use only by formulators in preparing pesticides for sale to the public, provided that:

(*1*) There is information readily available to the formulators on the composition, toxicity, methods of use, applicable restrictions or limitations, and effectiveness of the product for pesticide purposes;

(*2*) The label clearly states that the product is intended for use only in manufacturing, formulating, mixing, or repacking for use as a pesticide and specifies the type(s) of pesticide products involved;

(*3*) The product as finally manufactured, formulated, mixed, or repackaged is registered; and

(*4*) The Administrator determines that such directions are not necessary to prevent unreasonable adverse effects on man or the environment.

(2) *Contents of Directions for Use.* The directions for use shall include the following, under the headings "Directions for Use":

(i) The statement of use classification as prescribed in paragraph (j) of this section immediately under the heading "Directions for Use."

(ii) Immediately below the statement of use classification, the statement "It is a violation of Federal law to use this product in a manner inconsistent with its labeling."

(iii) The site(s) of application, as for example the crops, animals, areas, or objects to be treated.

(iv) The target pest(s) associated with each site.

(v) The dosage rate associated with each site and pest.

(vi) The method of application, including instructions for dilution, if required, and type(s) of application apparatus or equipment required.

(vii) The frequency and timing of applications necessary to obtain effective results without causing unreasonable adverse effects on the environment.

(viii) Specific limitations on reentry to areas where the pesticide has been applied, meeting the requirements concerning reentry provided by 40 CFR Part 170.

(ix) Specific directions concerning the storage and disposal of the pesticide and its container, meeting the requirements of 40 CFR Part 165. These instructions shall be grouped and appear under the heading "Storage and Disposal." This heading must be set in type of the same minimum sizes as required for the child hazard warning. (See Table in § 162.10(h)(1)(iv))

(ii) *Environmental hazards.* Where a hazard exists to non target organisms excluding humans and domestic animals, precautionary statements are required stating the nature of the hazard and the appropriate precautions to avoid potential accident, injury or damage. Examples of the hazard statements and the circumstances under which they are required follow:

(A) If a pesticide intended for outdoor use contains an active ingredient with a mammalian acute oral LD_{50} of 100 or less, the statement "This Pesticide is Toxic to Wildlife" is required.

(B) If a pesticide intended for outdoor use contains an active ingredient with a fish acute LC_{50} of 1 ppm or less, the statement "This Pesticide is Toxic to Fish" is required.

(C) If a pesticide intended for outdoor use contains an active ingredient with an avian acute oral LD_{50} of 100 mg/kg or less, or a subacute dietary LC_{50} of 500 ppm or less, the statement "This Pesticide is Toxic to Wildlife" is required.

(D) If either accident history or field studies demonstrate that use of the pesticide may result in fatality to birds, fish or mammals, the statement "This pesticide is extremely toxic to wildlife (fish)" is required.

(E) For uses involving foliar application to agricultural crops, forests, or shade trees, or for mosquito abatement treatments, pesticides toxic to pollinating insects must bear appropriate label cautions.

(F) For all outdoor uses other than aquatic applications the label must bear the caution "Keep out of lakes, ponds or streams. Do not contaminate water by cleaning of equipment or disposal of wastes."

(iii) *Physical or chemical hazards.* Warning statements on the flammability or explosive characteristics of the pesticide are required as follows:

Flash point	Required text
(A) Pressurized Containers	
Flash point at or below 20° F; if there is a flashback at any valve opening.	Extremely flammable. Contents under pressure. Keep away from fire, sparks, and heated surfaces. Do not puncture or incinerate container. Exposure to temperatures above 130° F may cause bursting.
Flash point above 20° F and not over 80° F or if the flame extension is more than 18 in long at a distance of 6 in from the flame.	Flammable. Contents under pressure. Keep away from heat, sparks, and open flame. Do not puncture or incinerate container. Exposure to temperatures above 130° F may cause bursting.
All other pressurized containers	Contents under pressure. Do not use or store near heat or open flame. Do not puncture or incinerate container. Exposure to temperatures above 130° F may cause bursting.
(B) Nonpressurized Containers	
At or below 20° F	Extremely flammable. Keep away from fire, sparks, and heated surfaces.
Above 20° F and not over 80° F	Flammable. Keep away from heat and open flame.
Above 80° F and not over 150° F	Do not use or store near heat or open flame.

(l) *Directions for Use*—(1) *General requirements*—(i) *Adequacy and clarity of directions.* Directions for use must be stated in terms which can be easily read and understood by the average person likely to use or to supervise the use of the pesticide. When followed, directions must be adequate to protect the public from fraud and from personal injury and to prevent unreasonable adverse effects on the environment.

(ii) *Placement of directions for use.* Directions may appear on any portion of the label provided that they are conspicuous enough to be easily read by the user of the pesticide product. Directions for use may appear on printed or graphic matter which accompanies the pesticide provided that:

(A) If required by the Agency, such printed or graphic matter is securely attached to each package of the pesticide, or placed within the outside wrapper or bag;

(x) Any limitations or restrictions on use required to prevent unreasonable adverse effects, such as:

(A) Required intervals between application and harvest of food or feed crops.

(B) Rotational crop restrictions.

(C) Warnings as required against use on certain crops, animals, objects, or in or adjacent to certain areas.

(D) [Reserved]

(E) For restricted use pesticides, a statement that the pesticide may be applied under the direct supervision of a certified applicator who is not physically present at the site of application but nonetheless available to the person applying the pesticide, unless the Agency has determined that the pesticide may only be applied under the direct supervision of a certified applicator who is physically present.

(F) Other pertinent information which the Administrator determines to be necessary for the protection of man and the environment.

(j) *Statement of Use Classification.* By October 22, 1976, all pesticide products must bear on their labels a statement of use classification as described in paragraphs (j) (1) and (2) of this section. Any pesticide product for which some uses are classified for general use and others for restricted use shall be separately labeled according to the labeling standards set forth in this subsection, and shall be marketed as separate products with different registration numbers, one bearing directions only for general use(s) and the other bearing directions for restricted use(s) except that, if a product has both restricted use(s) and general use(s), both of these uses may appear on a product labeled for restricted use. Such products shall be subject to the provisions of paragraph (j)(2) of this section.

(1) *General Use Classification.* Pesticide products bearing directions for use(s) classified general shall be labeled with the exact words "General Classification" immediately below the heading "Directions for Use." And reference to the general classification that suggests or implies that the general utility of the pesticide extends beyond those purposes and uses contained in the Directions for Use will be considered a false or misleading statement under the statutory definitions of misbranding.

(2) *Restricted Use Classification.* Pesticide products bearing direction for use(s) classified restricted shall bear statements of restricted use classification on the front panel as described below:

(i) *Front panel statement of restricted use classification.* (A) At the top of the front panel of the label, set in type of the same minimum sizes as required for human hazard signal words (see table in paragraph (h)(1)(iv) of this section), and appearing with sufficient prominence relative to other text and graphic material on the front panel to make it unlikely to be overlooked under customary conditions of purchase and use, the statement "Restricted Use Pesticide" shall appear.

(B) Directly below this statement on the front panel, a summary statement of the terms of restriction imposed as a precondition to registration shall appear. If use is restricted to certified applicators, the following statement is required: "For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification." If, however, other regulatory restrictions are imposed, the Administrator will define the appropriate wording for the terms of restriction by regulation.

[40 FR 28268, July 3, 1975; 40 FR 32329, Aug. 1, 1975; 40 FR 36571, Aug. 21, 1975, as amended at 43 FR 5786, Feb. 9, 1978. Redesignated and amended at 53 FR 15991, 15999, May 4, 1988]

APPENDIX F

Generic Data Call-In

No generic data are being called-in for:

hydroxytetracycline monohydrochloride and oxytetracycline calcium

APPENDIX G

Product Specific Data Call-In

This Notice is divided into six sections and seven Attachments. The Notice itself contains information and instructions applicable to all Data Call-In Notices. The Attachments contain specific chemical information and instructions. The six sections of the Notice are:

Section I - Why You Are Receiving This Notice
Section II - Data Required By This Notice
Section III - Compliance With Requirements Of This Notice
Section IV - Consequences Of Failure To Comply With This Notice
Section V - Registrants' Obligation To Report Possible Unreasonable Adverse Effects
Section VI - Inquiries And Responses To This Notice

The Attachments to this Notice are:

A - Data Call-In Chemical Status Sheet
B - Product-Specific Data Call-In Response Form
C - Requirements Status and Registrant's Response Form
D - EPA Grouping of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration
E - EPA Acceptance Criteria
F - List of Registrants Receiving This Notice
G - Cost Share and Data Compensation Forms, and Product Specific Data Report Form

SECTION I. WHY YOU ARE RECEIVING THIS NOTICE

The Agency has reviewed existing data for this active ingredient and reevaluated the data needed to support continued registration of the subject active ingredient. The Agency has concluded that the only additional data necessary are product specific data. No additional generic data requirements are being imposed. You have been sent this Notice because you have product(s) containing the subject active ingredient.

SECTION II. DATA REQUIRED BY THIS NOTICE

II-A. DATA REQUIRED

The product specific data required by this Notice are specified in Attachment C, Requirements Status and Registrant's Response Form. Depending on the results of the studies required in this Notice, additional testing may be required.

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

DATA CALL-IN NOTICE

MAR 30 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

CERTIFIED MAIL

Dear Sir or Madam:

This Notice requires you and other registrants of pesticide products containing the active ingredient identified in Attachment A of this Notice, the Data Call-In Chemical Status Sheet, to submit certain product specific data as noted herein to the U.S. Environmental Protection Agency (EPA, the Agency). These data are necessary to maintain the continued registration of your product(s) containing this active ingredient. Within 90 days after you receive this Notice you must respond as set forth in Section III below. Your response must state:

1. How you will comply with the requirements set forth in this Notice and its Attachments A through G; or

2. Why you believe you are exempt from the requirements listed in this Notice and in Attachment C, Requirements Status and Registrant's Response Form, (see section III-B); or

3. Why you believe EPA should not require your submission of product specific data in the manner specified by this Notice (see section III-D).

If you do not respond to this Notice, or if you do not satisfy EPA that you will comply with its requirements or should be exempt or excused from doing so, then the registration of your product(s) subject to this Notice will be subject to suspension. We have provided a list of all of your products subject to this Notice in Attachment B, Data Call-In Response Form, as well as a list of all registrants who were sent this Notice (Attachment F).

The authority for this Notice is section 3(c)(2)(B) of the Federal Insecticide, Fungicide and Rodenticide Act as amended (FIFRA), 7 U.S.C. section 136a(c)(2)(B). Collection of this information is authorized under the Paperwork Reduction Act by OMB Approval No. 2070-0107 (expiration date 12-31-92).

your products. This and other bases for issuance of NOIS due to failure to comply with this Notice are presented in Section IV-A and IV-B.

III-B. OPTIONS FOR RESPONDING TO THE AGENCY

The options for responding to this Notice for product specific data are: (a) voluntary cancellation, (b) agree to satisfy the product specific data requirements imposed by this notice or (c) request a data waiver(s).

A discussion of how to respond if you chose the Voluntary Cancellation option is presented below. A discussion of the various options available for satisfying the product specific data requirements of this Notice is contained in Section III-C. A discussion of options relating to requests for data waivers is contained in Section III-D.

There are two forms that accompany this Notice of which, depending upon your response, one or both must be used in your response to the Agency. These forms are the Data-Call-In Response Form, and the Requirements Status and Registrant's Response Form, Attachment B and Attachment C. The Data Call-In Response Form must be submitted as part of every response to this Notice. In addition, one copy of the Requirements Status and Registrant's Response Form must be submitted for each product listed on the Data Call-In Response Form unless the voluntary cancellation option is selected or unless the product is identical to another (refer to the instructions for completing the Data Call-In Response Form in Attachment B). Please note that the company's authorized representative is required to sign the first page of the Data Call-In Response Form and Requirements Status and Registrant's Response Form (if this form is required) and initial any subsequent pages. The forms contain separate detailed instructions on the response options. Do not alter the printed material. If you have questions or need assistance in preparing your response, call or write the contact person(s) identified in Attachment A.

1. Voluntary Cancellation - You may avoid the requirements of this Notice by requesting voluntary cancellation of your product(s) containing the active ingredient that is the subject of this Notice. If you wish to voluntarily cancel your product, you must submit a completed Data Call-In Response Form, indicating your election of this option. Voluntary cancellation is item number 5 on the Data Call-In Response Form. If you choose this option, this is the only form that you are required to complete.

If you chose to voluntarily cancel your product, further sale and distribution of your product after the effective date of cancellation must be in accordance with the Existing Stocks provisions of this Notice which are contained in Section IV-C.

II-B. SCHEDULE FOR SUBMISSION OF DATA

You are required to submit the data or otherwise satisfy the data requirements specified in Attachment C, Requirements Status and Registrant's Response Form, within the timeframes provided.

II-C. TESTING PROTOCOL

All studies required under this Notice must be conducted in accordance with test standards outlined in the Pesticide Assessment Guidelines for those studies for which guidelines have been established.

These EPA Guidelines are available from the National Technical Information Service (NTIS), Attn: Order Desk, 5285 Port Royal Road, Springfield, Va 22161 (tel: 703-487-4650).

Protocols approved by the Organization for Economic Cooperation and Development (OECD) are also acceptable if the OECD-recommended test standards conform to those specified in the Pesticide Data Requirements regulation (40 CFR § 158.70). When using the OECD protocols, they should be modified as appropriate so that the data generated by the study will satisfy the requirements of 40 CFR § 158. Normally, the Agency will not extend deadlines for complying with data requirements when the studies were not conducted in accordance with acceptable standards. The OECD protocols are available from OECD, 1750 Pennsylvania Avenue N.W., Washington, D.C. 20006.

All new studies and proposed protocols submitted in response to this Data Call-In Notice must be in accordance with Good Laboratory Practices [40 CFR Part 160.3(a)(6)].

II-D. REGISTRANTS RECEIVING PREVIOUS SECTION 3(c)(2)(B) NOTICES ISSUED BY THE AGENCY

Unless otherwise noted herein, this Data Call-In does not in any way supersede or change the requirements of any previous Data Call-In(s), or any other agreements entered into with the Agency pertaining to such prior Notice. Registrants must comply with the requirements of all Notices to avoid issuance of a Notice of Intent to Suspend their affected products.

SECTION III. COMPLIANCE WITH REQUIREMENTS OF THIS NOTICE

III-A. SCHEDULE FOR RESPONDING TO THE AGENCY

The appropriate responses initially required by this Notice for product specific data must be submitted to the Agency within 90 days after your receipt of this Notice. Failure to adequately respond to this Notice within 90 days of your receipt will be a basis for issuing a Notice of Intent to Suspend (NOIS) affecting

The time frames in the Requirements Status and Registrant's Response Form are the time frames that the Agency is allowing for the submission of completed study reports. The noted deadlines run from the date of the receipt of this Notice by the registrant. If the data are not submitted by the deadline, each registrant is subject to receipt of a Notice of Intent to Suspend the affected registration(s).

If you cannot submit the data/reports to the Agency in the time required by this Notice and intend to seek additional time to meet the requirements(s), you must submit a request to the Agency which includes: (1) a detailed description of the expected difficulty and (2) a proposed schedule including alternative dates for meeting such requirements on a step-by-step basis. You must explain any technical or laboratory difficulties and provide documentation from the laboratory performing the testing. While EPA is considering your request, the original deadline remains. The Agency will respond to your request in writing. If EPA does not grant your request, the original deadline remains. Normally, extensions can be requested only in cases of extraordinary testing problems beyond the expectation or control of the registrant. Extensions will not be given in submitting the 90-day responses. Extensions will not be considered if the request for extension is not made in a timely fashion; in no event shall an extension request be considered if it is submitted at or after the lapse of the subject deadline.

Option 2. Agreement to Share in Cost to Develop Data -- Registrants may only choose this option for acute toxicity data and certain efficacy data and only if EPA has indicated in the attached data tables that your product and at least one other product are similar for purposes of depending on the same data. If this is the case, data may be generated for just one of the products in the group. The registration number of the product for which data will be submitted must be noted in the agreement to cost share by the registrant selecting this option. 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, you must provide the name of the registrant who will be submitting the data. You must also provide EPA with documentary evidence that an agreement has been formed. Such 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. Section 3(c)(2)(B) provides that if the parties cannot resolve the terms of the agreement they may resolve their differences through binding arbitration.

Option 3. Offer to Share in the Cost of Data Development -- This option only applies to acute toxicity and certain efficacy data as described in option 2 above. If you have made an offer to pay in an attempt to enter into an agreement or amend an existing agreement to meet the requirements of this Notice and have been

2. Satisfying the Product Specific Data Requirements of this Notice There are various options available to satisfy the product specific data requirements of this Notice. These options are discussed in Section III-C of this Notice and comprise options 1 through 6 on the Requirements Status and Registrant's Response Form and item numbers 7a and 7b on the Data Call-In Response Form. Deletion of a use(s) and the low volume/minor use option are not valid options for fulfilling product specific data requirements.

3. Request for Product Specific Data Waivers. Waivers for product specific data are discussed in Section III-D of this Notice and are covered by option 7 on the Requirements Status and Registrant's Response Form. If you choose one of these options, you must submit both forms as well as any other information/data pertaining to the option chosen to address the data requirement.

III-C SATISFYING THE DATA REQUIREMENTS OF THIS NOTICE

If you acknowledge on the Data Call-In Response Form that you agree to satisfy the product specific data requirements (i.e. you select item number 7a or 7b), then you must select one of the six options on the Requirements Status and Registrant's Response Form related to data production for each data requirement. Your option selection should be entered under item number 9, "Registrant Response." The six options related to data production are the first six options discussed under item 9 in the instructions for completing the Requirements Status and Registrant's Response Form. These six options are listed immediately below with information in parentheses to guide registrants to additional instructions provided in this Section. The options are:

(1) I will generate and submit data within the specified timeframe (Developing Data)
(2) I have entered into an agreement with one or more registrants to develop data jointly (Cost Sharing)
(3) I have made offers to cost-share (Offers to Cost Share)
(4) I am submitting an existing study that has not been submitted previously to the Agency by anyone (Submitting an Existing Study)
(5) I am submitting or citing data to upgrade a study classified by EPA as partially acceptable and upgradeable (Upgrading a Study)
(6) I am citing an existing study that EPA has classified as acceptable or an existing study that has been submitted but not reviewed by the Agency (Citing an Existing Study)

Option 1. Developing Data -- If you choose to develop the required data it must be in conformance with Agency deadlines and with other Agency requirements as referenced herein and in the attachments. All data generated and submitted must comply with the Good Laboratory Practice (GLP) rule (40 CFR Part 160), be conducted according to the Pesticide Assessment Guidelines (PAG), and be in conformance with the requirements of PR Notice 86-5.

To meet the requirements of the DCI Notice for submitting an existing study, <u>all of the following three criteria must be clearly met</u>:

a. You must certify at the time that the existing study is submitted that the raw data and specimens from the study are available for audit and review and you must identify where they are available. This must be done in accordance with the requirements of the Good Laboratory Practice (GLP) regulation, 40 CFR Part 160. As stated in 40 CFR 160.3(j) " '[r]aw data' means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. 'Raw data' may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments." The term "specimens", according to 40 CFR 160.3(k), means "any material derived from a test system for examination or analysis."

b. Health and safety studies completed after May 1984 must also contain all GLP-required quality assurance and quality control information, pursuant to the requirements of 40 CFR Part 160. Registrants must also certify at the time of submitting the existing study that such GLP information is available for post-May 1984 studies by including an appropriate statement on or attached to the study signed by an authorized official or representative of the registrant.

c. You must certify that each study fulfills the acceptance criteria for the Guideline relevant to the study provided in the FIFRA Accelerated Reregistration Phase 3 Technical Guidance and that the study has been conducted according to the Pesticide Assessment Guidelines (PAG) or meets the purpose of the PAG (both available from NTIS). A study not conducted according to the PAG may be submitted to the Agency for consideration if the registrant believes that the study clearly meets the purpose of the PAG. The registrant is referred to 40 CFR 158.70 which states the Agency's policy regarding acceptable protocols. If you wish to submit the study, you must, in addition to certifying that the purposes of the PAG are met by the study, clearly articulate the rationale why you believe the study meets the purpose of the PAG, including copies of any supporting information or data. It has been the Agency's experience that studies completed prior to January 1970 rarely satisfied the purpose of the PAG and that necessary raw data are usually not available for such studies.

unsuccessful, you may request EPA (by selecting this option) to 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 joint data development/cost sharing program, but the other registrant(s) developing the data has refused to accept your offer. To qualify for this option, you must submit documentation to the Agency proving that you have made an offer to another registrant (who has an obligation to submit data) to share in the burden of developing that data. You must also submit to the Agency a completed EPA Form 8570-32, Certification of Offer to Cost Share in the Development of Data, Attachment G. In addition, you must demonstrate that the other registrant to whom the offer was made has not accepted your offer to enter into a costsharing agreement by including a copy of your offer and proof of the other registrant's receipt of that offer (such as a certified mail receipt). Your offer must, in addition to anything else, 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 section 3(c)(2)(B)(iii) and must not qualify this offer. The other registrant must also inform EPA of its election of an option to develop and submit the data required by this Notice by submitting a Data Call-In Response Form and a Requirements Status and Registrant's Response Form committing to 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 as required by this Notice. If the other registrant fails to develop the data or for some other reason is subject to suspension, your registration as well as that of the other registrant will normally be subject to initiation of suspension proceedings, unless you commit to submit, and do submit the required data in the specified time frame. In such cases, the Agency generally will not grant a time extension for submitting the data.

Option 4. Submitting an Existing Study -- If you choose to submit an existing study in response to this Notice, you must determine that the study satisfies the requirements imposed by this Notice. You may only submit a study that has not been previously submitted to the Agency or previously cited by anyone. Existing studies are studies which predate issuance of this Notice. Do not use this option if you are submitting data to upgrade a study. (See Option 5).

You should be aware that if the Agency determines that the study is not acceptable, the Agency will require you to comply with this Notice, normally without an extension of the required date of submission. The Agency may determine at any time that a study is not valid and needs to be repeated.

toxicology studies generally will have been classified as "core-guideline" or "core minimum." For all other disciplines the classification would be "acceptable." With respect to any studies for which you wish to select this option you must provide the MRID number of the study you are citing and, if the study has been reviewed by the Agency, you must provide the Agency's classification of the study.

If you are citing a study of which you are not the original data submitter, you must submit a completed copy of EPA Form 8570-31, Certification with Respect to Data Compensation Requirements.

Registrants who select one of the above 6 options must meet all of the requirements described in the instructions for completing the Data Call-In Response Form and the Requirements Status and Registrant's Response Form, as appropriate.

III-D REQUESTS FOR DATA WAIVERS

If you request a waiver for product specific data because you believe it is inappropriate, you must attach a complete justification for the request, including technical reasons, data and references to relevant EPA regulations, guidelines or policies. (Note: any supplemental data must be submitted in the format required by PR Notice 86-5). This will be the only opportunity to state the reasons or provide information in support of your request. If the Agency approves your waiver request, you will not be required to supply the data pursuant to section 3(c)(2)(B) of FIFRA. If the Agency denies your waiver request, you must choose an option for meeting the data requirements of this Notice within 30 days of the receipt of the Agency's decision. You must indicate and submit the option chosen on the Requirements Status and Registrant's Response Form. Product specific data requirements for product chemistry, acute toxicity and efficacy (where appropriate) are required for all products and the Agency would grant a waiver only under extraordinary circumstances. You should also be aware that submitting a waiver request will not automatically extend the due date for the study in question. Waiver requests submitted without adequate supporting rationale will be denied and the original due date will remain in force.

IV. CONSEQUENCES OF FAILURE TO COMPLY WITH THIS NOTICE

IV-A NOTICE OF INTENT TO SUSPEND

The Agency may issue a Notice of Intent to Suspend products subject to this Notice due to failure by a registrant to comply with the requirements of this Data Call-In Notice, pursuant to FIFRA section 3(c)(2)(B). Events which may be the basis for issuance of a Notice of Intent to Suspend include, but are not limited to, the following:

If you submit an existing study, you must certify that the study meets all requirements of the criteria outlined above.

If you know of a study pertaining to any requirement in this Notice which does not meet the criteria outlined above but does contain factual information regarding unreasonable adverse effects, you must notify the Agency of such a study. If such study is in the Agency's files, you need only cite it along with the notification. If not in the Agency's files, you must submit a summary and copies as required by PR Notice 86-5.

Option 5, Upgrading a Study -- If a study has been classified as partially acceptable and upgradeable, you may submit data to upgrade that study. The Agency will review the data submitted and determine if the requirement is satisfied. If the Agency decides the requirement is not satisfied, you may still be required to submit new data normally without any time extension. Deficient, but upgradeable studies will normally be classified as supplemental. However, it is important to note that not all studies classified as supplemental are upgradeable. If you have questions regarding the classification of a study or whether a study may be upgraded, call or write the contact person listed in Attachment A. If you submit data to upgrade an existing study you must satisfy or supply information to correct all deficiencies in the study identified by EPA. You must provide a clearly articulated rationale of how the deficiencies have been remedied or corrected and why the study should be rated as acceptable to EPA. Your submission must also specify the MRID number(s) of the study which you are attempting to upgrade and must be in conformance with PR Notice 86-5.

Do not submit additional data for the purpose of upgrading a study classified as unacceptable and determined by the Agency as not capable of being upgraded.

This option should also be used to cite data that has been previously submitted to upgrade a study, but has not yet been reviewed by the Agency. You must provide the MRID number of the data submission as well as the MRID number of the study being upgraded.

The criteria for submitting an existing study, as specified in Option 4 above, apply to all data submissions intended to upgrade studies. Additionally your submission of data intended to upgrade studies must be accompanied by a certification that you comply with each of those criteria as well as a certification regarding protocol compliance with Agency requirements.

Option 6, Citing Existing Studies -- If you choose to cite a study that has been previously submitted to EPA, that study must have been previously classified by EPA as acceptable or it must be a study which has not yet been reviewed by the Agency. Acceptable

for issuance of a Notice of Intent to Suspend. The grounds for suspension include, but are not limited to, failure to meet any of the following:

1. EPA requirements specified in the Data Call-In Notice or other documents incorporated by reference (including, as applicable, EPA Pesticide Assessment Guidelines, Data Reporting Guidelines, and GeneTox Health Effects Test Guidelines) regarding the design, conduct, and reporting of required studies. Such requirements include, but are not limited to, those relating to test material, test procedures, selection of species, number of animals, sex and distribution of animals, dose and effect levels to be tested or attained, duration of test, and, as applicable, Good Laboratory Practices.

2. EPA requirements regarding the submission of protocols, including the incorporation of any changes required by the Agency following review.

3. EPA requirements regarding the reporting of data, including the manner of reporting, the completeness of results, and the adequacy of any required supporting (or raw) data, including, but not limited to, requirements referenced or included in this Notice or contained in PR 86-5. All studies must be submitted in the form of a final report; a preliminary report will not be considered to fulfill the submission requirement.

IV-C EXISTING STOCKS OF SUSPENDED OR CANCELLED PRODUCTS

EPA has statutory authority to permit continued sale, distribution and use of existing stocks of a pesticide product which has been suspended or cancelled if doing so would be consistent with the purposes of the Act.

The Agency has determined that such disposition by registrants of existing stocks for a suspended registration when a section 3(c)(2)(B) data request is outstanding would generally not be consistent with the Act's purposes. Accordingly, the Agency anticipates granting registrants permission to sell, distribute, or use existing stocks of suspended product(s) only in exceptional circumstances. If you believe such disposition of existing stocks of your product(s) which may be suspended for failure to comply with this Notice should be permitted, you have the burden of clearly demonstrating to EPA that granting such permission would be consistent with the Act. You must also explain 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, distribution, and use. Unless you meet this burden the Agency will not consider any request pertaining to the continued sale, distribution, or use of your existing stocks after suspension.

1. Failure to respond as required by this Notice within 90 days of your receipt of this Notice.

2. Failure to submit on the required schedule an acceptable proposed or final protocol when such is required to be submitted to the Agency for review.

3. Failure to submit on the required schedule an adequate progress report on a study as required by this Notice.

4. Failure to submit on the required schedule acceptable data as required by this Notice.

5. Failure to take a required action or submit adequate information pertaining to any option chosen to address the data requirements (e.g., any required action or information pertaining to submission or citation of existing studies or offers, arrangements, or arbitration on the sharing of costs or the formation of Task Forces, failure to comply with the terms of an agreement or arbitration concerning joint data development or failure to comply with any terms of a data waiver).

6. Failure to submit supportable certifications as to the conditions of submitted studies, as required by Section III-C of this Notice.

7. Withdrawal of an offer to share in the cost of developing required data.

8. Failure of the registrant to whom you have tendered an offer to share in the cost of developing data and provided proof of the registrant's receipt of such offer or failure of a registrant on whom you rely for a generic data exemption either to:

a. inform EPA of intent to develop and submit the data required by this Notice on a Data Call-In Response Form and a Requirements Status and Registrant's Response Form;

b. fulfill the commitment to develop and submit the data as required by this Notice; or

c. otherwise take appropriate steps to meet the requirements stated in this Notice, unless you commit to submit and do submit the required data in the specified time frame.

9. Failure to take any required or appropriate steps, not mentioned above, at any time following the issuance of this Notice.

IV-B. BASIS FOR DETERMINATION THAT SUBMITTED STUDY IS UNACCEPTABLE

The Agency may determine that a study (even if submitted within the required time) is unacceptable and constitutes a basis

the voluntary cancellation or generic data exemption option is chosen, only the Data Call-In Response Form need be submitted.

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.

Sincerely yours,

Daniel M. Barolo, Director
Special Review and
Reregistration Division

Attachments

A - Data Call-In Chemical Status Sheet
B - Product-Specific Data Call-In Response Form
C - Requirements Status and Registrant's Response Form for the Product Specific Data Call-In
D - EPA Grouping of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration
E - EPA Acceptance Criteria
F - List of Registrants Receiving This Notice
G - Cost Share and Data Compensation Forms, and Product Specific Data Report Form

If you request a voluntary cancellation of your product(s) as a response to this Notice and your product is in full compliance with all Agency requirements, you will have, under most circumstances, one year from the date your 90 day response to this Notice is due, to sell, distribute, or use existing stocks. Normally, the Agency will allow persons other than the registrant such as independent distributors, retailers and end users to sell, distribute or use such existing stocks until the stocks are exhausted. Any sale, distribution or use of stocks of voluntarily cancelled products containing an active ingredient for which the Agency has particular risk concerns will be determined on case-by-case basis.

Requests for voluntary cancellation received after the 90 day response period required by this Notice will not result in the Agency granting any additional time to sell, distribute, or use existing stocks beyond a year from the date the 90 day response was due unless you demonstrate to the Agency that you are in full compliance with all Agency requirements, including the requirements of this Notice. For example, if you decide to voluntarily cancel your registration six months before a 3 year study is scheduled to be submitted, all progress reports and other information necessary to establish that you have been conducting the study in an acceptable and good faith manner must have been submitted to the Agency, before EPA will consider granting an existing stocks provision.

SECTION V. REGISTRANTS' OBLIGATION TO REPORT POSSIBLE UNREASONABLE ADVERSE EFFECTS

Registrants are reminded that FIFRA section 6(a)(2) states that if at any time after a pesticide is registered a registrant has additional factual information regarding unreasonable adverse effects on the environment by the pesticide, the registrant shall submit the information to the Agency. Registrants must notify the Agency of any factual information they have, from whatever source, including but not limited to interim or preliminary results of studies, regarding unreasonable adverse effects on man or the environment. This requirement continues as long as the products are registered by the Agency.

SECTION VI. INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding the requirements and procedures established by this Notice, call the contact person(s) listed in Attachment A, the Data Call-In Chemical Status Sheet.

All responses to this Notice (other than voluntary cancellation requests and generic data exemption claims) must include a completed Data Call-In Response Form and a completed Requirements Status and Registrant's Response Form (Attachment B for generic data and Attachment C for product specific data) and any other documents required by this Notice, and should be submitted to the contact person(s) identified in Attachment A. If

ATTACHMENT A

Product Specific DCI Chemical Status Sheet

INQUIRIES AND RESPONSES TO THIS NOTICE

Any questions in regards to this RED, should be directed to Mario F. Fiol, Chemical Review Manager, Reregistration Branch, Special Review and Reregistration Division, at (703) 308 - 8049.

If you have any questions regarding the product specific data requirements and procedures established by this Notice, please contact Benjamin C. Chambliss (703) 305 - 6900.

All responses to this Notice for the Product Specific data requirements should be submitted to:

Benjamin C. Chambliss, Product Manager 21
Herbicide and Fungicide Branch
Registration Division (H7505C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

RE: HYDROXYTETRACYCLINE MONOHYDROCHLORIDE AND OXYTETRACYCLINE CALCIUM

ATTACHMENT A

HYDROXYTETRACYCLINE MONOHYDROCHLORIDE AND OXYTETRACYCLINE CALCIUM

PRODUCT SPECIFIC DATA CALL-IN CHEMICAL STATUS SHEET

INTRODUCTION

You have been sent this Product Specific Data Call-In Notice because you have products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium.

This Product Specific Data Call-In Chemical Status Sheet, contains an overview of data required by this notice, and point of of contact for inquiries pertaining to the reregistration of hydroxytetracycline monohydrochloride and oxytetracycline calcium products. This attachment is to be used in conjunction with (1) the Product Specific Data Call-In Notice, (2) the Product Specific Data Call-In Response Form (Attachment B), (3) the Requirements Status and Registrant's Form (Attachment C), (4) EPA's Grouping of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration (Attachment D), (5) EPA Acceptance Criteria (Attachment E), (6) List of Registrants Receiving this Notice (Appendix F), and (7) the Cost Share and Data Compensation Forms (Attachment G) in replying to this Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium Product Specific Data Call-In. Instructions and guidance accompany each form.

DATA REQUIRED BY THIS NOTICE

The additional data requirements needed to complete the product specific database for hydroxytetracycline monohydrochloride and oxytetracycline calcium are contained in the Requirements Status and Registrant's Response (Attachment C). The Agency has concluded that additional data on hydroxytetracycline monohydrochloride and oxytetracycline calcium are needed for specific products. While product specific data requirements were imposed in the 1988 Registration Standard, a complete listing is provided in Attachment C. If you, as a registrant of a hydroxytetracycline monohydrochloride and/or oxytetracycline calcium product, responded to the 1988 Registration Standard and submitted the data relating to your specific product, simply choose response number 6 and cite the MRID number that was assigned to your study. Otherwise, these data are required to be submitted to the Agency within the time-frame listed. These data are needed to complete the reregistration of all eligible hydroxytetracycline monohydrochloride and oxytetracycline calcium products.

ATTACHMENT B

Product Specific Data Call-In Response Forms (Form A) plus Instructions

DRAFT COPY

United States Environmental Protection Agency
Washington, D. C. 20460

DATA CALL-IN RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary.

1. Company name and Address	2. Case # and Name	3. Date and Type of DCI
SAMPLE COMPANY NO STREET ADDRESS NO CITY, XX 00000	0655 Oxytetracycline	PRODUCT SPECIFIC MAR 30 1993

4. EPA Product Registration	5. I wish to cancel this product registration voluntarily.	6. Generic Data		7. Product Specific Data	
		6a. I am claiming a Generic Data Exemption because I obtain the active ingredient from the source EPA registration number listed below.	6b. I agree to satisfy Generic Data requirements as indicated on the attached form entitled "Requirements Status and Registrant's Response."	7a. My product is a MUP and I agree to satisfy the MUP requirements on the attached form entitled "Requirements Status and Registrant's Response."	7b. My product is an EUP and I agree to satisfy the EUP requirements on the attached form entitled "Requirements Status and Registrant's Response."
NNNNNN-NNNNN		N.A.	N.A.		

8. Certification

I certify that the statements made on this form and all attachments are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law.

Signature and Title of Company's Authorized Representative _____

9. Date

10. Name of Company Contact

11. Phone Number

INSTRUCTIONS FOR COMPLETING THE "DATA CALL-IN RESPONSE" FORM FOR PRODUCT SPECIFIC DATA

Item 1-4. Already completed by EPA.

Item 5. If you wish to voluntarily cancel your product, answer "yes". If you choose this option, you will not have to provide the data required by the Data Call-In Notice and you will not have to complete any other forms. Further sale and distribution of your product after the effective date of cancellation must be in accordance with the Existing Stocks provision of the Data Call-In Notice (Section IV-C).

Item 6. Not applicable since this form calls in product specific data only. However, if your product is identical to another product and you qualify for a data exemption, you must respond with "yes" to Item 7a (MUP) or 7B (EUP) on this form, provide the EPA reregistration numbers of your source (s); you would not complete the requirements status and registrant's response" form. Examples of such products include repackaged products and Special Local Needs (Section 24c) products which are identical to federally registered products.

Item 7a. For each manufacturing use product (MUP) for which you wish to maintain registration, you must agree to satisfy the data requirements by responding "yes."

Item 7b. For each end use product (EUP) for which you wish to maintain registration, you must agree to satisfy the data requirements by responding "yes." if you are requesting a data waiver, answer "yes" here; in addition, on the "Requirements Status and Registrant's Response" form under Item 9, you must respond with option 7 (Waiver Request) for each study for which you are requesting a waiver. See item 6 with regard to identical products and data exemptions.

Items 8-11. Self-explanatory.

Note: You may provide additional information that does not fit on this form in a signed letter that accompanies this form. For example, you may wish to report that your product has already been transferred to another that you have already voluntarily cancelled this product. For these cases, please supply all relevant details so that EPA can ensure that its records are correct.

ATTACHMENT C

Product Specific Data Call-In Requirements Status and Registrant's Response Forms (Form B) plus Instructions

product is similar. Enough to another product to qualify for this option. I certify that another party in the agreement is committing to submit or provide the required data; if the required study is not submitted on time, my product my be subject to suspension.

3. I have made offers to share in the cost to develop data (Offers to Cost Share). I understand that this option is available only for acute toxicity or certain efficacy data and only if EPA indicates in an attachment to this Data Call-In Notice that my product is similar enough to another product to qualify for this option. I am submitting evidence that I have made an offer to another registrant (who has an obligation to submit data) to share in the cost of that data. I am also submitting a completed " Certification of offer to Cost Share in the Development Data" form. I am including a copy of my offer and prooof of the other registrant's receipt of that offer. I am identifying the party which is committing to submit or provide the require data; if the required study is not submitted on time, my product may be subject to suspension. I understand that other terms under Option 3 in the Data Call-In Notice (Section III-C.1.) apply as well.

4. By the specified due date, I will submit an existing study that has not been submitted previously to the Agency by anyone (submitting an Existing Study). I certify that this study will meet all the requirements for submittal of existing data outlined in option 4 in the Data Call-In Notice (Section III-C.1.) and will meet the attached acceptance criteria (for acute toxicity and product chemistry data). I will attach the needed supporting information along with this response. I also certify that I have determined that this study will fill the data requirement for which I have indicated this choice.

5. By the specified due date, I will submit or cite data to upgrade a study classified by the Agency as partially acceptable and upgrade (upgrading a study). I will submit evidence of the Agency's review indicating that the study may be upgraded and what information is required to do so. I will provide the MRID or Accession number of the study at the due date. I understand that the conditions for this Option outlined Option 5 in the Data Call-In Notice (Section III-C.1.) apply.

6. By the specified due date, I will cite an existing study that the Agency has classified as acceptable or an existing study that has been submitted but not reviewed by the Agency (Citing an Existing Study). If I am citing another registrant's study, I understand that this option is available only for acute toxicity or certain efficacy data and only if the cited study was conducted on my product, an identical product or a product which EPA has "grouped" with one or more other products for purposes of depending on the same data. I may also choose this option if I am citing my own data. In either

INSTRUCTIONS FOR COMPLETING THE "REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE" FORM FOR PRODUCT SPECIFIC DATA

Item 1-3 Completed by EPA. Note the unique identifier number assigned by EPA in item 3. This number must be used in the transmittal document for any data submissions in response to this Data Call-In Notice.

Item 4. The guidelines reference numbers of studies required to support the product's continued registration are identified. These guidelines, in addition to the requirements specified in the Notice, govern the conduct of the required studies. Note that series 61 and 62 in product chemistry are now listed under 40 CFR 158.155 through 158.180, Subpart c.

Item 5. The study title associated with the guideline reference number is identified.

Item 6. The use patters (s) of the pesticide associated with the product specific requirements is (are) identified. For most product specific data requirements, all use patterns are covered by the data requirements. In the case of efficacy data, the required studies only pertain to products which have the use sites and/ or pests indicated.

Item 7. The substance to be tested is identified by EPA. For product specific data, the product as formulated for sale and distribution is the test substance, except in rare cases.

Item 8. The due date for submission of each study is identified. It is normally based on 8 months after issuance of the Reregistration Eligibility Documents unless EPA determines that a longer time period is necessary.

Item 9. Enter <u>Only one</u> of the following response codes <u>for each data requirement</u> to show how you intend to comply with the data requirements listed in this table. Fuller descriptions of each option are contained in the Data Call-In Notice.

1. I will generate and submit data by the specified due date (Developing Data). By indicating that I have chosen this option, I certify that I will comply with all the requirements pertaining to the conditions for submittal of this study as outlined in the Data Call-In Notice.

2. I have entered into an agreement with one or more registrants to develop data jointly (Cost Sharing). I am submitting a copy of this agreement. I understand that this option is available on for acute toxicity or certain efficacy data and only if EPA indicates in an attachment to this notice that my

United States Environmental Protection Agency
Washington, D. C. 20460

REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary.

1. Company name and Address
SAMPLE COMPANY
NO STREET ADDRESS
NO CITY, XX 00000

2. Case # and Name
0655 Oxytetracycline

EPA Reg. No. NNNNNN-NNNNN

3. Date and Type of DCI
PRODUCT SPECIFIC
ID# NNNNNN-RD-NNNN
1993

4. Guideline Requirement Number	5. Study Title	Protocol	Progress Reports 1	2	3	6. Use Pattern	7. Test Substance	8. Time Frame	9. Registrant Response
	Prod Chem - Regular Chemical								
61-1	Product identity & composition(1)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
61-2(a)	Descrip of starting materials,(1,2) production & formulation proc					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
61-2(b)	Discussion of formation of impurities (1,3)					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
62-1	Preliminary analysis (1,4)					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
62-2	Certification of limits (1,5)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
62-3	Analytical method (1)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
63-5	Melting point (6)					ABCDEFGHIJKLMNO	TGAI	8 mos.	
63-7	Density					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
63-8	Solubility					ABCDEFGHIJKLMNO	TGAI/PAI	8 mos.	
63-9	Vapor pressure					ABCDEFGHIJKLMNO	TGAI/PAI	8 mos.	
63-10	Dissociation constant					ABCDEFGHIJKLMNO	TGAI/PAI	8 mos.	
63-11	Octanol/water partition (8)					ABCDEFGHIJKLMNO	PAI	8 mos.	

10. Certification
I certify that the statements made on this form and all attachments are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law.

Signature and Title of Company's Authorized Representative _____

11. Date

12. Name of Company Contact

13. Phone Number

case, I will provide the MRID or Accession number (s) number (s) for the cited data on a "Product Specific Data Report" form or in a similar format. If I cite another registratrant's data, I will submit a completed "Certification With Respect To Data Compensation Requirements" form.

7. I request a waiver for this study because it is inappropriate for my product (Waiver Request). I am attaching a complete justification for this request, including technical reasons, data and references to relevant EPA regulations, guidelines or policies. [Note: any supplemental data must be submitted in the format required by P.R. Notice 86-5]. I understand that this is my only opportunity to state the reasons or provide information in support of my request. If the Agency approves my waiver request, I will not be require to supply the data pursuant to Section 3(c) (2) (B) of FIFRA. If the Agency denies my waiver request, I must choose a method of meeting the data requirements of this Notice by the due date stated by this Notice. In this case, I must, within 30 days of my receipt of the Agency's written decision, submit a revised "Requirements Status chosen. I also understand that the deadline for submission of data as specified by the original data cal-in notice will not change.

Items 10-13. Self-explanatory.

<u>NOTE:</u> You may provide additional information that does not fit on this form in a signed letter that accompanies this form. For example, you may wish to report that your product has already been transferred to another company or that you have already voluntarily cancelled this product. For these cases, please supply all relevant details so that EPA can ensure that its records are correct.

United States Environmental Protection Agency
Washington, D. C. 20460

FOOTNOTES AND KEY DEFINATIONS FOR GUIDELINE REQUIREMENTS

Case # and Name: 0655 Oxytetracycline

Key: MP = manufacturing-use product; EP = end-use product; provided formulators purchase their active ingredient(s) from a registered source, they need not submit or cite data pertaining to the purchased product.(NOTE: If a product is a 100 percent repackage of another registered product that is purchased, and any use for the product does not differ from those of the purchased and registered source, users are not subject to any data requirements identified in the tables.); TEP = typical end-use product; TGAI = technical grade of the active ingredient; PAI = "pure" active ingredient; PAIRA = "pure" active ingredient, radiolabeled.

Use Categories Key:

A - Terrestrial food crop	B - Terrestrial food feed crop	C - Terrestrial nonfood crop	D - Aquatic food crop	E - Aquatic nonfood outdoor
F - Aquatic nonfood industrial	G - Aquatic nonfood residential	H - Greenhouse food crop	I - Greenhouse nonfood crop	J - Forestry
K - Residential outdoor	L - Indoor feed	M - Indoor nonfood	N - Indoor Medical	O - Indoor residential

Footnotes: (The following notes are referenced in column two (5. Study Title) of the REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE form.)

Prod Chem - Regular Chemical

1 Requirements pertaining to product identity, composition, analysis, and certification of ingredients are detailed further in the following sections: *158.155 for product identity and composition (61-1); *158.160, 158.162, and 158.165 for description of starting materials and manufacturing process (61-2); *158.167 for discussion of formation of impurities (61-3); *158.170 for preliminary analysis (62-1); *158.175 for certification of limits (62-2); and *158.180 for enforcement analytical methods (62-3).
2 A schematic diagram and/or brief description of the production process will suffice if the pesticide is not already under full scale production and an experimental use permit is being sought.
3 If the pesticide is not already under full scale production and an experimental use permit is sought, a discussion of unintentional ingredients shall be submitted to the extent this information is available.
4 Required to support the registration of each manufacturing-use product (including registered TGAIs) as well as end-use products produced by an integrated system. Data on other end-use products will be required on a case-by-case basis. For pesticides in the development state, a rudimentary product analytical method and data will suffice to support an experimental use permit.
5 Certified limits are not required for inert ingredients in products proposed for experimental use.
6 Required if technical chemical is solid at room temperature.
8 Required if technical chemical is organic and non-polar.
38 Required for Calcium Oxytetracycline products only
39 Required for oxytetracycline Hydrochloride products only

Acute Toxic - Regular Chemical

1 Not required if test material is a gas or highly volatile.
2 Not required if test material is corrosive to skin or has pH less than 2 or greater than 11.5; such a product will be classified as Toxicity Category I on the basis of potential eye and dermal irritation effects.
3 Required if the product consists of, or under conditions of use will result in, an inhalable material (e. g., gas, volatile substances, or aerosol/particulate).
4 Required unless repeated dermal exposure does not occur under conditions of use.
36 Special testing (acute, subchronic, and/or chronic) is required for organophospates, and may be required for other cholinesterase inhibitors and other pesticides which have demonstrated a potential to adversely affect the visual system. Registrants should consult with the agency for development of protocols and methodology prior to initiation of studies.
37 Testing of the EP dilution is required if it can be reasonably anticipated that the results of such testing may meet the criteria for restriction to use by certified applicators specified in 40 CFR 152.170(b) or the criteria for initiation of special review specified in 40 CFR 154.7 (a)(1).

United States Environmental Protection Agency
Washington, D. C. 20460

REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary.

1. Company name and Address	2. Case # and Name	3. Date and Type of DCI
SAMPLE COMPANY NO STREET ADDRESS NO CITY, XX 00000	0655 Oxytetracycline EPA Reg. No. NNNNNN-NNNNN	PRODUCT SPECIFIC ID# NNNNNN-RD-NNNN MAR 30 1993

4. Guideline Requirement Number	5. Study Title	REQUIRED	Progress Reports 1	2	3	6. Use Pattern	7. Test Substance	8. Time Frame	9. Registrant Response
	Coefficient								
63-13	Stability					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
	Acute Toxic - Regular Chemical								
81-1	Acute oral toxicity-rat (1,36,37)					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
81-2	Acute dermal toxicity-rabbit/rat (1,2,37)					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
81-3	Acute inhalation toxicity-rat (3)					ABCDEFGHIJKLMNO	MP/EP and TGAI	8 mos.	
81-4	Primary eye irritation-rabbit (2)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
81-5	Primary dermal irritation (1,2)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	
81-6	Dermal sensitization (4)					ABCDEFGHIJKLMNO	MP/EP	8 mos.	

Initial to indicate certification as to information on this page (full text of certification is on page one).

Date

ATTACHMENT D

EPA's Grouping of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration

meet the data requirements for each product. The second form, "Requirements Status and Registrant's Response", lists the product specific data required for each product, including the standard six acute toxicity tests. A registrant who wishes to participate in a batch must decide whether he/she will provide the data or depend on someone else to do so. If a registrant supplies the data to support a batch of products, he/she must select one of the following options: Developing Data (Option 1), Submitting an Existing Study (Option 4), Upgrading an Existing Study (Option 5) or Citing an Existing Study (Option 6). If a registrant depends on another's data, he/she must choose among: Cost Sharing (Option 2), Offers to Cost Share (Option 3) or Citing an Existing Study (Option 6). If a registrant does not want to participate in a batch, the choices are Options 1, 4, 5 or 6. However, a registrant should know that choosing not to participate in a batch does not preclude other registrants in the batch from citing his/her studies and offering to cost share (Option 3) those studies.

Table I shows one batch including 2 products containing the active ingredient hydroxytetracycline monohydrochloride.

TABLE I

BATCHS	EPA REG. NO.	% Hydroxytetracycline monohydrochloride	FORMULATION
1	618-102	21.6 Hydroxytetracycline Monohydrochloride	Soluble Concentrate
	618-105	21.6 Hydroxytetracycline Monohydrochloride	Soluble Concentrate

Table II lists 3 products that were either considered not to be similar for purposes of acute toxycity or the Agency lacked sufficient information for decision making and were not placed in any batch. Registrants of these products of these products are responsible for meeting the acute toxicity data requirements for each product.

TABLE II

EPA Reg. No.	% Hydroxytetracycline Monohydrochloride and Oxytetracycline calcium	Formulation Type
1618-103	21.6% Hydroxytetracycline Monohydrochloride	Powder
618-104	31.6% Oxytetracycline Calcium	Powder
51946-01	50% Hydroxytetracycline Monohydrochloride	Powder

ATTACHMENT D

EPA'S BATCHING OF HYDROXYTETRACYCLINE MONOHYDROCHLORIDE AND OXYTETRACYCLINE CALCIUM END-USE PRODUCTS FOR MEETING ACUTE TOXICITY DATA REQUIREMENTS FOR REREGISTRATION

In an effort to reduce the time, resources and number of animals needed to fulfill the acute toxicity data requirements for reregistration of end-use products containing the active ingredients hydroxytetracycline monohydrochloride and oxytetracycline calcium, the Agency has batched products which can be considered similar for purposes of acute toxicity. Factors considered in the sorting process include each product's active and inert ingredients (identity, percent composition and biological activity), type of formulation (e.g., emulsifiable concentrate, aerosol, wettable powder, granular, etc.), and labeling (e.g., signal word, use classification, precautionary labeling, etc.). Note that the Agency is not describing batched products as "substantially similar" since some products within a batch may not be considered chemically similar or have identical use patterns.

Batching has been accomplished using the readily available information described above. Frequently acute toxicity data on individual end-use products has been found to be incomplete. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual end-use product should the need arise.

Registrants of end-use products within a batch may choose to cooperatively generate, submit or cite a single battery of six acute toxicological studies to represent all the products within that batch. It is the registrant's option to participate in the process with all the other registrants, only some of the other registrants, or only their own products within a batch, or to generate all the required acute toxicological studies for each of their own products. If a registrant chooses to generate the data for a batch, he/she must use one of the products within the batch as the test material. If a registrant chooses to rely upon previously submitted acute toxicity data, he/she may do so provided that the data base is complete and valid by today's standards (see acceptance criteria in Appendix G, Attachment E), the formulation tested is considered by EPA to be similar for acute toxicity, and the formulation has not been significantly altered since submission and acceptance of the acute toxicity data. Regardless of whether new data is generated or existing data is referenced, registrants must clearly identify the test material by EPA Registration Number.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In Notice and its attachments appended to the RED. The DCI Notice contains two response forms which are to be completed and submitted to the Agency within 90 days of receipt. The first form, "Data Call-In Response", asks whether the registrant will

ATTACHMENT E

EPA Acceptance Criteria

SUBDIVISION D

Guideline	Study Title
Series 61	Product Identity and Composition
Series 62	Analysis and Certification of Product Ingredients
Series 63	Physical and Chemical Characteristics

8. (continued)

____ Flow chart with chemical equations for each intended chemical reaction
____ Duration of each step of process
____ Description of purification procedures
____ Description of measures taken to assure quality of final product

9.___ Discussion of formation of impurities based on established chemical theory addressing (1) each impurity which may be present at $\geq$ 0.1% or was found at $\geq$ 0.1% by product analyses and (2) certain toxicologically significant impurities (see #3)

61 Product Identity and Composition

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.___ Name of technical material tested (include product name and trade name, if appropriate)
2.___ Name, nominal concentration, and certified limits (upper and lower) for each active ingredient and each intentionally-added inert ingredient
3.___ Name and upper certified limit for each impurity or each group of impurities present at ≥ 0.1% by weight and for certain toxicologically significant impurities (e.g., dioxins, nitrosamines) present at <0.1%
4.___ Purpose of each active ingredient and each intentionally-added inert
5.___ Chemical name from Chemical Abstracts index of Nomenclature and Chemical Abstracts Service (CAS) Registry Number for each active ingredient and, if available, for each intentionally-added inert
6.___ Molecular, structural, and empirical formulas, molecular weight or weight range, and any company assigned experimental or internal code numbers for each active ingredient
7.___ Description of each beginning material in the manufacturing process
    ____ EPA Registration Number if registered; for other beginning materials, the following:
    ____ Name and address of manufacturer or supplier
    ____ Brand name, trade name or commercial designation
    ____ Technical specifications or data sheets by which manufacturer or supplier describes composition, properties or toxicity
8.___ Description of manufacturing process
    ____ Statement of whether batch or continuous process
    ____ Relative amounts of beginning materials and order in which they are added
    ____ Description of equipment
    ____ Description of physical conditions (temperature, pressure, humidity) controlled in each step and the parameters that are maintained
    ____ Statement of whether process involves intended chemical reactions

62 Analysis and Certification of Product Ingredients

ACCEPTANCE CRITERIA

The following criteria apply to the technical grade of the active ingredient being reregistered. Use a table to present the information in items 6, 7, and 8.

Does your study meet the following acceptance criteria?

1.___ Five or more representative samples (batches in case of batch process) analyzed for each active ingredient and all impurities present at ≥ 0.1%
2.___ Degree of accountability or closure ≥ ca 98%
3.___ Analyses conducted for certain trace toxic impurities at lower than 0.1% (examples, nitrosamines in the case of products containing dinitroanilines or containing secondary or tertiary amines/alkanolamines plus nitrites; polyhalogenated dibenzodioxins and dibenzofurans) [Note that in the case of nitrosamines both fresh and stored samples must be analyzed.]
4.___ Complete and detailed description of each step in analytical method used to analyze above samples
5.___ Statement of precision and accuracy of analytical method used to analyze above samples
6.___ Identities and quantities (including mean and standard deviation) provided for each analyzed ingredient
7.___ Upper and lower certified limits proposed for each active ingredient and intentionally added inert along with explanation of how the limits were determined
8.___ Upper certified limit proposed for each impurity present at ≥ 0.1% and for certain toxicologically significant impurities at <0.1% along with explanation of how limit determined
9.___ Analytical methods to verify certified limits of each active ingredient and impurities (latter not required if exempt from requirement of tolerance or if generally recognized as safe by FDA) are fully described
10.___ Analytical methods (as discussed in #9) to verify certified limits validated as to their precision and accuracy

61 Product Identity and Composition

GUIDANCE FOR SUMMARIZING STUDIES

The following criteria apply to the technical grade of the active ingredient being reregistered. Items 1, 2, 3, and 5 can be satisfied for most registered products by submission of the Certified Statement of Formula Ingredients Page (EPA Form 8570-4). Items 7 and 8 can be satisfied for most technical grade active ingredients (TGAIs) by submission of a flow chart with chemical equations for each intended chemical reaction. The flow chart should include complete chemical structures and names for each reactant and product of all the reactions.

1. Name of technical material (include product name and trade name, if appropriate).
2. Description of each active and intentionally-added inert ingredient, including name, concentration, and certified limits.
3. Name and upper limit for all impurities present at $\geq$ 0.1% and those toxicologically significant impurities present at <0.1%.
4. The purpose of each active and intentionally-added inert ingredient.
5. Chemical name and Registry Number for each active and intentionally-added inert ingredient (if available).
6. Molecular, structural, and empirical formulas, molecular weight, and any experimental or internal code number for each active ingredient.
7. Description of each beginning material in the manufacturing process.
8. Description of manufacturing process.
9. Discussion of formation of impurities based on established chemical theory.

63 Physical and Chemical Characteristics

ACCEPTANCE CRITERIA

The following criteria apply to the technical grade of the active ingredient being reregistered.

Does your study meet the following acceptance criteria?

63-2 Color

___ Verbal description of coloration (or lack of it)
___ Any intentional coloration also reported in terms of Munsell color system

63-3 Physical State

___ Verbal description of physical state provided using terms such as "solid, granular, volatile liquid"
___ Based on visual inspection at about 20-25° C

63-4 Odor

___ Verbal description of odor (or lack of it) using terms such as "garlic-like, characteristic of aromatic compounds"
___ Observed at room temperature

63-5 Melting Point

___ Reported in C°
___ Any observed decomposition reported

63-6 Boiling Point

___ Reported in C°
___ Pressure under which B.P. measured reported
___ Any observed decomposition reported

63-7 Density, Bulk Density, Specific Gravity

___ Measured at about 20-25° C
___ Density of technical grade active ingredient reported in g/ml or the specific gravity of liquids reported with reference to water at 20° C. [Note: Bulk density of registered products may be reported in lbs/ft^3 or lbs/gallon.]

62 Analysis and Certification of Product Ingredients

GUIDANCE FOR SUMMARIZING STUDIES

The following criteria apply to the technical grade of the active ingredient being reregistered.

1. Number of representative samples analyzed for all active ingredients and all impurities at $\geq$ 0.1%.

2. Degree of accountability or closure in analyses in item #1.

3. Chemical names of toxic impurities which were analyzed for levels <0.1%.

4. Brief description(s) of analytical method(s) used to measure active ingredients and impurities in items #1 and #3.

5. Statement of precision and accuracy of method(s) in item #4.

6. Chemical name and quantities observed (range, mean, standard deviation) for each ingredient (actives and impurities) analyzed in item #1.

7. Proposed upper and lower certified limits for each active ingredient and intentionally added inert with brief explanation of how limits were determined.

8. Proposed upper certified limit for each impurity present at >=0.1% and certain toxicologically significant impurities at <0.1% with brief explanation of how limits were determined.

9. Brief description of analytical method(s) used to verify certified limits (if same methods as item #4, may reference latter).

10. Statement of precision and accuracy of method(s) in item #9 (may reference item #5 if applicable).

63 Physical and Chemical Characteristics

GUIDANCE FOR SUMMARIZING STUDIES

The following criteria apply to the technical grade of the active ingredient being reregistered.

1. Description of color.
2. Description of physical state.
3. Description of odor.
4. Indication of melting point (in C°).
5. Indication of boiling point (in C°).
6. Indication of density, bulk density, and specific gravity.
7. Indication of solubility.
8. Indication of vapor pressure.
9. Indication of dissociation constant.
10. Indication of octanol/water partition coefficient.
11. Indication of PH.
12. Description of stability.

63-8 Solubility

___ Determined in distilled water and representative polar and non-polar solvents, including those used in formulations and analytical methods for the pesticide

___ Measured at about 20-25° C

___ Reported in g/100 ml (other units like ppm acceptable if sparingly soluble)

63-9 Vapor Pressure

___ Measured at 25° C (or calculated by extrapolation from measurements made at higher temperature if pressure too low to measure at 25° C)

___ Experimental procedure described

___ Reported in mm Hg (torr) or other conventional units

63-10 Dissociation Constant

___ Experimental method described

___ Temperature of measurement specified (preferably about 20 - 25° C)

63-11 Octanol/water Partition Coefficient

___ Measured at about 20-25° C

___ Experimentally determined and description of procedure provided (preferred method-45 Fed. Register 77350)

___ Data supporting reported value provided

63-12 pH

___ Measured at about 20 - 25° C

___ Measured following dilution or dispersion in distilled water

63-13 Stability

___ Sensitivity to metal ions and metal determined

___ Stability at normal and elevated temperatures

___ Sensitivity to sunlight determined

SUBDIVISION F

Guideline	Study Title
81-1	Acute Oral Toxicity in the Rat
81-2	Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig
81-3	Acute Inhalation Toxicity in the Rat
81-4	Primary Eye Irritation in the Rabbit
81-5	Primary Dermal Irritation Study
81-6	Dermal Sensitization in the Guinea Pig
81-7	Acute Neurotoxicity in the Hen

81-1 Acute Oral Toxicity in the Rat

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g. solid, liquid, percent AI in technical, end-use product, etc.
2. The number of animals/dose/sex tested.
3. Dosing route and regimen.
4. Vehicle used
5. Doses tested and results
6. Individual observations on day of dosing and for at least 14 days.
7. Summarization of body weights
8. Summarization of gross necropsy
9. Significance of changes from the Acceptance Criteria

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc)
2.____ At least 5 young adult rats/sex/group
3.____ Dosing, single oral may be administered over 24 hrs.
4.*____ Vehicle control if other than water.
5.____ Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6.____ Individual observations at least once a day.
7.____ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
8.____ Individual daily observations.
9.____ Individual body weights.
10.____ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g., solid, liquid, percent AI in technical, end-use product, etc.
2. The number of animals/sex/dose
3. Weight range of animals
4. Verification of single, dermal exposure
5. Duration of dermal exposure
6. Statement of vehicle control
7. Doses tested and results
8. Preparation of application site
9. Area of application site (percent body surface)
10. Occlusion of test material on application site
11. Individual observations on day of dosing and for at least 14 days or until all animals appear normal (whichever is longer).
12. Summarization of body weights
13. Summarization of gross necropsy
14. Significance of changes from Acceptance Criteria

81-2 Acute Dermal toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1._____ Identify material tested (technical, end-use product, etc)

2._____ At least 5 animals/sex/group

3.*_____ Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.

4._____ Dosing, single dermal.

5._____ Dosing duration at least 24 hours.

6.*_____ Vehicle control, only if toxicity of vehicle is unknown.

7._____ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).

8._____ Application site clipped or shaved at least 24 hours before dosing

9._____ Application site at least 10% of body surface area.

10._____ Application site covered with a porous nonirritating cover to retain test material and to prevent ingestion.

11._____ Individual observations at least once a day.

12._____ Observation period to last at least 14 days.

13._____ Individual body weights.

14._____ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

81-3 Acute Inhalation Toxicity in the Rat

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g., solid, liquid, percent AI in technical, end-use product, etc.
2. Statement of the inhalability of test substance
3. The number of animals/sex/dose
4. Duration of inhalation exposure
5. Number of chamber air changes/hour and the percent oxygen content of chamber air
6. Ranges for chamber air temperature and relative humidity
7. Air flow rate
8. Analytical concentrations of test material in breathing zone
9. Results of aerosol particle-size determination
10. Doses tested (or limit dose of 5mg/L or highest attainable)
11. Individual observations on day of dosing and for at least 14 days.
12. Summarization of body weights
13. Summarization of gross necropsy
14. Significance of changes from Acceptance Criteria

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc)
2.____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3.____ At least 5 young adult rats/sex/group
4.____ Dosing, at least 4 hours by inhalation.
5.____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6.____ Chamber temperature, 22° C (±2), relative humidity 40-60%.
7.____ Monitor rate of air flow
8.____ Monitor actual concentrations of test material in breathing zone.
9.____ Monitor aerodynamic particle size for aerosols.
10.____ Doses tested, sufficient to determine a toxicity category or a limit dose (5 mg/L actual concentration of respirable substance).
11.____ Individual observations at least once a day.
12.____ Observation period to last at least 14 days.
13.____ Individual body weights.
14.____ Gross necropsy on all animals.

81-4 Primary Eye Irritation in the Rabbit

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g., solid, liquid, percent AI in technical, end-use product, etc.
2. State if material is corrosive, cause severe dermal irritation or has a pH of <2 or >11.5
3. Number of adult rabbits tested
4. State method of dosing, i.e., instillation into the conjunctival sac of one eye per animal
5. Dose administered
6. Note whether solid or granular test material has been ground to a fine dust
7. State whether eyes were washed and at what time post instillation (not less than 24 hours)
8. State whether eyes were examined and graded for irritation before dosing and at what periods after dosing
9. Individual daily observations afterwards, until eyes are normal or for 21 days
10. Significance of changes from Acceptance Criteria

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc)
2.____ Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.____ 6 adult rabbits
4.____ Dosing, instillation into the conjunctival sac of one eye per animal.
5.____ Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6.____ Solid or granular test material ground to a fine dust.
7.____ Eyes not washed for at least 24 hours.
8.____ Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9.*___ individual daily observations.

Criteria marked with a * are supplemental and may not be required for every study.

81-5 Primary Dermal Irritation Study

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g., solid, liquid, percent AI in technical, end-use product, etc.
2. State if material is corrosive, has a pH <2 or >11.5, or has a dermal LD 50 <200 mg/kg
3. Number of adult animals tested
4. Amount applied
5. Duration of dermal exposure
6. Preparation of application site (shaved or clipped at specified time before dosing)
7. Area of application site
8. Method for occlusion of application site
9. Note removal of test material and if skin was washed with water
10. State times post application when site was graded for irritation
11. Individual observations for day of dosing and individual daily observations thereafter
12. Significance of changes from Acceptance Criteria.

81-5 Primary Dermal Irritation Study

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1._____ Identify material tested (technical, end-use product, etc)
2._____ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3._____ 6 adult animals.
4._____ Dosing, single dermal.
5._____ Dosing duration 4 hours.
6._____ Application site shaved or clipped at least 24 hours prior to dosing
7._____ Application site approximately 6 cm.
8._____ Application site covered with a gauze patch held in place with nonirritating tape
9._____ Material removed, washed with water, without trauma to application site
10._____ Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 days (whichever is shorter).
11.*____ Individual daily observations.

Criteria marked with a * are supplemental and may not be required for every study.

81-6 Dermal Sensitization in the Guinea Pig

GUIDANCE FOR SUMMARIZING STUDIES

1. The form of pesticide tested, e.g., solid, liquid, percent AI in technical, end-use product, etc.
2. State if material is corrosive or has pH <2 or >11.5.
3. State specific method utilized
4. Complete description of specific method
5. Reference for the specific method employed
6. Note adherence of the protocol to that in the reference for the specific method utilized
7. State the positive control tested
8. Significance of changes from Acceptance Criteria

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

dose your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc)
2.____ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3.____ One of the following methods is utilized;
   _____ Freund's complete adjuvant test
   _____ Guinea pig maximization test
   _____ Split adjuvant technique
   _____ Buehler test
   _____ Open epicutaneous test
   _____ Mauer optimization test
   _____ Footpad technique in guinea pig
4.____ Complete description of test
5.*___ Reference for test.
6.____ Test followed essentially as described in reference document.
7.____ Positive control included (may provide historical data conducted within the last 6 months)

Criteria marked with a * are supplemental and may not be required for every study.

81-7 Acute Neurotoxicity in the Hen

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Study performed on an organophosphate cholinesterase inhibiting compound.
2.____ Technical form of the active ingredient tested.
3.*____ Positive control utilized.
4.____ Species utilized, domestic laying hen 8-14 months of age.
5.____ Dosing oral by gavage or capsule (dermal or inhalation may be used).
6.____ An acute oral LD is determined.
7.____ Dose tested equal to an acute oral LD or a limit test of 5000 mg/kg.
8.*____ Dosed animals may be protected with atropine and/or 2-PAM.
9.____ Sufficient test animals so that at least 6 survive.
10.____ Negative (vehicle) control group of at least 6 hens
11.*____ Positive control of at least 4 hens. (if used)
12.____ Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
13.____ Observation period 21 days after each dose.
14.____ Individual daily observations.
15.____ Individual body weights.
16.____ Individual necropsy not required.
17.____ Histopathology performed on all animals. Tissue to be fixed in sin preferably using whole animal perfusion techniques. At least three sections of each of the following tissues:
____brain, including medulla oblongata
____spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
____tibial nerve; proximal regions and branches
____sciatic nerve

Criteria marked with a * are supplemental and may not be required for every study.

ATTACHMENT F

List of Registrants sents this DCI

United States Environmental Protection Agency
Washington, D. C. 20460

LIST OF ALL REGISTRANTS SENT THIS DATA CALL-IN NOTICE

Case # and Name: 0655 Oxytetracycline

Co. Nr.	Company Name	Additional Name	Address	City & State	Zip
000618	MERCK & CO INC	AGENT FOR: MERCK & CO INC	HILLSBOROUGH RD	THREE BRIDGES NJ	08887
001007	PFIZER INC. - SPECIALTY CHEMICALS		235 EAST 42ND ST	NEW YORK NY	10017
051946	STAR BRITE CORPORATION		4041 SW 47TH AVENUE	FT. LAUDERDALE FL	33314

ATTACHMENT G

Product Specific Data Call-In Cost Share and Data Compensation Forms

United States Environmental Protection Agency
Washington, DC 20460

CERTIFICATION OF OFFER TO COST SHARE IN THE DEVELOPMENT OF DATA

Form Approved
OMB No. 2070-0106
Approval Expires 12-31-92

Please fill in blanks below.

Company Name	Company Number
Chemical Name	EPA Chemical Number

I Certify that:

My company is willing to develp and submit the data required by EPA under the authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), if necessary. However, my company would prefer to enter into an agreement with one or more registrants to develop jointly or share in the cost of developing data.

My firm has offered in writing to enter into such an agreement. That offer was irrevocable and included an offer to be bound by arbitration decision under section 3(c)(2)(B)(iii) of FIFRA if final agreement on all terms could not be reached otherwise. This offer was made to the following firm(s) on the following date(s):

Name of Firm(s)	Date of Offer

Certification:

I certify that I am duly authorized to represent the company name above, and that the statements that I have made on this form and all attachments therein are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature of Company's Authorized Representative	Date
Name and Title (Please Type or Print)	

EPA Form 8570-32 (5-91) Replaces EPA Form 8580-6, which is obsolete

EPA Form 8570-31 (4-90)

US Environmental Protection Agency
Washington, DC 20460

EPA

Product Specific Data Report

Registration Standard for:	EPA Registration Number	Form Approved OMB #2070-0057 Expires 11-30-89

Registration Guideline No.	Name of Test	Testing not required for my product listed above (Check below)	I am complying with Data Requirements by - Citing MR ID No.	Submitting Data (Attached) (Check below)	(For EPA Use Only) Accession numbers assigned
Sec. 158.120 Product Chemistry					
61-1	Identity of ingredients				
61-2	Statement of composition				
61-3	Discussion of formation of ingredients				
62-1	Preliminary analysis				
62-2	Certification of limits				
62-3	Analytical methods for enforcement limits				
63-2	Color				
63-3	Physical state				
63-4	Odor				
63-5	Melting point				
63-6	Boiling point				
63-7	Density, bulk-density, or specific gravity				
63-8	Solubility				
63-9	Vapor pressure				
63-10	Dissociation constant				
63-11	Octanol/water partition coefficient				
63-12	pH				
63-13	Stability				
63-14	Oxidizing/reducing reaction				
63-15	Flammability				
63-16	Explodability				
63-17	Storage stability				
63-18	Viscosity				
63-19	Miscibility				
63-20	Corrosion Characteristics				
63-21	Dielectric breakdown voltage				
Sec. 158.135 Toxicology					
81-1	Acute oral toxicity, rat				
81-2	Acute dermal toxicity, rabbit				
81-3	Acute inhalation toxicity, rat				
81-4	Primary eye irritation, rabbit				
81-5	Primary dermal irritation				
81-6	Dermal sensitization				

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Typed Name and Title	Signature	Date