United States
Environmental Protection
Agency

Prevention, Pesticides
And Toxic Substances
(7508C)

EPA 738-R-99-007
November 1999

Reregistration Eligibility Decision (RED)

3-Trifluoro-Methyl-4-Nitro-Phenol and Niclosamide

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

CERTIFIED MAIL

Dear Registrant:

I am pleased to announce that the Environmental Protection Agency has completed its reregistration eligibility review and decisions on the pesticide chemical case for the active ingredients TFM and Niclosamide. The enclosed Reregistration Eligibility Decisions (REDs), which were approved on September 30, 1999, contain the Agency's evaluation of the data base of these chemicals, its conclusions of the potential human health and environmental risks of the current product uses, and its decisions and conditions under which these uses and products will be eligible for reregistration. The RED includes the data and labeling requirements for products for reregistration. It may also include requirements for additional data (generic) on the active ingredients to confirm the risk assessments.

To assist you with a proper response, read the enclosed document entitled "Summary of Instructions for Responding to the RED." This summary also refers to other enclosed documents which include further instructions. You must follow all instructions and submit complete and timely responses. **The first set of required responses is due 90 days from the receipt of this letter. The second set of required responses is due 8 months from the date of this letter.** Complete and timely responses will avoid the Agency taking the enforcement action of suspension against your products.

If you have questions on the product specific data requirements or wish to meet with the Agency, please contact the Special Review and Reregistration Division representative Linda Propst at (703) 308-8165. Address any questions on required generic data to the Special Review and Reregistration Division representative Laura Parsons at (703) 305-5776.

Sincerely yours,

Lois A. Rossi, Director
Special Review and
Reregistration Division

Enclosures

SUMMARY OF INSTRUCTIONS FOR RESPONDING TO THE REREGISTRATION ELIGIBILITY DECISION (RED)

1. **DATA CALL-IN (DCI) OR "90-DAY RESPONSE"**--If **generic data** are required for reregistration, a DCI letter will be enclosed describing such data. If **product specific data** are required, a DCI letter will be enclosed listing such requirements. If **both generic and product specific data** are required, a combined Generic and Product Specific DCI letter will be enclosed describing such data. However, if you are an end-use product registrant only and have been granted a generic data exemption (GDE) by EPA, you are being sent only the **product specific** response forms (2 forms) with the RED. Registrants responsible for generic data are being sent response forms for both generic and product specific data requirements (4 forms). **You must submit the appropriate response forms (following the instructions provided) within 90 days of the receipt of this RED/DCI letter; otherwise, your product may be suspended.**

2. **TIME EXTENSIONS AND DATA WAIVER REQUESTS**--No time extension requests will be granted for the 90-day response. Time extension requests may be submitted only with respect to actual data submissions. Requests for time extensions for product specific data should be submitted in the 90-day response. Requests for data waivers must be submitted as part of the 90-day response. All data waiver and time extension requests must be accompanied by a full justification. All waivers and time extensions must be granted by EPA in order to go into effect.

3. **APPLICATION FOR REREGISTRATION OR "8-MONTH RESPONSE"**--**You must submit the following items for each product within eight months of the date of this letter (RED issuance date).**

a. **Application for Reregistration** (EPA Form 8570-1). Use only an original application form. Mark it "Application for Reregistration." Send your Application for Reregistration (along with the other forms listed in b-e below) to the address listed in item 5.

b. **Five copies of draft labeling** which complies with the RED and current regulations and requirements. Only make labeling changes which are required by the RED and current regulations (40 CFR 156.10) and policies. Submit any other amendments (such as formulation changes, or labeling changes not related to reregistration) separately. You may, but are not required to, delete uses which the RED says are ineligible for reregistration. For further labeling guidance, refer to the labeling section of the EPA publication "General Information on Applying for Registration in the U.S., Second Edition, August 1992" (available from the National Technical Information Service, publication #PB92-221811; telephone number 703-605-6000).

c. **Generic or Product Specific Data**. Submit all data in a format which complies with PR Notice 86-5, and/or submit citations of data already submitted and give the EPA identifier (MRID) numbers. Before citing these studies, you must **make sure that they meet the Agency's acceptance criteria** (attached to the DCI).

d. **Two copies of the Confidential Statement of Formula (CSF)** for each basic and each alternate formulation. The labeling and CSF which you submit for each product must comply with P.R.

Notice 91-2 by declaring the active ingredient as the **nominal concentration**. 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). A copy of the CSF is enclosed; follow the instructions on its back.

e. **Certification With Respect to Data Compensation Requirements**. Complete and sign EPA form 8570-31 for each product.

4. **COMMENTS IN RESPONSE TO FEDERAL REGISTER NOTICE**--Comments pertaining to the content of the RED may be submitted to the address shown in the Federal Register Notice which announces the availability of this RED.

5. **WHERE TO SEND PRODUCT SPECIFIC DCI RESPONSES (90-DAY) AND APPLICATIONS FOR REREGISTRATION (8-MONTH RESPONSES)**

By U.S. Mail:

Document Processing Desk **(RED-SRRD-PRB)**
Office of Pesticide Programs (7504C)
EPA, 401 M St. S.W.
Washington, D.C. 20460-0001

By express:

Document Processing Desk **(RED-SRRD-PRB)**
Office of Pesticide Programs (7504C)
Room 266A, Crystal Mall 2
1921 Jefferson Davis Hwy.
Arlington, VA 22202

6. **EPA'S REVIEWS**--EPA will screen all submissions for completeness; those which are not complete will be returned with a request for corrections. EPA will try to respond to data waiver and time extension requests within 60 days. EPA will also try to respond to all 8-month submissions with a final reregistration determination within 14 months after the RED has been issued.

REREGISTRATION ELIGIBILITY DECISION

3-Trifluoro-Methyl-4-Nitro-Phenol

CASE 3082

and

Niclosamide

CASE 2455

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TFM AND NICLOSAMIDE REREGISTRATION ELIGIBILITY DECISION TEAM

Office of Pesticide Programs:

Biological and Economic Analysis

Arnold Aspelin	LUIS Representative for TFM
Richard Peacock	LUIS Representative for Niclosamide
William Gross	Herbicide and Insecticide Branch
Timothy Kiely	Economic Analysis Branch

Environmental Fate and Effects Assessment

Thomas Steeger	Environmental Risk Branch IV
Dana Spatz	Environmental Risk Branch IV

Health Effects Risk Assessment

William Hazel	Reregistration Branch 1
Whang Phang	Reregistration Branch 1
Virginia Dobozy	Reregistration Branch 1
Jeffery Dawson	Reregistration Branch 1

Registration Support

Daniel Peacock	Rodenticide and Insecticide Branch

Risk Management

Laura Parsons	Reregistration Branch I
Mark Wilhite	Reregistration Branch I

GLOSSARY OF TERMS AND ABBREVIATIONS

ADI	Acceptable Daily Intake. A now defunct term for reference dose (RfD).
AE	Acid Equivalent
a.i.	Active Ingredient
ARC	Anticipated Residue Contribution
CAS	Chemical Abstracts Service
CI	Cation
CNS	Central Nervous System
CSF	Confidential Statement of Formula
DFR	Dislodgeable Foliar Residue
DRES	Dietary Risk Evaluation System
DWEL	Drinking Water Equivalent Level (DWEL) The DWEL represents a medium specific (i.e. drinking water) lifetime exposure at which adverse, non carcinogenic health effects are not anticipated to occur.
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
FAO/WHO	Food and Agriculture Organization/World Health Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GLC	Gas Liquid Chromatography
GM	Geometric Mean
GRAS	Generally Recognized as Safe as Designated by FDA
HA	Health Advisory (HA). The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.
HDT	Highest Dose Tested
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg 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, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LD_{lo}	Lethal Dose-low. Lowest Dose at which lethality occurs.
LEL	Lowest Effect Level
LOC	Level of Concern
LOD	Limit of Detection
LOEL	Lowest Observed Effect Level
LOAEL	Lowest Observed Adverse Effect Level
LUIS	Label User Information System
MATC	Maximum Acceptable Toxicant Concentration
MCLG	MaximumContaminant Level Goal (MCLG) The MCLG is used by the Agency to regulate contaminants in drinking water under the Safe Drinking Water Act.
µg/g	Micrograms Per Gram
Fg/L	Micrograms per liter
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MP	Manufacturing-Use Product

MPI	Maximum Permissible Intake
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.
N/A	Not Applicable
NOEC	No Observable Effect Concentration
NPDES	National Pollutant Discharge Elimination System
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
OP	Organophosphate
OPP	Office of Pesticide Programs
Pa	pascal, the pressure exerted by a force of one newton acting on an area of one square meter.
PADI	Provisional Acceptable Daily Intake
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRN	Pesticide Registration Notice
Q^*_1	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RS	Registration Standard
RUP	Restricted Use Pesticide
SLN	Special Local Need (Registrations Under Section 24 © of FIFRA)
TC	Toxic Concentration. The concentration at which a substance produces a toxic effect.
TD	Toxic Dose. The dose at which a substance produces a toxic effect.
TEP	Typical End-Use Product
TGAI	Technical Grade Active Ingredient
TLC	Thin Layer Chromatography
TMRC	Theoretical Maximum Residue Contribution
torr	A unit of pressure needed to support a column of mercury 1 mm high under standard conditions.
WP	Wettable Powder
WPS	Worker Protection Standard

EXECUTIVE SUMMARY

EPA has completed its reregistration eligibility decisions for the pesticides trifluoro-4-nitro-m-cresol (TFM; Case 3082) and niclosamide (Case 2455) and determined that all lampricide uses, when labeled and used as specified in this document, are eligible for reregistration. There are two Special Local Needs labels for niclosamide which are eligible for reregistration assuming monitoring programs similar to those conducted by the U.S. Fish and Wildlife Service (USFWS) are instituted for these uses. The public health mollusicide use of niclosamide against snails that carry vectors for swimmer's itch has been voluntarily canceled by the registrant. The public health use for use of niclosamide against snails that carry vectors for schistosomiasis is ineligible for reregistration at this time. These reregistration eligibility decisions include a comprehensive reassessment of the required target data base supporting the use patterns of currently registered products.

This document contains the reregistration eligibility decisions for two compounds which are used alone or in combination against the same pest. TFM is the main chemical used to kill sea lamprey larvae in tributaries to the Great Lakes, the Finger Lakes, and Lake Champlain. Niclosamide is used to kill sea lamprey larvae in combination with TFM; granular niclosamide is also used in situations where TFM would not be appropriate, such as very deep waters, where it is cost prohibitive to treat the entire water column. Tributaries are screened for larvae which are ready to transform to the adult stage and when populations are high enough, the stream is treated. Streams harboring sea lamprey larvae are treated once every three to five years. Additionally, niclosamide is used as a mollusicide to kill freshwater snails which are vectors for human and fish disease agents.

There are no tolerances for TFM and niclosamide because the Agency considers the uses of these compounds to be non-food. Based on current use pattens and exposure profiles, residues in and on food and/or feed or in drinking water are not expected to occur. Therefore, a dietary risk assessment is not required.

Human risks from exposures to TFM and niclosamide do not exceed levels of concern for the currently registered uses. The USFWS exerts tight control over the use of these compounds including: (I) public notification prior to treating Great Lake tributaries to eliminate exposure to riparian water users including fishermen, boaters, and swimmers; (ii) dissemination of information describing the treatment programs and the associated application locations, dates, and duration; (iii) constant monitoring of the treated stream for TFM and niclosamide concentrations during treatment; (iv) if requested by a given state, concentrations at public water utility intakes are monitored and notification of state and local officials is made regarding monitoring results to permit implementation of activated charcoal use, if necessary; and (v) prohibition of irrigation during treatment.

There are ecological concerns with the use of these compounds since impacts are expected to non-target aquatic organism populations; however, the benefits of controlling the populations of the introduced sea lamprey are expected to outweigh the risks to aquatic organisms. Most nontarget species are far less sensitive to the lampricides than are sea lampreys, and only a few are as sensitive. Pretreatment assessments that determine abundance and distribution of sea lamprey larvae are used to identify specific

streams and stream reaches that require lampricide treatment. Sensitive nontarget species in the streams are identified prior to treatment, and measures are taken to protect them during applications of lampricides. Threatened or endangered species are identified through consultation with state and federal agencies. Procedures then are modified or developed, and employed to protect these species. Prior to treatment, toxicity tests and in-stream studies assess the effects of treatment on sensitive species or species of concern, and the results indicate if a modification of treatment procedures is required to assure the safety of nontarget organisms.

The USFWS which holds the registrations for these compounds has refined the use practices over the past several years in order to lower the impacts of these applications on non-target organisms and to lower occupational and non-occupational exposure to people. Additional mitigation required by the Agency includes minor clarifications of label language. Aerial applications were prohibited on some of the current labels and will be prohibited on all new labels in order to lessen chances of nontarget human and other terrestrial animal exposures to these restricted use compounds.

Some additional data are required to understand the photodegradation potential of TFM and niclosamide in water, and the aerobic and anaerobic aquatic behavior of niclosamide. The following data requirements are being held in reserve pending the results of an ongoing monitoring study the USFWS is currently conducting: the potential chronic effects of TFM and TFM/niclosamide mixture on fish and aquatic invertebrates, and the chronic sediment toxicity of niclosamide.

Before reregistering the products containing TFM and niclosamide, the Agency is requiring that product specific data, revised Confidential Statements of Formula (CSF), and revised labeling be submitted within eight months of the issuance of this document. These data include product chemistry and acute toxicity testing for each registration. After reviewing these data and any revised labels and finding them acceptable in accordance with Section 3(c)(5) of FIFRA, the Agency will reregister a product. 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.

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 development and the submission of data to fulfill the requirements. The fifth phase is a review by the U.S. Environmental Protection Agency (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 ingredients 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 evaluate whether the pesticide meets the "no unreasonable adverse effects" criterion of FIFRA.

This document presents the Agency's decision regarding the reregistration eligibility of the registered uses of TFM and niclosamide. The document consists of six sections. Section I is the introduction. Section II describes TFM and niclosamide, their uses, data requirements, and regulatory history. Section III discusses the human health and environmental assessment based on the data available to the Agency. The human health assessment for TFM is discussed first, followed by the human health assessment for niclosamide. Next the environmental fate and ecotoxicity assessment of TFM is followed by this assessment for niclosamide. The final topic of Section III is a combined exposure and risk characterization of the two chemicals. Section IV presents the reregistration decision for TFM and niclosamide. Section V discusses the reregistration requirements for TFM and niclosamide. Finally, Section VI contains the Appendices which support this Reregistration Eligibility Decision. Additional details concerning the Agency's review of applicable data are available on request.

II. CASE OVERVIEW

A. Chemical Overview

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

- **Common Name:** Lampricid®, TFM
- **Chemical Name:** 3-Trifluoromethyl-4-nitrophenol (IUPAC)
  ",","-trifluoro-4-nitro-m-cresol, sodium salt (CAS)
- **Chemical Family:** phenol
- **CAS Registry Number:** 88-30-2

! **OPP Chemical Code:** 036201
! **Empirical Formula:** $C_7H_4F_3NO_3$
! **Basic Manufacturer:** Clariant International (Germany)
H & S Chemical Company,

packed for USFWS (USA) and Fisheries and Oceans Canada, Ottawa, Ontario (Canada).

! **Common Name:** Bayluscide, niclosamide
! **Chemical Name:** 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (IUPAC)
2-amino ethanol salt of 2',5'-dichloro-4'-nitro salicylanilide (CAS)
! **Chemical Family:** halogenated mononitrobenzamide
! **CAS Registry Number:** 1420-04-8
! **OPP Chemical Code:** 077401
! **Empirical Formula:** $C_{13}H_8Cl_2N_2O_4$
! **Basic Manufacturer:** Bayer, Specialty Products, Inc.

packed for USFWS (USA) and Fisheries and Oceans Canada, Ottawa, Ontario (Canada).

B. Use Profile

TFM and Niclosamide:

Type of Pesticide: lampricides
Use Sites: tributaries to the Great Lakes, the Finger Lakes and Lake Champlain
Target Pests: Larval stage of the Sea Lamprey (*Petromyzon marinus*)
Formulation Types:
TFM: Liquid concentrate (38%), Bar (solid)
Niclosamide 70% Wettable Powder, Granular (3.2% and 5%)

Niclosamide

Type of Pesticide: Mollusicide for use against fresh water snails
Use Sites: Special Local Needs labels: Commercial ponds for growing ornamental fish in FL and AR
Public Health Uses: Swimmer's Itch in MI, MN and WI, Schistosomiasis in Puerto Rico

Formulation Types: 70% Wettable Powder in FL, AR, and Puerto Rico
5% Granular in MI, MN, and WI

Method and Rates of Application:

TFM is the primary chemical used to control sea lamprey; niclosamide is used with TFM under circumstances when TFM alone would pose too much risk to non-target organisms or would be cost prohibitive. Niclosamide alone is also used as a survey tool for determining lamprey larval populations and under certain conditions alone to treat deep, turbid waters. Specific application instructions and formulas for application rates are included in the *Manual for Application of Lampricides in the U.S. Fish and Wildlife Service Sea Lamprey (Petromyzon Marinus) Control Program including Standard Operating Procedures (1993).* The different application methods complement each other to achieve effective control. There are various non-chemical means of control, such as weirs, traps, and a sterile male release program in place, but these non-chemical methods are not adequate to control lamprey populations without the use of TFM and niclosamide.

The liquid sodium salt formulation of TFM accounts for the majority of the applications. Most of these liquid TFM applications are made with a direct-siphoning meter pump system in which the liquid formulation is withdrawn from 5-gallon containers and routed directly into the treated stream. A rapid calculation for larger bodies of water is 1 ppm TFM in 1 acre-foot of water requires 0.75 gallons of TFM per surface area treated. Liquid TFM is also applied to many stagnant bodies of water that are connected to or isolated from the main river during treatment by backpack sprayer or by boat.

The TFM bar formulation is sometimes applied to small springs and tributaries to give a controlled release of TFM over a period of time. The rate of release depends on water velocity and temperature. Each bar is used to treat 0.25 ft^3 per second of discharge at 1 ppm for 8 hours at 18EC or 0.8 ppm for 10 hours at 12EC. For best results, the USFWS manual recommends that TFM bars should be suspended at least one inch above the stream bottom to permit movement of water on all sides and should be placed where current velocity is < 0.5 feet per second.

The wettable powder (WP) formulation of niclosamide is generally used to make a liquid slurry which is not to exceed 20 pounds of the 70 WP (14 lb ai) in 100 gallons of water. Additionally, the concentration in the treated stream should not exceed 2 percent of the corresponding TFM concentration. The slurries are prepared in an open system and since niclosamide is not readily soluble in water, the slurry is constantly agitated and is delivered to the water surface by a peristaltic pump.

Applications of the granular 3.2% niclosamide formulation are used as a survey tool to "detect and collect sea lamprey larvae in deep and turbid waters where electrofishing is ineffective." Applications are made using a gasoline powered backpack blower device that spreads the granules over a wide area. This formulation can also be used in specific treatment areas where the water depth makes the use of TFM cost prohibitive.

Decisions regarding application rates and times are based on both abiotic and biotic factors including pH, stream discharge, time of day, temperature, total alkalinity, in-field bioassays, and lamprey population assessment data. Spreadsheet-based models incorporating the aforementioned factors have been developed to assist in determining application rates; the inter-relationship of the model input parameters is based on historical data collected from previous applications to specific streams and, as such, these predictive models are stream specific. Predicted treatment concentrations based on physico-chemical data are then modified based on in-field flow-through bioassays used to establish the site-specific $LC_{99.9}$ for sea lamprey larvae and the LC_{25} for brown trout. In Lake Superior and upper Lake Michigan, streams tend to have soft water with pH less than 8.2 and thus require lower application rates and are less likely to be candidates for niclosamide treatment. In the lower tier of the Great Lake, tributaries harboring lamprey may exhibit hardnesses exceeding 200 ppm with a pH range 8.1 - 8.7. These streams tend to have greater diurnal pH fluctuations and may require that lampricide applications be adjusted to reflect changing pH.

The manual states that while water concentrations of TFM are not to exceed 12 ppm, typical target concentrations are generally 1 to 6 ppm. Niclosamide target concentrations in hard water streams have ranged from 25 to 35 ppb; however, treatment concentrations are not allowed to exceed 50 ppb (personal communication, Dorance Brege, U.S. Fish and Wildlife Service Treatment Supervisor 1999).

The wettable powder formulation of niclosamide is also labeled for use in ornamental fish ponds in Florida and Arkansas. The product is applied to the bottom of drained ponds which are filled immediately. The filled ponds are then allowed to sit undisturbed for at least four days before ornamental fish are added (personal communication Craig Watson, Director, Tropical Aquaculture Laboratory, August,1999).

The Fish and Wildlife Service has made some aerial applications of Bayluscide 3.2% granular formulation to the St. Mary's River in the US and Canada. The application is being made with a helicopter and the rate is similar to the granular application from a boat. This one-time aerial application is to treat 1562 surface acres of the St. Mary's River in Michigan over a three year period from 1998-2000. It is not physically or economically feasible to treat the St Mary's River by boat since the time period when Bayluscide application can be made is very short in order to protect spawning fish and nesting osprey.

C. Estimated Usage of Pesticide

According to the U.S. Fish and Wildlife Service (Johnson and Weisser 1996), of the 5,339 streams tributary to the Great Lakes, only 309 in the US are known to be or have been infested with sea lampreys; there are 130 infested streams in Canada. Of the US streams, about 300 (<6%) have been treated since the chemical control of sea lampreys began in the 1960's. Currently, 166 streams (<3% of the total number of tributaries) are treated on a 3 - 5 year cycle. In a normal treatment year, 30 to 40 U.S. tributaries receive applications of lampricides. An average of approximately 80,000 pounds of TFM active ingredient and approximately 300 pounds of niclosamide active ingredient were applied in the Great Lakes from 1993 to 1997.

Specific use data were received from the USFWS for the years 1993 through 1997. Tables 1 and 2 summarize the use of both compounds during these years.

Table 1: Summary of TFM use by the USFWS in the Great Lakes Region (1993-1997)

Lake	1993	1994	1995	1996	1997
pounds active ingredient used					
Superior	6717	19991	15997	12083	18768
Michigan	18150	31219	25507	29811	22959
Huron	40371	26953	24065	14605	27926
Erie	0	9561	414	5981	2815
Ontario	9438	7026	10307	11001	6442
Total	74676	94750	76290	73481	78910

Table 2: Summary of Niclosamide use by the USFWS in the Great Lakes Region (1993-1997)

Lake	1993	1994	1995	1996	1997
pounds active ingredient used					
Superior	0	53	114	18	197
Michigan	0	251	53	207	103
Huron	74	33	198	16	89
Erie	0	0	0	0	0
Ontario	7	16	0	33	21
Total	81	353	365	274	410

D. Data Requirements

The Agency required the registrants to submit studies as specified in 40 CFR Section 158. Data from these studies are sufficient to characterize the risks associated with the uses described in this document. Appendix B includes all data requirements identified by the Agency for currently registered uses needed to support reregistration.

E. Regulatory History

The sea lamprey (*Petromyzon marinus*) is a primitive eel-like fish distinguished from other fishes by its lack of paired fins and jaws. Sea lampreys are closely related to the hagfish, and are generally found as adults in saltwater. Most of the life of a sea lamprey is spent as a larva burrowed in the sediment of fresh water streams. In this life stage, the animal is not harmful to other fish and feeds by

filtering food from stream water. Sea lampreys may remain in the larval stage from 3 to more than 17 years before transforming into the parasitic (predatory) stage. Parasitic stage lampreys feed by attaching to fish and rasping deep wounds from which they suck blood, body fluids, and pieces of flesh. The results of such attacks are often fatal for the host fish.

Sea lampreys were introduced to the Great Lakes when the Welland Canal around Niagara Falls was constructed in 1829; by the late 1940's, lampreys had severely impacted the commercial and sport fisheries in the Great Lakes. Early attempts to control sea lampreys began in 1953 with the installation of mechanical traps in spawning streams, but these measures were largely unsuccessful. No effective control was accomplished until the advent of a chemical control program with TFM (Lamprecid®) and niclosamide (Bayluscide) in the late 1950's. According to the USFWS "the successful chemical control of sea lampreys has allowed reestablishment of a robust sport and commercial fishery in the Great Lakes." These compounds have been used since that time to manage the sea lamprey populations in the Great Lakes, the Finger Lakes, and Lake Champlain. The use of these chemicals is managed by the Great Lakes Fisheries Commission and its agents. The Commission was established by the *Convention on Great Lakes Fisheries Between the United States of America and Canada* to enhance and protect fisheries in the Great Lakes.

In 1964, the U.S. Department of Agriculture (USDA), the Agency's predecessor for pesticide regulation under FIFRA, registered its first product with TFM, a liquid formulation for control of sea lamprey larvae. In the same year, USDA first registered a product containing niclosamide, a wettable powder formulation for control of sea lamprey larvae and snails. In 1967, USDA registered two manufacturing-use products containing niclosamide. In 1968, USDA registered its first granular niclosamide products for sea lamprey larvae and snail control. In 1984, the EPA registered a new form of TFM, a bar formulation, for sea lamprey control.

Currently the Agency has two registered TFM products, a liquid and bar formulation, for sea lamprey larvae. It has also currently registered seven niclosamide products, five federal (Section 3 under FIFRA) and two Special Local Need (Section 24c under FIFRA) products.

TFM (Lamprecid®) is an aquatic non-food outdoor use chemical. The lampricides (TFM and niclosamide) Phase 4 review dated 03/21/92 summarized regulatory conclusions on the available residue chemistry data and specified that additional data were required for reregistration purposes. Additional submissions of data have been received since the Phase 4 Review was issued. There are currently no tolerances for TFM or niclosamide residues in/on food/feed commodities. The Agency has determined that the TFM residues in fish are parent TFM and the TFM-glucuronide conjugate.

III. SCIENCE ASSESSMENT

A. Physical Chemistry Assessment for TFM

TFM (Lamprecid®) is chemically ",","-trifluoro-4-nitro-m-cresol. Pure TFM is a yellow to orange crystalline solid, with a melting point of 76° C and ionization constant of 4.4×10^{-7}. The TGAI is a dark red-brown liquid with a boiling point of 135-138° C, a density of 1.463 g/mL, and a vapor pressure of 22 mm Hg at 25° C. TFM is soluble in water (0.498 g/100 g water at 25° C), and highly soluble in most organic solvents. Aqueous solutions of TFM are acidic with free phenol (pK = 6.07) and form phenolate salts in alkali conditions.

B. Human Health Assessment for TFM

1. Toxicology Assessment

a. Acute Toxicity

The data on acute mammalian toxicity are summarized in Table 3. TFM has acute oral LD_{50} values of 141 and 160 mg/kg for males and females, respectively (Toxicity Category II). The acute dermal toxicity is minimal, as indicated by a $LD_{50} > 2000$ mg/kg (Toxicity Category III). It produced slight skin irritation (Toxicity Category IV) and caused eye irritation which was cleared within seven days after application (Toxicity Category III). It was not a dermal sensitizer. The acute inhalation data are not available.

Table 3. Summary of the Results of Acute Toxicity Studies on Technical Grade TFM[1]				
GUIDE-LINE #	**STUDY TYPE**	**MRID #**	**RESULTS**	**TOXICITY CATEGORY**
81-1	Acute oral-rat	40999204 41898102	LD_{50} = 160 mg/kg (M) LD_{50} = 141 mg/kg (F);	II
81-2	Acute dermal-rabbit	40999205 41898103	LD_{50} > 2000 mg/kg;	III
81-3	Acute inhalation			Not available
81-4	Primary eye irritation - rabbits	40999207 41898104	Eye irritant (corneal opacity, conjunctival redness, chemosis, & discharge; all clear by day 7 after treatment)	III
81-5	Primary dermal irritation - rabbits	40999206 41898105	Slight erythema seen on the treatment site.	IV
81-6	Dermal sensitization	41898106	Not a dermal sensitizer	

1. The acute toxicity endpoints, listed above, are for informational purposes only. The data supporting these endpoints may or may not meet current acceptability criteria. The acceptability status of these data may be reassessed during product reregistration.

b. Subchronic Toxicity

The results did not show significant toxicity in two 90-day feeding studies in rats and in a 6-month feeding study in dogs.

In a 90-day feeding study in rats (MRID 00112726), groups of weanling SD rats (10/sex/group) were fed diets containing TFM (82.4%) at concentrations of 500, 900, 1620, 2916, or 5248 ppm for 90 day. The control groups (20/sex) received the untreated diet. The results showed that body weight, food consumption, food efficiency, and hematological parameters were similar to those of the controls. Observation data did not indicate any clinical signs in the treated rats. For clinical chemistry, there was a decrease in aspartate aminotransferase (SGOT or AST) in both treated males and females of all groups. However, this change did not show a dose-related effect, and was not considered biologically significant. All other clinical parameters were similar to those of the controls. Organ weights, gross pathology, and histological data did not show a treatment-related effect. The NOAEL for this study was 5248 ppm (525 mg/kg/day, based on 1 ppm=0.1 mg/kg for young rats) which was the highest dose tested. No LOAEL was established.

In a second 90-day feeding study in rats (MRID 00112727), groups of weanling SD rats (10/sex/group) were fed diets containing TFM (90%) at concentrations of 500, 900, 1620, 2916, or 5248 ppm for 90 days. The control groups (20/sex) received the untreated diet. The results showed that body weights of the 2916 and 5248 ppm groups were consistently decreased (10-13%) in males from week 3 to the end of the study. The decrease was statistically significant. Food consumption, and

hematological parameters were similar to those of the controls. Clinical signs were not seen in the treated or control rats. There was a decrease in the aspartate aminotransferase (SGOT) activity in both males and females at 5248 ppm on the 21 day examination period, but by 90 day examination period the SGOT values of 5248 ppm animals were similar to those of the controls. The alkaline phosphatase level was slightly increased in both males and females of 5248 ppm groups, but no statistical significance was found. At sacrifice, liver weights of the 2916 and 5248 ppm females were slightly increased. No gross pathology and histological changes were observed. The LOAEL of this study was 2916 ppm (292 mg/kg/day, based on 1 ppm=0.1 mg/kg/day) based on decreased in body weights; the NOAEL was 1620 ppm (162 mg/kg/day).

A 90-day feeding study in dogs is not available, but there is a 6-month feeding study in dogs. In the 6-month feeding study in dogs (MRID 00112725), groups of beagle dogs (4/sex/dose; 8-10 weeks old) received TFM (85.6%) in the diet at concentrations of 300, 1250, or 5000 ppm for 6 months. The controls (4/sex) received 2% corn oil by weight. The results showed that a decrease in body weights was seen in both males (12-15%) and females (8-16%) of the 5000 ppm level beginning at 10 weeks. The body weight gains in these dogs were also decreased. Food consumption and food efficiency in 5000 ppm males and females also decreased, but not markedly. Clinical signs, hematology, clinical chemistry, and urinalysis values were similar between the control and the treated animals. No treatment-related changes in organ weight were seen in any treatment groups. Treatment-related gross and histological changes were not found in TFM treated dogs. Under the conditions of this study, the LOAEL was 5000 ppm (125 mg/kg/day; based on 1 ppm =0.025 mg/kg/day) based on decreases in body weights and body weight gains; the NOAEL was 1250 ppm (31.25 mg/kg/day).

c. Developmental Toxicity

In a developmental toxicity study (MRID 00131201), pregnant COBS® CD® (SD) Br rats (25/group) received TFM (85.9% a.i.) by gavage at doses of 0 (corn oil vehicle), 25, 125, or 250 mg/kg/day on gestation days (GD) 6-15, inclusive. It was not specified whether doses were adjusted for percent active ingredient. On GD 20, all dams were sacrificed and all fetuses were examined for external malformations/variations. Approximately one-half of each litter was placed in Bouin's fixative for subsequent visceral examination and the remainder stained for skeletal examination.

All animals in the control, low-, and mid-dose groups survived until scheduled sacrifice. Two high-dose dams died during the treatment interval, one on GD 6 and the other on GD 12 and the study author stated that the deaths were treatment related. The only other clinical sign of toxicity was salivation which was observed in 0/25, 0/25, 2/25, and 22/25 (p # 0.01) animals in the 0, 25, 125, and 250 mg/kg/day groups, respectively. There were no significant differences in maternal body weights between the treated and control groups at any time during gestation. Food consumption was not measured. Therefore, the maternal toxicity LOAEL is 250 mg/kg/day based on salivation and mortality. The corresponding maternal toxicity NOAEL is 125 mg/kg/day.

No treatment-related effects were observed for gravid uterine weights, number of fetuses/litter, pre- and postimplantation loss, numbers of corpora lutea/dam, number of implantations/dam,

resorptions/dam, fetal body weights, or fetal sex ratios. No statistically significant differences in the incidence rates of any external, visceral, or skeletal malformations/variations were observed in the treated litters as compared to the controls. Therefore, the NOAEL for developmental toxicity is 250 mg/kg/day (highest dose tested).

d. Mutagenicity

The available mutagenicity studies showed that TFM did not induce mutation in Ames assays (MRID 42551801). TFM was shown to be negative in a mouse micronucleus assay *(in vivo)* (MRID 42187101) and in an unscheduled DNA synthesis assay with primary rat hepatocytes (MRID 40999202). However, TFM produced chromosomal aberrations in an *in-vitro* cytogenetic assay in CHO cells, in the presence and absence of metabolic activation (MRID 40999201).

In an Ames assay (MRID 42551801), TFM (40.24%) was tested on *Salmonella* strains TA98, TA100, TA1535, TA1537, and TA1638. The doses used were 75, 100, 200, 300, or 400 µg/plate in the presence and absence of the metabolic activation. The positive controls were 4-nitroquinoline-N-oxide, benzo(a)pyrene and N-methyl-N-nitro-N-nitroso-2-amino fluorene. TFM was shown to be negative for mutagenicity under the conditions of this test.

In a mouse micronucleus assay (MRID 42187101), groups of mice (5/sex/dose) received a single administration of TFM by gavage at doses of 80, 400, or 800 mg/kg. A negative control group (corn oil), a positive control group (cyclophos-phamide, 80 mg/kg), and a secondary dose group (10 mice/sex)(TFM at 800 mg/kg) were included in this study. At 800 mg/kg of TFM, there were deaths within the first 24 hours after dosing. The results showed that under the conditions of this study, TFM did not induce a significant increase in the incidence of micronucleated marrow polychromatic erythrocytes. Therefore, TFM is considered as negative in the *in vivo* mouse micronucleus assay.

In an unscheduled DNA synthesis assay (MRID 40999202), freshly prepared rat hepatocytes were exposed to TFM (. 86%) at final concentrations of 0.025, 0.05, 0.101, 0.252, 0.504, 1.01, 2.52, or 5.04 Fg/ml. Concentrations $\geq$ 10.09 Fg/ml were not listed because there was complete cytotoxicity and some precipitation. At 5.04 Fg/ml, 5% of the cells died. Under the conditions of this study, TFM was negative for mutagenicity.

In an *in vitro* cytogenetic assay (MRID 40999201), cultured CHO cells were exposed to TFM (86%) at concentrations of 49.6, 99.2, 149, or 198 Fg/ml for 17.25 hrs. in absence of the S9 metabolic activation. In the presence of the S9 activation, the CHO cells were exposed to TFM at concentrations of 115, 384, 769, 1150, or 1540 Fg/ml for 2 hrs. After exposure to TFM, the treated cells were washed with buffered saline, and complete McCoy's a medium containing 0.1 Fg/ml Colcemid was added to the washed cells. The cells were then incubated for 2.5 hrs (without S9) or 7.5 hrs (with S9). The metaphase cells were then harvested, and slides prepared for analysis. The results showed that, without S9 activation, TFM at concentrations of 149 and 198 Fg/ml induced chromosomal aberrations, consisting mainly of simple chromatid breaks. In the presence of S9 activation, 1150 and 1540 Fg/ml of TFM

caused a statistically significant and dose-related increase in chromosomal aberrations, consisting of simple chromatid and chromosome breaks.

2. Dose Response Assessment

TFM has been classified as a low-volume and nonfood use chemical based on the quantity used, the method of application, and the rapid dissipation of any possible residues in fish and water. Therefore, the acute and chronic dietary toxicity endpoints and a dietary risk assessment are not required for TFM.

Based on the use and possible exposure scenarios, the relevant exposure is short-term occupational dermal exposure. No residential exposure is expected because TFM is applied in a very limited use area and extensive public notification is required by the USFWS to eliminate exposure to riparian water users including fishermen, boaters and swimmers. Inhalation toxicity endpoints for risk assessment were not selected because significant inhalation exposure is not expected; also TFM is a viscous dark liquid and certain formulations are in the form of solid bars.

Table 4. Summary of the Results of Subchronic Toxicity Studies on TFM

GUIDE-LINE #	STUDY TYPE	MRID No.	RESULTS	ENDPOINT
82-1a	feeding studies	00112726 rats	no treatment related effects	NOAEL = 5249 ppm (525 mg/kg/day) LOAEL not established
82-1a		00112727 rats	decreased body weights	NOAEL = 1620 ppm (162 mg/kg/day) LOAEL = 2916 ppm (292 mg/kg/day)
82-1b		00112725 dogs	decreased body weights and body weight gains	NOAEL = 1250 ppm (31 mg/kg/day) LOAEL = 5000 ppm (125 mg/kg/day)
83-3	developmental	00131201 rats	maternal salivation and mortality	NOAEL = 125 mg/kg/day LOAEL = 250 mg/kg/day
			litter no treatment related effects	NOAEL = 250 mg/kg/day LOAEL not established
84-2	mutagenicity	42551801	negative (Ames assay)	
		42187101	negative (mouse micro-nucleus assay)	
		40999202	negative (UDS assay)	
		40999201	positive (*in vitro* cytogenetic assay)	

a. Dermal and Inhalation Exposure (any time period)

A short-term dermal endpoint of 125 mg/kg/day was chosen based on a rat developmental toxicity study. The toxic effect was not developmental in nature with salivation and mortality as the effect in the dams. This is the most pertinent toxicity study to use for a dermal endpoint, and although no males

were evaluated, the endpoint has been applied to account for exposures to the general population including both males and females.

Although an inhalation toxicity endpoint was not selected, exposures contributed by the inhalation route were combined with the dermal exposures as a conservative measure.

b. Cancer Classification

There is an acceptable chronic feeding study in hamsters, and the results do not indicate that TFM induced an increase in any tumor incidence (MRID 00081184). A chronic feeding study in rats was also conducted in 1975 (MRID 00059379), but the results are not conclusive regarding whether TFM induced an increase in any specific tumor incidence. It should be noted that the chronic toxicity studies were conducted in the 1970's prior to implementation of the EPA Guidelines (1982) for toxicity testing. Because TFM is a nonfood use, the Agency does not require a cancer study.

3. Exposure Assessment

a. Dietary Exposure From Food and Drinking Water

TFM has been classified as a low-volume and nonfood use chemical based on the quantity used, the method of application, the USFWS restrictions against irrigation and drinking water removal from streams during treatment, and the rapid dissipation of any possible residues in fish and water. Therefore, the dietary exposure is expected to be minimal and a dietary risk assessment is not required for TFM.

b. Occupational/Residential Exposure

Based on the use and possible exposure scenarios, the relevant exposure is occupational dermal and inhalation exposure. No residential exposure is expected because TFM is applied in a very limited use area and extensive public notification is required by the Fish and Wildlife Service to eliminate exposure to riparian water users including fishermen, boaters, and swimmers.

4. Risk Characterization and Occupational Exposure

The USFWS program for the chemical control of sea lampreys using TFM and niclosamide is presented in the *Manual for Application of Lampricides in the U.S. Fish and Wildlife Service Sea Lamprey Control Program including Standard Operating Procedures* (1993). This manual focuses on minimizing occupational and general public exposures by specifying the manner in which applications are made (i.e., techniques and equipment), the level of risk mitigation for those occupationally exposed, and the approaches commonly used to reduce risks to the general public resulting from the use of treated waterways (e.g., swimming, fishing, or boating) or through drinking water exposures are mandated. This program served as the basis for the exposure/risk assessment completed for TFM and niclosamide.

Several issues pertain to the quality of the assessment and should be considered when interpreting the results of the occupational handler risk assessment. These include:

- No chemical-specific exposure data were submitted. As a result, all handler analyses were completed using surrogate data from the Pesticide Handlers Exposure Database (PHED).

- The backpack handler assessment was completed using "low quality" PHED data, due to the lack of a more acceptable data set.

- Use information provided for the years 1993 through 1997 served as the basis for this assessment. Specifically, data from 1997 were selected as being representative of TFM and niclosamide use patterns. The upper ranges of these application rates were accepted as representing a reasonable limit to the daily use capacity (i.e., maximum amount in a single day that can be applied). However, based on personal communication between J. Dawson (EPA) and Terry Morse (USFWS) on 9/28/98, handling of the TFM necessary to treat larger rivers (e.g. 1500 to >3000 kg/stream) would actually be conducted by 3-5 workers over, perhaps, 3-5 days.

The use patterns, based on the USFWS manual, and current labeling indicate 4 major occupational exposure scenarios for TFM based on the specified types of equipment and application techniques that can potentially be used to make applications. These scenarios include:

(1a) mixing/loading/application of liquid TFM via direct metering pump from 6 gallon end-use product drums (low chemical use treatment events);
(1b) mixing/loading/application of liquid TFM via direct metering pump from drum filled by open pour of 6 gallon end-use product drums (larger chemical use treatment events);
(2) mixing/loading/application of liquid TFM using backpack sprayers for supplementary still water applications; and
(3) applicator (i.e., placement) of TFM bars.

Even though 4 exposure scenarios were identified for the use of TFM, exposures/risks were only calculated for scenarios 1b and 2 because these scenarios present the highest exposures for TFM.

Risks associated with two occupational TFM scenarios were calculated using the variables associated with 41 actual USFWS treatments of Great Lakes tributaries conducted in 1997. Exposure estimates were based on PHED data, assumed 100% dermal and inhalation absorption, and assumed a 70-kg body weight. A margin of exposure (MOE) of 100 or greater is considered to not be of concern. MOEs for mixer/loader/applicators applying TFM via metering pumps and wearing maximum PPE as per the USFWS Manual were 100-14,186 for 38 of the 41 stream applications. In the remaining three streams, MOEs were 66, 68, and 96 for high treatment volumes of greater than 2100 kg/treatment/day. This assessment assumes that the treatment amount was handled per day by one mixer/loader/applicator and so the values are thought to be conservative because the USFWS has informed the Agency that larger applications are actually made by a crew of 3-5 handlers over a period of 3-5 days.

MOEs were calculated for the backpack sprayer scenarios assuming that 1% of the treatment amount for the 41 stream treatments from 1997 was applied via a backpack sprayer. MOEs were 106-15,571 for 39 stream scenarios; the other two treatments resulted in MOEs of 73 and 75. Again, this assessment assumes that the treatment amount was handled per day by one mixer/loader/applicator and so the values are thought to be conservative because the USFWS has informed the Agency that larger applications are actually made by a crew of 3-5 handlers over a period of 3-5 days. In the case of the backpack spray scenario, The USFWS provided additional information that details how much TFM was applied by backpack spray in 1997. The amount applied in four treatments ranged from 3.1 to 55.2 kg/treatment which would result in MOE's of 45 to 807 if these applications were made by one mixer/loader/applicator in one day. Again, since these were also assumed to be 3-5 handlers over a period of 3-5 day, the Agency has no concern for those fairly infrequent scenarios where large treatments result in apparent MOEs below 100.

C. Physical Chemistry Assessment for Niclosamide

Niclosamide is a yellow crystalline solid; pure niclosamide (ethanolamine salt) decomposes at 208° C, has a bulk density of 1.59 g/cm^3 at 22° C, and a vapor pressure of 9.9 x 10^{-9} mm Hg at 25EC. Niclosamide is practically insoluble in water (1.05 x 10^{-5} g/100 mL).

D. Human Health Assessment for Niclosamide

1. Toxicology Assessment

a. Acute Toxicity

The following table summarizes the available acute toxicity data for niclosamide.

Table 5: Acute Toxicity of Niclosamide.

Guideline #	Study Type	MRIDs #	Results and Toxicity Category
81-1	Acute Oral - rat	42552301*	Single dose 1000 mg/kg; no mortality or clinical signs LD50 > 1000 mg/kg. Toxicity Category in females III or higher; could not be determined in males.
81-2	Acute Dermal - rabbit	42552301*	No mortality or clinical signs; LD50>2000 mg/kg. Toxicity Category III for females; could not be determined for males.
81-4	Primary Eye Irritation	42552305*	Evidence of eye irritation (iritis, corneal opacity, chemosis, redness) at 72 hours. Toxicity category not assigned because eyes were not examined beyond 72 hours.
81-5	Primary Skin Irritation	42552305	Toxicity Category IV based on no irritation in animals with unabraded skin.
81-6	Dermal Sensitization	42552306	Moderate dermal sensitizer.

* Submitted studies were not acceptable to fulfill guidelines, but provided some useful information for risk assessment.

b. Subchronic Toxicity

The available subchronic studies are summarized below.

Subchronic toxicity in rats

In a subchronic toxicity study (MRID 42552307), Bayer 73 (niclosamide) (purity not given; batch 8059410, formula 11089) was administered to 20 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 300, 1250, or 5000 ppm (0, 30, 125 and 500 mg/kg/day, respectively), for 90 days.

There were no treatment-related deaths. Clinical signs were not provided, but were reportedly similar in control and treated groups. The weekly and terminal body weights of treated rats were # 7.4% lower than that of controls (p # 0.05) for terminal body weight in both sexes given 5000 ppm and in males given 1250 ppm and overall body weight gains were # 8.6% lower than of controls, but these small decreases were not toxicologically significant. There were no treatment-related effects on food consumption or food utilization efficiency. Urinalysis, clinical chemistry and hematology analysis revealed no notable differences from the controls, although most clinical chemistry and some hematology parameters required by EPA Guidelines were not assayed. The small but statistically significant alterations (# 9.9%, p # 0.05 or 0.01) in the absolute and/or relative weights of the liver, kidneys, heart, spleen, and gonads in one or both sexes lacked histopathological correlates, were often unrelated to dose, and were not toxicologically significant. There were no treatment-related gross or microscopic lesions.

Under the conditions of this study, a LOAEL cannot be established for either male or female rats because there were no treatment-related findings. The NOAEL is $ 5000 ppm (500 mg/kg/day).

This subchronic toxicity (Guideline 82-1a) study is classified as unacceptable and not upgradeable because the animals were not adequately dosed; the maximum dose was well below the limit intake of 1000 mg/kg/day. Additionally, numerous parameters required by the Agency study guidelines (e.g. compound analysis in the diet, clinical chemistry) were not measured.

Subchronic toxicity in dogs

In a subchronic toxicity study (MRID 42552309), Bayer 73 (niclosamide) (70% wettable powder; batch 0053050) was administered for 180 days to 3 beagle dogs/sex/dose in the diet at dose levels of 0, 62.5, 250, or 1000 ppm (0, 1.56, 6.25, or 25 mg/kg/day, respectively). No statistical analysis was performed on the study results.

No animals died or exhibited any toxic signs during the study. The biweekly body weights and daily food consumption of treated and control dogs were similar. Body weight gains were not clearly treatment-related in either sex, and were within approximately 8% of controls at 1000 ppm for the major part of the study (weeks ½-24 for males and ½-20 for females). There were no treatment-related effects on any clinical chemistry, hematology, or urinalysis parameters, and the rates of bromsulfophthalein and phenol-sulfonephthalein clearance were similar in treated and control groups. The bone marrow myeloid/erythroid ratio of high-dose males and females was much lower than that of controls (4.3/1 in controls vs. 1.0/1 for males and 2.0/1 for females), suggestive of lowered WBC production or elevated erythrocyte production, but neither possibility was substantiated by the hematology results.

Microscopic lesions were seen primarily in the lungs, kidneys, and liver of both sexes, but these lesions could not be definitively attributed to treatment because they were seen in both treated and control dogs (incidence of 0/3 to 2/3 per dose). Additionally, none of the histology findings were correlated with gross lesions or alterations in clinical chemistry parameters.

Based on the lack of definitive treatment-related findings under the conditions of this study, a LOAEL cannot be established for either male or female dogs. The NOAEL is $ 1000 ppm (highest dose tested; calculated as 25 mg/kg/day.

This subchronic toxicity (Guideline 82-1b) study is classified as unacceptable and not upgradeable because the animals were not adequately dosed; the maximum dose was well below the limit intake of 1000 mg/kg/day recommended by the guideline. Additionally, 4 dogs/sex should have been used and data for a number of other parameters (e.g. compound analysis in the diet, some clinical chemistry parameters) were not provided.

Subchronic toxicity in hamsters

In a subchronic toxicity study (MRID 42552308), Bayer 73 (niclosamide) (purity not given; batch 8059410, formula 11089) was administered to 20 Syrian hamsters/sex/dose in the diet at dose levels of 0, 300, 1250, or 5000 ppm (0, 39, 177, and 726 mg/kg/day, respectively, calculated by the reviewer) for 90 days.

No treatment-related clinical signs of toxicity were observed in the study, and there were no treatment-related deaths. However, the treatments caused the hamsters in all dose groups, except for low-dose females, to have significantly lower body weights compared to controls ($P < 0.05$) at the termination of the experiment and probably much earlier. At the termination of the experiment, the reductions in body weights compared to controls were 8.6%, 9.3%, and 14.3% in males fed 300 ppm, 1250 ppm, and 5000 ppm, respectively. In females, the reductions were 5.5% (not significant), 9.7%, and 11.0%, at the same doses, respectively. The percent reductions in body weight gain over the 13 weeks were 12.0%, 12.0%, and 20.7% in males, and 8.2%, 14.3% and 17.3% in females at the respective doses. Food consumption was decreased in the 5000 ppm group males and females at week 1 but was then relatively consistent across treated groups. If the reduced food consumption had been caused by palatability alone, it is expected that the animals would adjust and consume equal or increased amounts for the remainder of the study and that the body weights would rebound. However, there was continued decreased body weights in the treated animals, especially the 5000 ppm group males and females. Therefore, it is concluded that there was a treatment-related effect on body weight and body weight gain. The effect is more pronounced in the 5000 ppm group males and somewhat in the 5000 ppm group females. There was an associated decrease in the weights of certain organs and in the animals' efficiency of food utilization. There were no treatment-related effects on hematology, clinical chemistry, urinalyses, gross pathology, or histopathology.

The LOAEL is 5000 ppm (726 mg/kg/day) in males and females based on decreased body weight and body weight gain. The NOAEL is 1250 ppm (177 mg/kg/day).

This subchronic study is classified as unacceptable/guideline but upgradeable to acceptable/guideline upon furnishing missing information regarding compound purity. Numerous endpoints were not tested for, including many clinical chemistry parameters and a few hematology parameters; however the study can be used for regulatory purposes if the compound purity is supplied.

c. Chronic Toxicity/Carcinogenicity

Chronic toxicity and carcinogenicity studies are not required for non-food use chemicals. However, if available, the studies could substitute for missing subchronic studies. A chronic toxicity study in rats (MRID 42698001C) has been submitted, but it has been classified as unacceptable. The National Cancer Institute conducted bioassays in rats and mice with niclosamide in 1978. Osborne-Mendel rats and B6C3F1 mice were treated with clonitralid (synonym for niclosamide) in the diet at concentrations of 28,433 (.1421 mg/kg/day) or 14,216 (.711 ppm) for rats, and 549 (.78 mg/kg/day) or 274 ppm (.39 mg/kg/day) for mice for 78 weeks. Because of inadequate survival among male mice, the results could

not be considered conclusive in this sex. There was no evidence that clonitralid was carcinogenic to male and female rats and female mice.

d. Developmental Toxicity

The available study does not satisfy the developmental toxicity testing requirements.

Developmental toxicity in rabbits

In a developmental toxicity study (MRID 42552310), pregnant New Zealand white rabbits were administered Bayer 73 (niclosamide, 70%, a.i.; Batch No. 0053050) by gavage at doses of 0, 20, 60, and 180 mg/kg/day on gestation days (GD) 8-18, inclusive. Does were deemed pregnant if live fetuses were observed at cesarean section (GD 29) resulting in only 10, 10, 10, and 7 animals used per group, respectively. All fetuses were sexed, weighed, examined for external malformations/variations, and X-rayed for subsequent skeletal examination. One-half of the fetuses were preserved in Bouin's solution for razor blade sectioning by the Wilson technique. The other half were preserved in formaldehyde and subjected to gross necropsy.

No evidence of maternal toxicity was observed in this study. Mean fetal body weights of the treated groups were 83-89% of the control group level, but there was a corresponding increase in the number of fetuses/litter. Statistical analysis of fetal body weights did not account for litter size and fetal body weights of the treated groups were within the expected range for the rabbit. Therefore, the decrease in fetal body weights is not considered treatment-related. When the incidence rates of peritoneal hemorrhage observed in fetuses during either Wilson's examination or gross necropsy are combined, 0/10, 4/10, 5/10, and 4/7 litters in the 0, 20, 60, and 180 mg/kg/day groups, respectively, contained affected fetuses. The incidence rate is statistically significant (p # 0.05) in all treated groups. Lack of a clear dose-response in the number of litters affected, involvement of only one fetus in each affected litter, and few numbers of litters evaluated, make peritoneal hemorrhage an equivocal treatment-related effect.

Several major deficiencies in the conduct of this study make it inadequate for the evaluation of the potential developmental toxicity of Bayer 73 in the rabbit. Therefore, LOAELs for maternal and developmental toxicity could not be established.

This Guideline 83-3b study is classified as unacceptable (not upgradable) and does not satisfy the Agency guideline requirements for a developmental toxicity study in rabbits. This study is inadequate for determining either a maternal or developmental toxicity LOAEL. All animals were not treated concurrently, only females with live fetuses were included in the study, inappropriate statistical analyses were used for fetal body weight data, the use of X-ray films is inadequate for fetal skeletal evaluation, and the dosing solutions were not analyzed for concentration, homogeneity, or stability.

e. Mutagenicity

The mutagenicity testing requirements have not been fully satisfied. The *Salmonella typhimurium* reverse mutation assay (Ames assay) has not been fulfilled.

Chromosome Aberration in Bone Marrow Cells

In a mammalian cell cytogenetics assay (chromosome aberration in bone marrow cells) (MRID 43677902), male and female Crl:CD(ICR) BR mice, 15/sex/group, were exposed to niclosamide (98.9%) at doses of either 1250, 2500 or 5000 mg/kg by a single gavage administration. At 6, 18, or 30 hours after test substance administration, 5/sex/group were sacrificed at each period. Bone marrow cells were harvested immediately after sacrifice. The vehicle control was corn oil. The positive control, which was cyclophosphamide, was adequate. There is no evidence of chromosome aberrations in bone marrow cells induced over background.

This study is classified as acceptable/guideline. It satisfies the requirement for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

Mammalian Forward Gene Mutation Assay

In a mammalian cell gene mutation assay (thymidine kinase locus) (MRID 43677901), L5178Y mouse lymphoma cells cultured *in vitro* were exposed to niclosamide (98.9%) in dimethylsulfoxide at concentrations of 2.50 to 80.0 ug/ml in the presence and absence of mammalian metabolic activation.

Without S9 activation, trial 1 was aborted due to excessive cytotoxicity. In trial 2, doses of 30 to 80 ug/ml were excessively cytotoxic; the remaining six doses of 2.50 to 25.0 ug/ml produced no increase in the number of mutant colonies. Survival (relative growth) was relatively constant at 15.5 to 19.9% over the six doses.

With S9 activation, trials 1 and 3 were aborted due to excessive cytotoxicity. In trial 2, at doses of 1.25 to 40 ug/ml, severe cytotoxicity was observed at > 3.75 ug/ml. At 1.25, 2.5 and 3.75 ug/ml, there was no increase in mutant colonies. In trial 4, at doses of 2.5 to 40.0 ug/ml, there was no increase in mutation frequency. There was a dose-related increase in relative growth (9.0% at 40.0 ug/ml to 76% at 2.5 ug/ml). There was no increase in the mutant frequency with niclosamide at cytotoxic doses (25.0 ug/ml -S9; 40 ug/ml +S9). The positive controls induced the appropriate response.

This study is classified as acceptable/guideline. It satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

E. Dose Response Assessment

a. Dietary

Niclosamide is classified as a low-volume, and nonfood use chemical based on the quantity used, the method of application, and the rapid dissipation of residues in fish and water. As a nonfood use chemical, the acute and chronic dietary endpoints for niclosamide are not necessary and a reference dose is not required.

b. Short/Intermediate Term Occupational and Residential

No endpoints were established for niclosamide. Short and intermediate term exposures may occur, but are not expected to be substantial based on the low volume used. Long term exposure and, therefore, long-term risk is not expected.

There are no residential uses.

1. Exposure Assessment

a. Dietary Exposure From Food and from Drinking Water

Niclosamide is classified as a low-volume and nonfood use chemical based on the quantity used, the method of application, the USFWS restrictions against irrigation and drinking water removal from streams during treatment, and the rapid dissipation of any possible residues in fish and water. Therefore, the dietary exposure is expected to be minimal and a dietary risk assessment is not required for niclosamide.

b. Occupational/Residential Exposure

It is anticipated that regardless of whether niclosamide is used to control sea lampreys or fresh water snails, the application methods and exposure issues are similar for handlers. As a result, the USFWS sea lamprey control program manual was used as a basis for the niclosamide and TFM exposure/risk assessment. The specifics of this manual and available labeling should be the basis for any niclosamide and TFM use. Postapplication scenarios to swimmers, boaters and fisherman should result in minimal exposure from the lampricide use of niclosamide based on the USFWS program.

There are currently two Special Local Needs labels for use of niclosamide in commercial aquaculture for the production of ornamental fish in Florida and Arkansas. The water from this treatment is not released and the fish are not used as a food source. There should be limited occupational and no residential exposure from these uses.

2. Risk Characterization

a. Dietary Risk including Drinking Water Risk

There is no reasonable expectation of humans being exposed to niclosamide residues in the diet via water, fish, irrigated crops, and livestock for the following reasons: (I) the low use volume (300 lb ai/yr); (ii) the infrequency of use (every 3-5 yr **if** a given stream harbors lamprey); (iii) the very tight control USFWS has over the use of niclosamide including 24-hr irrigation and potable water intake restrictions, other label restrictions, door-to-door as well as broadcast riparian user notification and enforcement particularly for sport fishermen, etc.; (iv) the fact that the treated water moves as a slug down the treated stream resulting in only a 1-3 day exposure interval every 3-5 years; (v) what is, in effect, infinite dilution as treated stream water enters the Great Lakes, where virtually all of the commercial fishing occurs; (vi) the rapid and complete dissipation of niclosamide residues from treated streams; (vii) the very low level of bioconcentration as well as the rapid and complete depuration of niclosamide residues from exposed fish; and (viii) based on reasons given above, residues of niclosamide in irrigated crops and livestock are not expected.

b. Occupational/Residential Risk

It has been determined that there is a potential for exposure from handling niclosamide-containing products during the application process (i.e., mixer/loaders and mixer/loader/applicators) as well as from various post-application activities such as recreational boating and swimming. The two potential niclosamide exposure scenarios are: (I) mixing/loading/application of niclosamide wettable powder slurry and (ii) loading/application of niclosamide granules using powered backpack blowers for population survey applications. However, based on the extremely low usage (300 lb ai/yr), the infrequency of use, and the risk mitigation measures already implemented by USFWS, occupational exposure and risk assessments have not been conducted for niclosamide.

F. Environmental Assessment for TFM

1. Ecological Toxicity Data

a. Summary

The information in this assessment is based on a combination of both open literature and studies specifically conducted to meet EPA data requirements. While all of the data included in this assessment were considered scientifically sound, open literature studies were not subject to the rigorous standards currently required under Good Laboratory Practice (GLP) protocols. Given the range of protocols over which ecotoxicity data were collected, there is some uncertainty over how the toxicity of TFM may have been effected had the studies been conducted under GLP standards. Based on ecological effects data, the toxicity potential of TFM can be characterized as follows:

- Avian acute-**nontoxic** (>5, 000 ppm)
- Mammalian acute-**moderately toxic** (>141 to 160 mg/kg)
- Mammalian chronic (>5,000 mg/kg)
- Fish (freshwater acute)- **slightly to highly toxic** (0.60 to 37 mg/L)
- Invertebrates (freshwater) acute- **slightly to moderately toxic** (3.8 to 22.3 mg/L)
- Aquatic plants- **toxic** (1.2 to > 15 mg/L)

Mammals were the only animal group for which chronic toxicity data were available and for this group there were no chronic effects noted.

Environmental factors influenced the toxicity of TFM. In general TFM was more toxic as water temperature increased and pH and water hardness decreased. When TFM is used in combination with niclosamide, the toxicity potential of the combined lampricides was additive.

b. Toxicity to Terrestrial Animals

(1) Avian Acute Oral, Subacute Dietary and Chronic

The acute oral toxicity data suggest that TFM analytical and formulated grade material is moderately to slightly toxic (LD_{50} 250-546 mg/kg) to avian species and practically non-toxic (LC_{50} > 5,000 ppm) on a subacute dietary basis (MRID 00022923; Acc # 160000). Avian chronic reproduction studies are not required.

(2) Mammals, Acute and Chronic

TFM has acute oral LD_{50} values of 141 and 160 mg/kg for males and females, respectively (MRID 40999204 and 41898102).

(3) Insects

A honey bee acute contact study using the TGAI is not required for TFM because its use, *i.e.*, streams and rivers, will not result in honey bee exposure.

c. Toxicity to Freshwater Aquatic Organism

(1) Freshwater Fish, Acute and Chronic

Acute toxicity of TFM ranges from being slightly toxic to highly toxic for freshwater fish species. The most sensitive species tested was the channel catfish, *Ictalurus punctatus* (96 hour LC_{50} = 0.60 mg/L in soft, reconstituted well water, pH 7.2 to 7.6), while the least sensitive species tested was the bluegill sunfish, *Lepomis macrochirus* (96 hour LC_{50} = 37 mg/L in hard well water, pH 8.3 to 8.5).

In a study comparing the toxicity of TFM to native species of lampreys with sea lampreys, the toxicity of TFM to lamprey larvae was highest in the sea lamprey, intermediate in the northern brook lamprey (*Icthymyzon fossor*), and lowest in the American brook lamprey (*Lamptera appendix*) (King *et al.* 1985).

Because TFM is also used in combination with niclosamide, toxicity tests for the combination of these two chemicals were conducted by Bills and Marking (1976). Of the fish tested, channel catfish was again the most sensitive species to TFM alone (LC_{50} = 0.75 mg/L) and to the combination of the two chemicals (LC_{50} = 0.615 mg/L). In general, the data show that the combination of TFM and niclosamide was at most additive under various test conditions.

Although fish life cycle data are not available for TFM, there are acute data available for various developmental stages of fish. All the early developmental stages of walleye *(Stizostedion vitreum*) from gametes to sac fry were more resistant to TFM than were similar developmental stages of sea lamprey larvae. Olson and Marking (1973) examined the toxicity of TFM to six developmental stages of the rainbow trout and found that sac fry were the most sensitive life stage studied. Exposure to TFM during sea lamprey embryonic development increased the frequency of abnormalities that lead to increased mortalities (Piavis and Howell 1975; NRCC 1985).

TFM treatments have been associated with induction of hepatic mixed function oxyganase activity and altered levels of circulating steroids in fish and induced hepatic vitellogenesis in primary cultures of rainbow trout hepatocytes (Hewitt et al. 1997). As such, TFM acts as an estradiol agonist and has a demonstrated endocrine disrupting effect. Since the data on various developmental stages represented disjointed acute studies, chronic toxicity data on fish were not available and as such, a fish full life cycle study of both technical grade TFM and TFM/niclosamide mixture is required to address this deficiency.

Abundance of sea lamprey peaked in several Great Lakes before chemical control began. The sex ratio in these peak populations were predominately males (68-71%). Following a decade of lampricide treatments, populations of sea lampreys showed marked declines and the sex ratios in these populations shifted toward a predominance of females accounting for 72% of the population (Henrich, et al, 1979). This publication by Henrich concludes that lampricides reduced the populations of sea lampreys in the Great Lakes and contributed to the sequential shifting of the sex composition from a predominance of males to a predominance of females. There are no data to support that the endocrine mediated effect associated with TFM is related to the observed sex-ratio shifts among TFM-treated populations of sea lamprey.

(2) Freshwater Invertebrates, Acute and Chronic

In acute toxicity tests, TFM was moderately to slightly toxic to aquatic invertebrates (24 hour LC_{50} range: 3.8 to 22.3 mg/L). When TFM is used in combination with niclosamide (98:2 by weight), LC_{50} values for the mixture ranged from 1.5 mg/L (moderately toxic) to greater than 100.0 mg/L (practically non-toxic). The most tolerant species tested were crayfish, dragonflies, snipeflies, and

dobsonflies. The most sensitive species were snails and aquatic earthworms. These data indicate that the mixture of TFM and niclosamide enhanced the toxicity of TFM to some aquatic invertebrates.

There are no chronic toxicity data available for aquatic invertebrates. An aquatic invertebrate life cycle study (72-4) of both technical grade TFM and TFM/niclosamide mixture is required to address this deficiency.

(3) Toxicity to Estuarine/Marine Organisms

Because the use of TFM is unlikely to directly enter into estuarine/marine environments, toxicity testing for these species is not required.

d. Toxicity to plants

TFM inhibited the growth of aquatic plants; 9 out of 10 species of algae tested suffered 50% growth inhibition at concentrations less than 10 ppm (Maki *et al*. 1975). Concentrations as high as 30 mg/L arrested growth, but did not kill algae. The algae resumed normal growth when exposure to TFM was stopped (Maki et al. 1975). The Tier II results indicate that *Nitzschia sp*. is the most sensitive (EC_{50} 1.2 mg/L) of the nonvascular aquatic plants tested. The Tier II guideline is fulfilled (Maki. *et al.*, 1975).

The herbicidal activity of various salts of TFM has been reported (Gilderhus and Johnson 1980). TFM decreased the growth of *Anacharis sp., Cabomba sp.,* and *Ceratophyllum sp.* at concentrations of 15 - 25 ppm in standing water and at 100 ppm in flowing water (Schnick 1972). Canadian pondweed (*Elodea canadensis*), when exposed to TFM for 24 hours, suffered a loss in weight at exposure concentrations greater than 5 ppm, while plants exposed to 35 ppm died (Maki and Johnson 1977). However, plants exposed at concentrations as high as 20 ppm recovered after TFM exposure was terminated. TFM was toxic to Eurasian water milfoil (*Myriophylum spicatum*) causing a 60-85% reduction in biomass at concentrations between 10 - 25 ppm. In general, TFM does not appear to cause long-term adverse effects to aquatic plants except for a temporary reduction in growth (NRCC, 1985).

2. TFM Environmental Fate and Transport

The information in this assessment is based primarily on open literature studies submitted by the registrant to fulfill EPA data requirements. Unless otherwise noted, the data cited here are not from studies conducted according to Subdivision N guidelines, but nonetheless are considered scientifically valid and may be used in assessing the fate and transport of TFM in the environment. Because the open literature studies were not conducted according to the rigorous standards required under Subdivision N, there is some degree of uncertainty associated with the data, particularly if one is comparing the results of these studies to studies for other chemicals conducted according to Subdivision N guidance.

C TFM is chemically and biologically very stable. The compound possesses many of the chemical features known to impart persistence to organic compounds.

- There is conflicting evidence on whether TFM photodegrades in water.

- TFM remains toxic for long periods (>80 days) in aqueous systems; however, toxicity decreases in sediment-water systems over time. In sediment-water systems, irreversible sorption of reduced-TFM [R-TFM; 4-amino-3-(trifluoromethyl)phenol] to sediments was reported. R-TFM is capable of binding to other organic components of the sediment through the amino group or be polymerized to longer chain compounds.

- TFM was converted to reduced-TFM with a half-life of less than one week under both aerobic and anaerobic aquatic metabolism conditions. It must be stressed that when reduced-TFM is reported as a reaction product, degradation has not occurred. TFM has just undergone a chemical reduction and under appropriate conditions, reduced-TFM may be re-oxidized to TFM.

- The tendency for TFM to bind to sediments is not strong, readily reversed, and is very pH dependent. Binding tends to decrease as pH increases.

- Based on studies with the rainbow trout, TFM is not expected to accumulate in fish.

- In the environment, the sorption and degradation of TFM by sediments is expected to occur primarily in the lakes and not in the tributary streams. TFM is expected to remain in solution in the lake system and persist for long periods of time.

TFM ($C_7H_4F_3NO_3$; M.W. 207.11) is chemically and biologically very stable. An examination of its structure, *i.e*., aromatic, fluoro-containing, m-substituted phenol, shows that the compound possesses many of the chemical features known to impart persistence to organic compounds. Its pK_a is 6.07 and the effect of pH on the toxicity appears to follow closely to the concentration of the lipid-soluble, free phenol form of TFM. This pH sensitivity is used to maximize effectiveness. As pH increases, toxicity, bioaccumulation, and adsorption to sediment decrease. Aqueous solubility of the sodium salt is 5 g/L.

a. TFM Degradation

In an acceptable Hydrolysis guideline study, Reynolds (1997, MRID 44429501) found that ^{14}C-TFM was stable in sterile buffered aqueous solutions at pH's 5, 7, and 9 at 25EC in the dark for 30 days. No degradation products were identified. In bioassay experiments, Thingvold (1975) found that the toxicity of TFM was not altered over the course of 5 to 8 weeks by buffering aqueous solutions at pH values of 6.5, 7.7, 8.5, or 9.5. Carey and Fox (1981) demonstrated in distilled water systems buffered at pH 5, 6, 7, 8, or 9 that TFM was stable in the dark controls of a photodegradation study. The hydrolysis study requirement is fulfilled.

Photolysis may be an important route of degradation in the environment, however there is conflicting evidence on this. In the Carey and Fox study, the authors found that TFM photodegraded in unbuffered distilled water under natural sunlight with a half-life of 3.3 days. The principle identified

photoproduct was 2,5-dihydroxybenzoic acid. There was no build-up of photoproducts and by the end of the experiment (11 days), most of the TFM degradation products were unextractable. These authors believe that under appropriate weather conditions, the photodegradation half-life in a shallow stream would be on the order of several days. Contrary to this, Thingvold (1975) found that solutions of TFM were very stable in the presence of sunlight thus indicating that photodecomposition is an unlikely dissipator of TFM from the Great Lakes environment. This contradiction leads to some uncertainty as to whether photolysis plays a role in the dissipation of TFM. Based on this uncertainty, an additional aqueous photolysis study is required.

b. TFM Metabolism

In a study designed to evaluate the degradation of TFM where aquatic sediments are not an influential factor, Thingvold (1981) found no evidence of microbial degradation of TFM over test periods of up to 80 days. Thingvold demonstrated, using bioassay experiments, that TFM remains toxic for long periods in aqueous systems; however, toxicity decreases in sediment-water systems. In sediment-water systems, irreversible sorption to sediments was reported. It is likely that the bound residue was not TFM, but the reduced form of TFM (4-amino-3-(trifluoromethyl)phenol. Thingvold (1975) found no evidence that indicated that TFM degrades in the presence or absence of auxiliary carbon sources, or under aerobic or anaerobic conditions, in sediment-free aqueous systems. Carey, Fox and Schleen (1988) report that with the exception of reduction of the nitro group to an amino group under anaerobic conditions, TFM is chemically and biologically very stable. However, these authors believe that this reduction is not likely to be an important route of environmental degradation since TFM is almost completely ionized at the pH of most natural waters and does not partition strongly to sediment where anaerobic conditions exist. In addition, it must be noted that when reduced TFM is reported as a reaction product, degradation has not occurred. TFM has merely been reduced and under appropriate conditions, reduced-TFM may be re-oxidized to TFM (Carey and Fox, 1981).

In an acceptable anaerobic aquatic metabolism guideline study, Fathulla (1996, MRID 43887601) found that ^{14}C-TFM applied to a loamy sand sediment/water system degraded rapidly in the dark under anaerobic conditions with a half-life of 2.1 days. The major degradate was 4-amino-3-(trifluoromethyl)phenol, reduced TFM (R-TFM), which comprised 38.2% at approximately 4 hours, and increased to a maximum of 94.1% of the applied radioactivity on day 14 of anaerobicity and then decreased to 26.6% on day 178 and finally disappeared by day 273. $^{14}CO_2$ was the only volatile component found in the traps, reaching 7.7% of applied on day 273. Radioactivity recovered in the water layer ranged from 71.7 to 87.7% of applied on days 0 through 92. After day 92, the majority of the radioactivity partitioned to the sediment (41-49% of this radioactivity was bound). pH ranged from 5.43 (day 3) to 8.34 (day 273). Under aerobic conditions, Fathulla (1995, MRID 43781801) demonstrated in an acceptable aerobic aquatic metabolism study that ^{14}C-TFM applied to a loamy sand sediment/water system degraded rapidly in the dark under aerobic conditions with a half-life of 5.4 days. The major degradate was reduced TFM, which comprised 38.4% at approximately 7 days, 30.2% on day 15, 1.2% on day 21 and 0.7% on day 30. $^{14}CO_2$ was the only volatile component found in the traps, reaching 7.8% of applied on day 30. The pH ranged from 7.51 (day 1) to 8.83 (day 30). Radioactivity recovered in the water layer ranged from 91.6 to 30.2% of applied on days 0 through 30. On day 30,

the majority of the radioactivity partitioned to the sediment (45% of this radioactivity was bound). Based on these data, the anaerobic aquatic metabolism and aerobic aquatic metabolism study requirements are fulfilled.

c. TFM Mobility

Dawson (1986) studied the adsorption of TFM by bottom sediments (Table 6), and found that increases in pH lead to decreases in K_d, while increases in organic carbon result in increases in K_d. Overall, the mobility of TFM, as determined by Dawson is medium to very high. The table below provides the results at 20°C for systems at pH 6 and 8. Based on these data, the leaching and absorption/desorption study requirement is fulfilled.

Table 6: Absorption (K_d) of Trifluoromethyl nitrophenol (TFM) by four different bottom sediments at pH 6 and 8 (Dawson 1986).

sediment	soil type	sand/silt/clay	organic matter	CEC meq/100g	K_d pH 6	K_d pH 8
Cedar River	sandy loam	64/32/4	9.0	13.2	11.7	2.01
Ford River	loamy sand	84/14/2	5.0	4.6	6.65	1.46
Tahquamenon River	sand	96/2/2	0.9	1.1	1.11	0.157
Arkansas River	loam	44/46/10	2.5	6.2	5.66	0.749

Carey, Fox, and Schleen (1988) also noted that the tendency for TFM to bind to sediments is not strong, readily reversed, and is very pH dependent. Un-ionized TFM (acidic solution) is more readily absorbed than ionized forms (basic solutions) (Dawson *et al*. 1986). On the other hand, Thingvold (1975) claims that TFM is sorbed by sediments in a rapid and irreversible manner, so much so that it is difficult to extract with organic solvents. Thingvold believes the binding may involve the NO_2 group converting to the NH_2 form. This then would mean that rather than TFM binding, it is reduced-TFM that is bound. R-TFM is capable of binding to other organic components of the sediment through the amino group, or being polymerized to longer chain compounds, which would explain the difficulty in extracting TFM from the sediment.

In the environment, the sorption and degradation of TFM by sediments is expected to occur primarily in the lakes and not in the tributary streams. Most of the TFM will be quickly flushed into the lakes. The amount removed by sorption to the stream sediments is unknown, but is likely to be minimal. In the lake environment, degradation of TFM must occur in a primarily sediment-free system, given the high ratio of water to sediment and the lack of sediments containing appreciable amounts of organic material (Thingvold, 1975). As such, TFM is expected to remain in solution in the lake system and persist for long periods of time at low concentrations.

d. TFM Accumulation

The amount of TFM uptake by fish has been correlated to pH and total hardness of the water. Ten times as much TFM was found in fish residing in soft-acid water as compared to hard-alkaline water (Thingvold, 1975). According to Thingvold, TFM is not readily metabolized by aquatic organisms and is generally excreted in an unaltered form. In an acceptable fish accumulation study conducting according to Subdivision N guidelines (MRID 44666501), TFM residues accumulated in rainbow trout that were exposed to nonradiolabeled plus uniformly phenyl ring-labeled [^{14}C]TFM, at a nominal concentration of 62.0 Fg/L, under flow-through aquarium conditions at a pH of 7.8. Maximum bioconcentration factors, based on total radioactivity, were 50.3X for viscera, 1.3X for fillet, and 8.4X for whole body tissues. The maximum mean concentrations of [^{14}C]residues were 3.0 ± 0.9-1.7 ppm for the viscera tissue, 0.08 ± 0.03 ppm for the fillet tissue and 0.5 ± 0.1-0.2 ppm for the whole fish tissue. Accumulation plateaus were generally reached by 3 days in the viscera, fillet, and whole fish tissues. Parent compound was present at 1.4 ± 0.05 ppm in the viscera, and 0.006 ± 0.006 ppm in the fillet tissues. The major metabolite TFM-glucuronide was present at 0.9 ± 0.2 ppm in the viscera, and 0.036 ± 0.003 ppm in the fillet tissue samples. Two unidentified metabolites (Unknowns 1 and 3) were present at 0.7 ± 0.03 ppm and 0.09 ± 0.01 ppm, respectively, in the viscera; an unidentified minor metabolite (Unknown 2) was present at 0.034 ppm (1 of 4 replicates). Depuration was rapid, with >98.7% of total accumulated [^{14}C]residues eliminated by days 4, 15, and 11, respectively, from the viscera, fillet, and whole body tissue samples. Based on these data, the accumulation in fish study requirement is fulfilled.

3. TFM Aquatic Exposure Assessment

Since TFM is added directly to water, the estimated environmental concentrations (EECs) used in this evaluation were based on projected treatment concentrations. Application rates for TFM are based on pH, alkalinity, temperature, stream/river discharge rates, and bioassay data. Spreadsheet-based models incorporating the aforementioned factors have been developed to assist in determining applications rates and were used in predicting exposure concentrations used in the present risk assessment.

G. Environmental Assessment for Niclosamide

1. Ecological Exposure and Risk Characterization for Niclosamide

a. Summary

The information in this assessment is based on a combination of both open literature and studies specifically conducted to meet EPA data requirements. While all of the data included in this assessment were considered scientifically sound, open literature studies were not subject to the rigorous standards currently required under Good Laboratory Practice (GLP) protocols. Given the range of protocols over which the ecotoxicity data were collected, there is some uncertainty over how the toxicity results may have been impacted by this lack of GLP standards. Based on ecological effects data, the toxicity potential of niclosamide can be characterized as follows:

- Avian acute- **moderately toxic** (LD_{50} 60 mg/kg)
- Avian subacute dietary- practically **nontoxic** (LC_{50} > 5,419 mg/kg diet()
- Mammalian acute- practically **nontoxic** (LD_{50} >1,000 mg/kg)
- Fish (freshwater acute)- highly toxic to **very highly toxic** (LC_{50} 0.03 - 0.23 mg/L)
- Invertebrates (freshwater) acute- slightly to **very highly toxic** (EC_{50} 0.034 - > 50 mg/L)
- Invertebrates (freshwater) chronic- (NOAEC 0.03 mg/L; LOEC 0.05 mg/L)
- Aquatic plants- toxic (0.04 to > 1,450 mg/L)

Environmental factors influenced the toxicity of niclosamide. In general niclosamide was more toxic as pH and water hardness decreased. When niclosamide is used in combination with TFM, the toxicity potential of the combined lampricides was additive.

b. Toxicity to Terrestrial Animals

(1) Avian Acute Oral, Subacute Dietary and Chronic

The acute oral toxicity data suggest that niclosamide ranges in toxicity from being moderately toxic to practically nontoxic (LD_{50} 60 to > 2,000 mg/kg) to avian species (MRIDs 43677701, 43677702, and 44180301) and practically non-toxic (LC_{50} > 5,419 ppm) on a subacute dietary basis (MRIDs 44180302 and 44180303). Avian chronic reproduction studies are not required. The guideline requirements for acute studies have been fulfilled.

(2) Mammals, Acute and Chronic

Niclosamide was practically nontoxic to small mammals on an acute oral basis (LD_{50} > 1,000 mg/kg) (MRID 4255223-01). No chronic toxicity data were available.

(3) Insects

A honey bee acute contact study using the TGAI is not required for niclosamide because its use (aquatic sites) will not result in honey bee exposure.

c. Toxicity to Aquatic Animals

(1) Freshwater Fish, Acute and Chronic

The data indicate that the acute toxicity of niclosamide ranges from being highly toxic to very highly toxic for freshwater fish species. The most sensitive species tested were the rainbow trout, *Onchorhynchus mykiss* (LC_{50} = 0.03 mg/L), sea lamprey, *Petromyzon marinus,* (LC_{50} = 0.049 mg/L) and the bluegill sunfish, *Lepomis marcrochirus*, (LC_{50} = 0.049 mg/L). The freshwater fish acute toxicity requirement has been fulfilled (MRID 43679302, 44206101).

Because niclosamide is also used in combination with TFM, toxicity tests for the combination of these two chemicals are used to assess risk. Results of tests specifically conducted to address this issue show that the channel catfish was the most sensitive species to TFM (LC_{50} = 0.75 mg/L), niclosamide (LC_{50} = 0.0125 mg/L) and to the combination of these chemicals (LC_{50} = 0.615 mg/L). Based on the results of this study the authors concluded that the mixture of TFM:niclosamide was at most additive under various test conditions (Bills and Marking 1976).

No data were provided on the chronic toxicity of niclosamide to fish. Thus, the guideline studies for the fish early life stage and fish full life cycle are not fulfilled and represent data gaps.

(2) Freshwater Invertebrates, Acute, Chronic

In acute toxicity tests, niclosamide was slightly to very highly toxic to aquatic invertebrates (EC_{50} range: 0.034 to > 50 mg/L). The acute freshwater invertebrate study requirement has been fulfilled (MRID 44174804).

When TFM is used in combination with niclosamide (98:2 by weight), LC_{50} values for the mixture ranged from 1.5 mg/L (moderately toxic) to greater than 100.0 mg/L (practically non-toxic) among freshwater invertebrates. The most tolerant species tested were crayfish, dragonflies, snipeflies, and dobsonflies. The most sensitive species were turbellarians, snails, and aquatic earthworms and appeared to affect organisms inhabiting sediments. These data indicate that the mixture of TFM and niclosamide are additive for the toxicity of TFM to aquatic invertebrates.

Given niclosamide's potential to adsorb to sediments, the use of formulations specifically designed to slowly release the chemical at the water-sediment interface, and the acute toxicity of niclosamide to aquatic invertebrates, acute and chronic data on sediment toxicity testing using chironomids is necessary since these organisms would be highly exposed.

(3) Toxicity to Estuarine and Marine Organisms

Because the use of niclosamide is unlikely to directly enter into estuarine/marine environments, toxicity testing for these species is not required.

d. Toxicity to Aquatic Plants

Niclosamide inhibited the growth of aquatic plants; diatoms suffered 50% growth inhibition at concentrations less than 130 ppb. Green algae exhibited a considerable range in sensitivity to the effects of niclosamide; EC_{50} values ranged from 0.41 to 1,450 ppm. The studies submitted for review did not comply with recommended guidelines, and were classified as supplemental.

2. Niclosamide Environmental Fate and Transport

The information in this assessment is based primarily on open literature studies submitted by the registrant to fulfill EPA data requirements. Unless otherwise noted, the data cited here are not from studies conducted according to Subdivision N guidelines, but nonetheless are considered scientifically valid and may be used in assessing the fate and transport of niclosamide in the environment. Because the open literature studies were not conducted according to the rigorous standards required under Subdivision N, there is some degree of uncertainty associated with the data, particularly if one is comparing the results of these studies to studies for other chemicals conducted according to Subdivision N guidance.

There are insufficient data available to adequately assess the environmental fate of niclosamide.

- In addition to dilution and dispersion, sorption to sediments and suspended particulates and possibly photodegradation (in clear shallow waters), are the major routes of dissipation of niclosamide. Neither hydrolysis nor volatilization from soil or water surfaces should be major fate processes for this compound.

- In most aquatic environments, niclosamide will adsorb to suspended solids and sediment. Though niclosamide does tend to bind to sediments, the binding is by no means irreversible, thus non-target species and benthic organisms, in particular, will be exposed to niclosamide for extended periods of time.

- It is unclear what role, if any, aerobic and anaerobic microbial degradation plays in the dissipation of niclosamide in the aquatic environment.

- In the lake environment, degradation of niclosamide would be expected to occur in a primarily sediment-free system, given the high ratio of water to sediment. As such, niclosamide is expected to remain in solution in the lake system and persist for long periods of time.

- Based on the bioconcentration factors and the rapid rate of depuration, accumulation in fish is not expected.

a. Niclosamide Chemical Degradation

Niclosamide does not appear to undergo hydrolytic degradation, however it does photodegrade in water. In a supplemental study that addressed both the hydrolysis and aqueous photolysis data requirements (MRID 42552313), [^{14}C]niclosamide did not degrade either in buffered solutions adjusted to pH 5.0, 6.9, or 8.7; or in pond water (pH 7.0-7.8) incubated in the dark for up to 56 days. Niclosamide ranged from 93 to 99% of the total radioactivity from each TLC plate in the study. Under photolytic conditions, niclosamide degraded with a half-life of 3.3 days in a pH 6.9 buffered solution that was irradiated by long-wave UV light for up to 14 days. A new photodegradation in water study is needed because, among other deficiencies, degradates were not identified, material balances were not

reported, and the output of the light source may not have been comparable with natural sunlight. Therefore, there is a high degree of uncertainty surrounding the photolysis half-life. However, based on this supplemental study and the UV/visible spectrum of niclosamide (max. 330 nm), it does appear that niclosamide is susceptible to photodegradation in water, and this will be a significant route of dissipation only in clear and shallow water bodies.

b. Niclosamide Mobility

In an acceptable batch equilibrium study (Dawson *et al.*, 1986) (MRID 42552315, 42552316), it was found that the mobility of niclosamide was dependent on the pH of the system. Mobility appeared to increase at higher pH's. It should be noted that niclosamide reportedly precipitates from aqueous solutions when the pH is less than 6.5.

Table 7: Average dissociation constants (Kd) for niclosamide at differing pH and sediment type.

sediment	% organic matter	pH 6.5	pH 7.0	pH 8.0	pH 9.0
		average K_d			
Tahquamenon River sand	0.9	17	14	5	1
Ford River loamy sand	5.0	60	79	41	12
Arkansas loam	2.5	199	129	39	15
Cedar River sandy loam	9.0	316	85	69	7

Under acidic and neutral conditions, niclosamide was not mobile. At pH 8, niclosamide was moderately mobile in the sand sediment, but not mobile in the other three sediments. In alkaline (pH 9) conditions, niclosamide was very mobile in the sand and moderately to slightly mobile in the loamy sand, loam, and sandy loam sediments. In most aquatic environments, niclosamide will adsorb to suspended solids and sediment.

A supplemental mobility study identified the major route of dissipation for niclosamide from the water column, excluding dilution or dispersion, is adsorption to the sediment (MRID 42552317). Niclosamide concentrations decreased in the water column at a faster rate in beakers with lake water and sediment exposed to sunlight than in beakers without sediment exposed to sunlight. There was no difference in disappearance rates of niclosamide between light and dark beakers without sediment, indicating that photolysis may not play a major role in the dissipation of niclosamide. After 96 hours, 71% of the niclosamide was still present in beakers with sediment exposed to sunlight, versus 107% in light exposed beakers without sediment and 110% in dark beakers without sediment. In a test that eliminated microbial and photolytic processes, niclosamide concentrations decreased faster in sterile dark test tubes with sediment than in sterile dark test tubes without sediment. This study also found no difference in disappearance rates of niclosamide among non-sterile light test tubes with sediment, sterile light test tubes with sediment and sterile dark test tubes with sediment. In the presence of sediment, the half-life of niclosamide in the water column was less than 10 days.

In the lake environment, degradation of niclosamide must occur in a primarily sediment-free system, given the high ratio of water to sediment. As such, niclosamide is expected to remain in solution in the lake system and persist for long periods of time.

Volatilization from dry and moist soil surfaces, or from water surfaces should not be a major fate process for this compound. The measured vapor pressure is 9.9×10^{-9} mm Hg at 25EC and the estimated Henry's Law constant is 6.5×10^{-10} atm-m^3/mole.

No data have been provided concerning the mobility of niclosamide degradates. However, previous information suggested that aminoniclosamide binds to sediment as well. Since aminoniclosamide is said to be 80-fold less toxic than parent niclosamide, confirmatory mobility data on this degradate is not required.

c. Niclosamide Bioaccumulation

In a supplemental study (MRID 44128201), bioconcentration factors were determined to be 49x for edible tissue, 215x for whole fish, and 916x for viscera in rainbow trout. The concentration of radioactive residues in the fish increased very rapidly to a plateau during the first three days of exposure. Depuration was rapid and fairly complete by day 10 of the elimination period. There is some degree of uncertainty surrounding the results of this study since neither the radioactivity in the water, nor the accumulated radioactivity in the fish tissues was identified, but was assumed to be parent niclosamide. There is reason for concern that photodegradates may have been present in the test tank, particularly since it appears that niclosamide may be susceptible to photolysis and that a small amount of acetone, a photosensitizer, was used as a co-solvent. However, given the stability of niclosamide to hydrolysis at the pH values in the study, and the flow-through design of the experiment, significant degradation of niclosamide in the exposure tank would not be expected.

d. Niclosamide Field Studies

A monitoring study (MRID 42552317) was conducted in Seneca Lake, New York to describe the distribution, dispersion, and dissipation of niclosamide in the water column after an application and to assess its bioaccumulation by, and toxicity to, two species of caged, non-target fish.

Granular Bayer 73 was applied at a nominal rate of 110 kg/ha (2300 ug/L, assuming dissolution into the bottom 10 cm of water). Niclosamide concentrations in the lake water samples ranged from <10 to 573 ug/L. Concentrations were generally lowest at the surface and highest at the bottom (0.1 m). Although there is an expectation that niclosamide is released from granules into the bottom 5 cm of the water column, it was found throughout the water column; a result of either mixing or premature release. Concentrations greater than 40 ug/L were measured at all depths and stations within the treatment area. After 48 hours, all concentrations were below 30 ug/L. Concentrations were below the detection limit (10 ug/L) by 96 hours after application.

Niclosamide residues in fish muscle tissue were consistent with water concentration and distribution patterns. Residues ranged from 0 to 858 ng/g and were highest in fish from the bottom depth at all stations. Residues increased until 14-24 hours after application and then declined.

The selective toxicity of granular niclosamide is based on the assumption that dissolution takes place at the sediment-water interface, implying that non-target fish could escape lethal concentrations whereas sea lamprey larvae, which live in the substrate and are relatively weak swimmers, would be killed. However, the results of this investigation show that both lampreys and non-target fish will be exposed to niclosamide throughout the water column.

3. Niclosamide Aquatic Exposure Assessment

Since niclosamide is added directly to water, the estimated environmental concentrations (EECs) used in this evaluation were based on projected treatment concentrations derived from when niclosamide is applied with TFM. Application rates for the TFM/niclosamide mixture are based on pH, temperature, stream/river discharge rates and bioassay data. Treatment levels of niclosamide have historically ranged between 25 to 35 ppb (personal communication, Terry Bills, Fishery Biologist, U. S. Geological Survey Biological Resource Division 1999); this range of treatment levels was used in the aquatic risk assessment.

H. Environmental Exposure and Risk Characterization for TFM and Niclosamide

a. Risk presumptions

Risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of this integration is called the quotient method. Risk quotients (R.Q.) are calculated by dividing exposure estimates by acute and chronic ecotoxicity values.

RQ = EXPOSURE/TOXICITY

RQ values are then compared to OPP's levels of concern (LOCs). These LOCs are used by OPP to analyze potential risk to nontarget organisms and the need to consider regulatory action. The criteria indicate that a pesticide used as directed has the potential to cause adverse effects on nontarget organisms. LOCs currently address the following risk presumption categories: (1) **acute high** -- potential for acute risk is high; regulatory action may be warranted in addition to restricted use classification, (2) **acute restricted use** -- the potential for acute risk is high, but may be mitigated through restricted use classification, (3) **acute endangered species** - endangered species may be adversely affected, and (4) **chronic risk** - the potential for chronic risk is high regulatory action may be warranted. Currently, the Agency does not perform assessments for chronic risk to plants, acute or chronic risks to nontarget insects, or chronic risk from granular/bait formulations to birds or mammals.

The ecotoxicity test values (measurement endpoints) used in the acute and chronic risk quotients are derived from required studies. Examples of ecotoxicity values derived from short-term laboratory

studies that assess acute effects are: (1) LC50 (fish and birds), (2) LD50 (birds and mammals), (3) EC50 (aquatic plants and aquatic invertebrates) and (4) EC25 (terrestrial plants). Examples of toxicity test effect levels derived from the results of long-term laboratory studies that assess chronic effects are: (1) LOAEC (birds, fish, and aquatic invertebrates), (2) NOAEC (birds, fish and aquatic invertebrates), and (3) MATC (fish and aquatic invertebrates). For birds and mammals, the NOAEC generally is used as the ecotoxicity test value in assessing chronic effects, although other values may be used when justified. Generally, the MATC (defined as the geometric mean of the NOAEC and LOAEC) is used as the ecotoxicity test value in assessing chronic effects to fish and aquatic invertebrates. However, the NOAEC is used if the measurement end point is production of offspring or survival.

Risk presumptions and the corresponding RQ values and LOCs, are tabulated below.

Table 8: Risk Presumptions for Terrestrial and Aquatic Animals

Risk Presumption	RQ	LOC		LOC
Birds and Mammals			Aquatic Animals	
Acute High Risk	EEC[1]/LC50 or LD50/sqft[2] or LD50/day[3]	0.5	EEC/LC50 or EC50	0.5
Acute Restricted Use	EEC/LC50 or LD50/sqft or LD50/day (or LD50 < 50 mg/kg)	0.2	EEC/LC50 or EC50	0.1
Acute Endangered Species	EEC/LC50 or LD50/sqft or LD50/day	0.1	EEC/LC50 or EC50	0.05
Chronic Risk	EEC/NOAEC	1	EEC/MATC or NOAEC	1

[1] abbreviation for Estimated Environmental Concentration (ppm) on avian/mammalian food items

[2] (mg/ft^2)/(LD50 x wt. of bird)

[3] (mg of toxicant consumed/day)/ (LD50 x wt. of bird)

Table 9. Risk Presumptions for Plants

Risk Presumption	Terrestrial and Semi-Aquatic Plants		Aquatic Plants	
	RQ	LOC	RQ	LOC
Acute High Risk	EEC[1]/EC25	1	EEC[2]/EC50	1
Acute Endangered Species	EEC/EC05 or NOAEC	1	EEC/EC05 or NOAEC	1

[1] EEC = lbs ai/A

[2] EEC = (ppb/ppm) in water

b. Environmental Risk Assessment

In order to evaluate the potential risk to aquatic and terrestrial organisms from the use of TFM and niclosamide, risk quotients (RQ) are calculated from the ratio of estimated environmental concentrations (EECs) to ecotoxicity values; all calculated values can be found in an appendix to the Environmental Fate and Effects Division Niclosamide Risk Assessment (July, 1999). For this analysis, avian EECs were based on the maximum application rate reported, *i.e.*, 12 ppm of TFM. Aquatic EECs were based on actual predicted application rates for TFM. Since much of the TFM toxicity data were

collected using pH range 7.2-7.6, the predicted concentrations of TFM in the water, based on model outputs, ranged from 0.7-2.2 ppm (personal communication, Dorrance Brege, U. S. Geological Survey Biological Resource Division 1999). These rates are based on pH, alkalinity, temperature, stream/river discharge rates and bioassay data that have been incorporated into a spread-sheet format by the U. S. Fish and Wildlife Service. Based on application rates and past use history it has been determined that typical EECs from the use of niclosamide will range from 25 to 35 ppm. All risk quotient calculations for niclosamide will be based on these EECs. RQ values are then compared to levels of concern (LOC) criteria that are used by the Office of Pesticide Programs in the determination of potential risk to nontarget organisms and the resulting need for possible regulatory action.

c. Exposure and Risk to Non-target Terrestrial Organisms

TFM and niclosamide are only registered for use on aquatic sites; therefore, the typical terrestrial analysis of risk, based on exposures developed by Hoerger and Kenega (1972) and as modified by Fletcher *et al.* (1994) is not applicable for establishing the risk of TFM to non-target terrestrial species. However, because numerous avian, *i.e.*, waterfowl and shorebirds, and mammalian species (muskrats, beavers, raccoons and numerous other small mammals) typically utilize aquatic environments as nesting and/or feeding habitats and may be exposed to TFM and or niclosamide via contaminated water, it is appropriate to use the aquatic EECs for conducting the risk assessment to terrestrial species.

Calculated acute RQ values show that there is virtually no acute risk to birds or mammals from the use of TFM or niclosamide (RQ < 0.1). RQ values for chronic exposure were not calculated; no chronic concerns are expected.

d. Exposure and Risk to Non-Target Freshwater Aquatic Organisms.

(1) Acute Fish

For TFM, RQ values based on 1, 24, and 96-hr LC_{50} values and predicted treatment levels of 2.2 ppm and 0.7 ppm exceeded acute high risk levels of concern. Based on 1-hr LC_{50} values and an exposure level of 0.7 to 2.2 ppm, acute high risk LOCs were exceeded for 33% of the species tested. Using 24-hr LC_{50} values and an exposure level of 0.7 ppm, acute high risk LOCs were exceeded for 17% of the species tested.

TFM RQ values for the various developmental stages of fish were calculated for predicted treatment concentrations of 0.7 ppm and 2.2 ppm. Acute high risk LOCs are exceeded for 17% of the developmental stages at treatment concentrations of 0.7 ppm and all of the developmental stages at a treatment concentration of 2.2 ppm. Green eggs and eyed eggs were the most sensitive developmental stages based on RQ.

TFM RQ values were examined over a range of pH (6.5 - 9.5) for rainbow trout, and were based on predicted treatment concentrations for each of the pH levels. Predicted treatment concentrations ranged from a low of 0.2 ppm at pH 6.5 to a high of 9 ppm at pH 9.5. RQ values were

relatively consistent (range 0.16 to 0.39) for minimum target concentrations and underscore how treatment levels are adjusted relative to pH to reflect changes in toxicity. At maximum projected treatment concentrations (range 0.6 - 9 ppm), RQ values range from 0.36 to 1.2; acute high risk, restricted use and endangered species LOCs are exceeded at pH values less than 8.1. At minimum predicted application rates ranging from 0.2 to 1.6 ppm, restricted use and endangered species LOCs are exceeded for rainbow trout at all pH levels.

For niclosamide, RQ values based on 96-hr LC_{50} values and predicted treatment levels of 25 ppb and 35 ppb exceeded acute high risk levels of concern. Acute high risk LOCs were exceeded for sea lamprey and rainbow trout at a treatment level of 25 ppb; at 35 ppb, acute high risk LOCs were exceeded for the majority (60%) of the species tested. The following table summarizes risk quotients for freshwater fish tested.

Table 10: Summary of risk quotients to fresh water fish species based on predicted treatment levels of niclosamide at 25 and 35 ppb.

Species Flow-through or Static	EEC (ppm)	96-hour LC_{50} (ppm)	RQ	EEC (ppm)	RQ
Rainbow trout	0.025	0.03	0.83*	0.035	1.3*
Bluegill sunfish	0.025	0.094	0.27**	0.035	0.37**
Sea lamprey	0.025	0.049	0.5*	0.035	0.71*
Carp (*Cyprinus carpio*)	0.025	0.120	0.21**	0.035	0.29**
Green sunfish (*Lepomis cyanellus*)	0.025	0.170	0.15**	0.035	0.50*

* Acute high risk, acute restricted use and endangered species LOCs exceeded.
** Acute restricted use and endangered species LOCs exceeded.
***Endangered species LOCs exceeded

Niclosamide RQ values were examined over a range of pH (6.5 - 9.5) for rainbow trout and were based on treatment concentrations of 25 and 35 ppb. The data indicate that as water becomes more acidic, the risk to fish increases by roughly a factor of 10.

RQ values for the mixture of TFM/niclosamide (98:2 by weight), based on predicted treatment concentration of 0.7 ppm and 2.2 ppm and niclosamide of 25 to 35 ppb indicate that acute high risk LOCs are exceeded. It should be noted however, that niclosamide is typically added to TFM to reduce the amount of TFM needed. Thus, predicted TFM treatment concentrations of 0.7 to 2.2 ppm for water with pH 7.2 to 7.6 would be considered high.

(2) Chronic Fish

No chronic toxicity data for TFM or niclosamide were available for fish. Since little is known about the persistence of these compounds, it is not possible to predict the likelihood of fish being exposed to toxic levels. Given the dilution potential with the volume of water in the lakes, there is little

concern about toxic levels in the Great Lakes themselves. However, due to the uncertainty regarding persistence, there may be chronic concerns for organisms downstream from the application site prior to dilution in the lake.

(3) Acute Aquatic Invertebrates

Aquatic acute high risk, acute restricted use, and endangered species LOCs are exceeded for aquatic invertebrates at the typical use rates of TFM. Acute restricted use and endangered species LOCs are exceeded for 67% of the aquatic invertebrates at the predicted minimum concentration in water pH 7.2 - 7.6. At the maximum predicted treatment concentration, acute restricted use and endangered species LOCs are exceeded for 83% of the aquatic invertebrates tested.

For niclosamide, acute high risk LOCs are exceeded for aquatic earthworms and flatworms. Aquatic acute high risk, acute restricted use, and endangered species LOCs are exceeded for aquatic invertebrates at the typical use rates of niclosamide.

Aquatic invertebrate RQ values for the mixture of TFM and niclosamide at the minimum predicted concentration of 0.7 ppm TFM, range from 0.03 to 0.46, while RQ values for the maximum predicted treatment concentration of 2.2 ppm TFM range from 0.08 to 1.47. Acute restricted use and endangered species LOCs are exceeded for aquatic invertebrates at minimum predicted treatment concentrations for waters of pH 7.2 - 7.6. The data indicate that of the species tested, flatworms are at the greatest risk from the use of mixture of TFM and niclosamide to control the sea lamprey. Data suggest that aquatic invertebrates feeding on bottom sediments are more likely to be at risk to TFM/niclosamide treatments and exposures may be a result of ingestion of TFM/niclosamide bound to detritus.

The TFM/niclosamide mixture results in higher toxicity to aquatic invertebrates; however, the increase in toxicity is not proportional to that of the lamprey. In other words, lampreys undergo a marked increase in toxicity to the TFM/niclosamide compared to the relatively small increase in sensitivity exhibited by aquatic invertebrates. This differential toxicity between sea lamprey larvae and nontarget aquatic invertebrates as a result of using the TFM/niclosamide mix is exploited to enhance mortality of sea lamprey larvae while reducing effects on nontargets (pers. comm. Terry Bills, Fishery Biologist, U.S. Geological Survey 1999).

e. Plants

For TFM, the RQ values for aquatic plants, at the minimum treatment level of 0.7 ppm, range from <0.2 to 0.58, while the RQ values for the maximum treatment level of 2.2 ppm range from < 0.15 to 1.83. Acute high risk and endangered species LOCs are exceeded for aquatic plants at the typical use rates of TFM.

No acute levels of concern were exceeded for the aquatic plant species tested with niclosamide. At the typical maximum treatment rate of 35 ppb for niclosamide, green algae were the most sensitive with an RQ of 0.85.

f. Endangered Species

Freshwater fish and aquatic invertebrate endangered species LOCs are exceeded for TFM and niclosamide and aquatic plant endangered species LOCs are exceeded for TFM. The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that will eliminate the adverse impacts. At present, the program is being implemented on an interim basis as described in a Federal Register notice (54 FR 27984-28008, July 3, 1989), and is providing information to pesticide users to help them protect endangered species on a voluntary basis. As currently planned, the final program will call for label modifications referring to required limitations on pesticide uses, typically as depicted in county-specific bulletins or by other site-specific mechanisms as specified by state partners. A final program, which may be altered from the interim program, will be described in a future Federal Register notice.

The U.S. Fish and Wildlife Service's lamprey control program routinely engages in Section 7 consultations when endangered/threatened species are suspected to be present in treatment areas. In studies conducted on lake sturgeon (*Acipenser fulvescens*), concentrations of TFM approximately 1.3 times the $LC_{99.9}$ of sea lamprey larvae were not lethal to juvenile lake sturgeons (Johnson *et al.* 1999). If endangered or threatened species were known to inhabit projected treatment sites, treatment concentrations of the lampricides would be adjusted to minimize impact to these species. Adjustments would include the use of TFM/niclosamide mix to broaden the differential toxicity of these compounds, and thus increase toxicity to sea lamprey larvae while holding the toxicity to nontarget species relatively constant (personal communication, Terry Bills, Fishery Biologist, U.S. Geological Survey Biological Resource Division 1999; Bills et al. 1985). According to the U.S. Fish and Wildlife Service (personal communication, Terry Morse, Treatment Supervisor, U.S. Fish and Wildlife Service 1999), if treatment concentrations could not be adjusted to minimize impact to sensitive nontarget species, then the identified habitats would not be subjected to lampricide use.

I. Environmental Risk Characterization for TFM and Niclosamide

TFM is both chemically and biologically stable and without evidence to the contrary is expected to remain toxic for long periods of time. However, mitigation of its effects at the treatment site is likely to occur as a result of the flushing action of the stream/river. TFM is a phenolic compound and behaves as a weak acid; its neutral form (free phenol) is more likely to cross cell lipid membranes, and thus its uptake and toxicity are strongly dependent on pH (Bills *et al.* 1988); however, at the pH of most natural streams/rivers, the majority of the compound will be in the ionized form. Un-ionized TFM was more readily adsorbed than the ionized (phenolate) form; however, the adsorption process was readily reversible.

Decisions regarding application rates and times are based on both abiotic and biotic factors including pH, stream discharge, time of day, temperature, in-field bioassays and population assessment data. Spreadsheet-based flow models have been developed to assist in determining application rates, flowtimes, and dilution factors. Models are developed only for streams with complex treatment scenarios, including marked diurnal fluctuations in pH or physical/chemical changes. These models permit greater latitude in explaining possible effects of input factors on treatment concentrations and start times of applications. Predicted treatment concentrations for specific locations, based on physico-chemical data or in-stream toxicity tests, are intended to result in a concentration greater than the $LC_{99.9}$ for sea lamprey while being substantially less than the LC_{25} for brown trout. This improves treatment effectiveness for sea lampreys, yet minimizes the effect on nontarget species. Predicted treatment concentrations based on physico-chemical data may be modified on the basis of data produced by on-site flow-through toxicity tests. In Lake Superior and upper Lake Michigan, streams tend to have soft water with pH less than 8.2 and thus require lower application rates, *i.e*., less than 6 ppm. In the lower tier of the Great Lake, tributaries harboring lamprey may exhibit hardnesses exceeding 200 ppm with a pH range 8.1 - 8.7. Care must be taken in selecting application rates for streams with large diurnal pH fluctuations. Typically, initial target concentrations remain primarily based on the lower observed pH values because of the increased toxicity potential of TFM at lower pH. TFM target concentrations in hard water streams may range from 1 to 6 ppm. While application rates as high as 12 ppm have been reported, the cost effectiveness of TFM at this concentration would be better offset by applying TFM/niclosamide mix (99:1) and as such, applications of TFM at greater than 9 ppm would rarely occur (personal communication, Dorance Brege, U.S. Fish and Wildlife Service Treatment Supervisor 1999).

Estimated environmental TFM concentrations used in this evaluation (range 0.7 - 2.2 ppm) are projected treatment concentrations derived from a nomograph developed by U.S. Fish and Wildlife Service reflecting toxicity over ranges in both pH and alkalinity that were representative of the conditions under which most of the toxicity data were reported, *i.e*., pH range 7.2 - 7.6 and water hardness 44 mg/L as $CaCO_3$. Estimated environmental concentrations of niclosamide used in this evaluation (25 to 35 ppb) were based on typical concentrations reported by the Fish and Wildlife Service. At the predicted treatment levels, acute high risk, acute restricted use, and endangered species LOCs are exceeded for aquatic animals. Use of the TFM/niclosamide mixture results in larger exceedences of the LOCs; however, the mixture tends to exhibit a marked increase in toxicity to sea lamprey larvae while nontarget organisms exhibit only a moderate increase. Although TFM is likely to have an immediate effect on the aquatic community, the data suggest that most organisms recover quickly and the treatment area community structure returns to pre-treatment conditions within approximately 6 months (Kolton et al.,1986). Additionally, a genuine effort is made to document where sensitive populations reside and steps are undertaken to avoid treatments at concentrations known to be toxic to these organisms. The long-term effects to more sensitive species, such as indigenous lampreys, and to aquatic communities downstream from the treatment sites where chronic effects may be more likely, remain uncertain.

Because of the nature of the use of TFM and niclosamide, *i.e.*, applied to flowing water, it is difficult to characterize the magnitude of the ecological effects associated with use of the chemical. Aquatic organisms in the treatment area are expected to be impacted to some extent during the proposed 12-hr treatments. Impacts to aquatic communities in terms of food-web structure are unknown. The two

Special Local Needs labels for niclosamide are for application to ponds in which ornamental fish are grown; these fish ponds are contained, an NPDES permit is required for water release and there should be very low exposure to nontargets from this use. Therefore, the risks associated with this use of niclosamide are expected to be neglible.

In the environment, the sorption and degradation of TFM by sediments is expected to occur primarily in the lakes and not in the tributary streams. Most of the TFM will be quickly flushed into the lakes. The amount removed by sorption to the stream sediments is unknown, but is likely to be minimal. In the lake environment, degradation of TFM and niclosamide must occur in a primarily sediment-free system, given the high ratio of water to sediment and the lack of sediments containing appreciable amounts of organic material (Thingvold, 1975). As such, TFM is expected to remain in solution in the lake system and persist for long periods of time at low concentrations.

In addition to dilution and dispersion, sorption to sediments and suspended particulates and possibly photodegradation (in clear shallow waters), are the major routes of dissipation of niclosamide. Neither hydrolysis nor volatilization from soil or water surfaces should be major fate processes for this compound. In most aquatic environments, niclosamide will adsorb to suspended solids and sediment. Though niclosamide does tend to bind to sediments, the binding is by no means irreversible, thus non-target species and benthic organisms in particular, will be exposed to niclosamide for extended periods of time. It is unclear what role, if any, aerobic and anaerobic microbial degradation plays in the dissipation of niclosamide in the aquatic environment.

Although TFM and niclosamide are not expected to bioaccumulate in aquatic organisms, two potential exposure scenarios exist. Aquatic animals may be directly exposed to lampricide in the water as the chemical block moves through during roughly a 24-hr period. Additionally, predatory animals may be exposed through the consumption of prey incapacitated by lampricide treatments. However, in a study of the lampricide niclosamide, it was estimated that the common tern (*Sterna hirundo*), a shore bird which is a state-listed endangered species in Michigan, would have to consume roughly 16.8 times its body weight in contaminated sea lamprey larvae to approach toxic levels (Hubert *et al*. 1999).

While TFM and niclosamide treatments will likely impact stream/river community structure in the short term, data suggest that most organisms recover quickly and the treatment area community structure returns to pre-treatment conditions within approximately 6 months (Kolton et al.,1986). This recovery is site specific and may take much longer in certain environments and certain species may be significantly impacted, most notably the indigenous lamprey species that may populate treatment areas. In general, however, native lamprey species have tended to populate the upper reaches of tributary streams whereas the sea lamprey is more likely to inhabit lower reaches of the stream. Thus, nontarget species that may have been affected in the treatment area are repopulated through downstream migration from untreated areas. Furthermore, retreatment of the stream will not occur for at least 3 to 5 years.

It is believed that, given the current application rates, the effects of TFM and niclosamide are mitigated solely by the flushing action of the stream through the treatment site. Effects on the aquatic environment downstream from the treatment site are unknown and would depend heavily on the

stream/river discharge rate, water temperature, pH and alkalinity and the proximity of sensitive nontarget organisms. While treatment areas have demonstrated a capacity to recover, the downstream acute and chronic effects, where TFM is most likely to be deposited, remain uncertain.

Exposure to TFM during embryonic development increased the frequency of abnormalities that lead to increased mortalities and stream treatments with lampricides have resulted in a shift in sex ratios among lampreys over a 16-yr period. TFM treatments have been associated with induction of hepatic mixed function oxyganase activity and altered levels of circulating steroids in fish and induced hepatic vitellogenesis in primary cultures of rainbow trout hepatocytes. As such, TFM acts as an estradiol agonist and has a demonstrated endocrine disrupting effect. The potential for TFM to result in endocrine disrupting effects on fish populations in treatment areas has been considered remote based on the fact that streams are treated at most once every 3 to 5 years, exposure duration is less than 24 hours and TFM has not been demonstrated to persist in treatment areas (Hewitt et al. 1998). However, the duration of exposure to fish downstream of the application site has not been adequately characterized and thus the potential for an endocrine disrupting effect cannot be dismissed.

1. Terrestrial

TFM and niclosamide are only registered for use on aquatic sites. However, because numerous avian, (waterfowl and shorebirds) and mammalian species (muskrats, beavers, raccoons and numerous other small mammals) typically utilize aquatic environments as nesting and/or feeding habitats, and may be exposed to TFM and niclosamide via contaminated water, there is some potential for exposure to terrestrial species. Additionally, the aerial application of the niclosamide 3.2% granular formulation may serve as a route of exposure to nontarget terrestrial organisms.

Based on the available toxicity data there is very little risk from either acute oral, acute dermal or subacute dietary exposure to mammals or birds. Acute RQs for both birds and mammals (< 0.01) show that there is minimal risk from the concentrations likely even at a maximum treatment concentrations. In addition, during the nearly forty years of TFM use to control the sea lamprey, there are no actual field reports documenting any acute mortality to avian or mammalian species.

There are no available chronic toxicity data for TFM or niclosamide for avian species. However, because of the very low levels of exposure and the relatively short time that terrestrial species will be exposed, chronic risk to terrestrial species is expected to be very low.

2. Aquatic

TFM and niclosamide are applied directly to water and maintained at a desired concentration for a specified period of time, *i.e*., generally 12 hours. A number of environmental factors influence the toxicity of TFM; these factors include stream/river discharge rate, pH, and temperature. Of all of the water quality parameters investigated, pH had the greatest influence on the toxicity of TFM to aquatic organisms as pH affects the availability and uptake of TFM by aquatic organisms. In general, the lower the pH, the greater the uptake and thus, the greater the toxicity.

TFM ranged in toxicity from slightly to highly toxic to freshwater fish. Based on 1-hr LC_{50} values, acute high risk, acute restricted use and endangered species LOCs were exceeded for 33% of the species tested while acute restricted use and endangered species LOCs were exceeded for all of the species at predicted maximum treatment concentrations of 2.2 ppm. At the minimum predicted treatment concentration of 0.7 ppm and based on 96-hr LC_{50} values, acute high risk, acute restricted use and endangered species LOCs were exceeded for all of the species tested.

Studies described in NRCC (1985) have suggested that native lamprey (*Ichthyomyzon* spp. and *Lampetra* spp.) are less sensitive (9-hr $LC_{99.9}$ 2.0 and 2.5 mg/L), than the sea lamprey (9-hr $LC_{99.9}$ 1.4 mg/L) and that this differential sensitivity may lessen the impact to native species.

TFM was slightly to moderately toxic to freshwater invertebrates; acute restricted use and endangered species LOCs are exceeded for 67% of the aquatic invertebrates at the predicted minimum concentration of 0.7 ppm in water pH 7.2 - 7.6. At the maximum treatment concentration of 2.2 ppm for these waters, acute restricted use and endangered species LOCs were exceeded for 83% of the aquatic invertebrates tested. Tricopterans appeared to be particularly sensitive to the effects of TFM. Their sensitivity to the lampricide is consistent with the observation that bottom dwelling organisms that feed on detritus may have increased exposure to the lampricide by ingestion of TFM-bound sediments (pers. comm. Terry Bills, Fishery Biologist, U.S. Geological Survey Biological Resource Division 1999). Since 1981, the U.S. Fish and Wildlife Service has examined the effect of lampricide applications on more than 200 aquatic macroinvertebrates. Based on the data, it is estimated that greater than 95% of the nontarget macroinvertebraes survive exposure to lampricide applications. Recovery of the 6 sensitive nontarget organisms that were identified (*Hexagenia, Litobranchia, Chimarra, Dolophilodes, Glossosoma, and Simuljum*) often begins within days or weeks after exposure, and the short- and long-term diversity and health of the aquatic communities remains stable. The most apparent effect of TFM based on field observations was an immediate reduction in macroinvertebrate density that was attributed to increased downstream drift and mortality of sensitive organisms (NRCC 1985). Particulate feeding macroinvertebrates were the most sensitive to the effects of TFM and may reflect increased uptake of TFM by ingestion of TFM bound to particulate matter.

The effects of niclosamide on non-target aquatic invertebrates from sea lamprey control operations have been reported (Gilderhus, 1979). Although niclosamide treatment reduced the total number of aquatic invertebrates by 56% in the first 7 days after treatment, this effect was transitory.

TFM was toxic to aquatic plants and resulted in the inhibition of growth; at concentrations of greater than 35 ppm, TFM was herbicidal. Acute high risk and endangered species LOCs were exceeded in 20% of the plants evaluated at 2.2 ppm TFM. There are limited data on the effects of niclosamide on aquatic plants.

Since 1994, a broad range of nontarget mortality has been reported following application of both TFM and niclosamide (document reference numbers I008982-001 and I008983). Nontarget mortality affected 32 species of fish, 4 species of amphibians, and 4 groups of invertebrates (Table 11) during application of lampricides in tributaries of the Great Lakes, Lake Champlain, and Finger Lakes during

1994 - 1998. The most notable fish kills have occurred following the aerial application of the 5% granular formulation of niclosamide and resulted in approximately 169,000 fish killed. During September 1994, application of niclosamide to the Ausable River system, a tributary of Lake Champlain, killed approximately 33,000 indigenous American brook lamprey (*Lampetra appendix*) and silver lamprey (*Ichthyomyzon unicuspis*) combined. As recently as May 1999, nontarget fish mortality (log perch; *Percina caprodes*) was reported following TFM applications and resulted from a downward shift in pH in poorly buffered (low alkalinity) waters that increased the toxicity of TFM. These data indicate that despite efforts to minimize impact to nontarget species, there are occasional situations where nontarget mortality occurs. The incident reports on Lake Champlain suggest that nontarget mortality was enhanced following aerial application of the 5% granular formulation of niclosamide. The magnitude of nontarget mortality following this application verifies EPA's concern that aerial application of niclosamide is the least controlled application method and as such is the most susceptible to nontarget mortality.

Table 11: List of nontarget species or taxa experiencing mortality during application of lampricide in streams and deltas of streams tributary to the Great Lakes, Lake Champlain and the Finger Lakes of the U. S. during 1994-1998.			
Invertebrates			
annelids	Phylum Annelida (segmented worms: earthworms, aquatic worms, and leeches)	burrowing mayflies	Family Ephemeridae (burrowing mayflies)
Hexagenia	*Hexagenia spp.*	Mayflies	Order Ephemeroptera (mayflies)
Amphibians			
frogs	Family Ranidae (frogs)	salamanders	Order Candata (salamanders)
Northern two-lined salamander	*Eurycea bislineata*	red-spotted newt	*Notrophthalmus viridescens viridescens*
Fishes			
American brook lamprey	*Lampetra appendix*	banded killifish	*Fundulus diaphanus*
blackchin shiner	*Notropis heterodon*	blacknose dace	*Rhinichthys atratulus*
bluegill	*Lepomis macrochirus*	brown bullhead	*Ameiurus nebulosus*
bullheads	*Ameiurus spp*	common carp	*Cyprinus carpio*
common shiner	*Lusilus cornutus*	creek chub	*Semotilus atromaculatus*
emerald shiner	*Notropis atherinoides*	hornyhead chub	*Nocomis biguttatus*
johnny darter	*Etheostoma nigrum*	largemouth bass	*Micropterus salmoides*
logperch	*Percina caprodes*	longnose dace	*Rhinichthys cataractae*
mimic shiner	*Notropis volucellus*	minnows	Family Cyprinidae (carps and minnows)
Northern hog sucker	*Hypentelium nigricans*	perches	Family Percidae (perches)
redhorses	*Moxostoma spp.*	rock bass	*Ambloplites repestris*
silver lamprey	*Ichthyomyzon unicuspis*	smallmouth bass	*Micropterus dolomieu*
spottail shiner	*Notropis hudsonius*	stonecat	*Noturus flavus*
suckers	Family Catastomidae (suckers)	tadpole madtom	*Noturus gyrinus*
tessellated darter	*Etheostoma olmstedi*	trout perch	*Percopsis omiscomaycus*
white sucker	*Catostomus commersoni*	fishes	Osteichthyes (boney fish)

Although adverse effects to certain species and/or taxa have been observed, the evidence suggests that these effects are only transitory and do not threaten any populations of aquatic species.

Although there have been some cases where recolonization of affected populations have taken up to 6 or 7 months, most streams recovered to pretreatment levels in a matter of days or weeks. Recolonization of the treated areas usually occurs from untreated, upstream portions of the tributary although some recolonization may also occur from sediments that were too deep to be exposed.

3. Uncertainties

The environmental fate and ecological effects of TFM and niclosamide characterized in this document are restricted to the specific treatment site and focus on the acute toxicity of the lampricides given projected treatment levels selected to achieve a sea lamprey $LC_{99.9}$ with little nontarget mortality.

Given the persistence of TFM and niclosamide, mitigation of their effects relies predominately on the flushing action of the stream/river tributaries and eventual deposition and dilution in the Great Lakes. Initial assessments of the ecological effects assumed that both TFM and niclosamide would not be persistent in the treatment area and that the eventual dilution of both compounds in the Great Lakes would render chronic-effect studies unnecessary. However, the Agency is uncertain to the degree to which treatment site concentrations of TFM and niclosamide are rendered ineffective, meaning that the potential for chronic effects is uncertain particularly in the mixing zones at the confluence of tributaries with the Great Lakes. While the data suggest that treatment areas recover to pre-treatment community structure, certain species are sensitive to the effects of TFM and niclosamide. Although the direct effects of lampricide treatments have been partially characterized, the secondary effects on food chains and the ability of nontarget species to feed during the recovery period is uncertain. Although the ecological data gaps identified in this document may address uncertainties over potential chronic effects, the environmental fate of TFM and niclosamide downstream of application sites, *i.e*., the stream/river deltas is uncertain without monitoring studies to quantify TFM and niclosamide concentrations in the mixing zones.

Also, chemical-specific uncertainties are that the potential effects of TFM as an endocrine disruptor are difficult to characterize. Additionally, the newer formulations of niclosamide (3.2% granular) that result in its slow release along the stream/river bottom pose an unknown risk in terms of both acute and chronic toxicity to nontarget sediment-dwelling organisms.

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 ingredient 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 TFM and niclosamide 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 TFM and niclosamide. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of TFM and niclosamide, 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 TFM and the lampricide uses of niclosamide, and to determine that TFM and niclosamide can be used as low volume, restricted use compounds, as specified in this document, without resulting in unreasonable adverse effects to humans and the environment. The Agency therefore finds that all products containing TFM and niclosamide as the active ingredients are eligible for reregistration. The reregistration of particular products is addressed for lampricide uses in Section V of this document.

The Agency made its reregistration eligibility determination based upon the data required for reregistration, the current guidelines for conducting acceptable studies to generate such data, published scientific literature, and the data identified in Appendix B. Although the Agency has found that all uses of TFM and niclosamide 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 TFM and niclosamide, if new information comes to the Agency's attention or if the data requirements for registration or the guidelines for generating such data) change.

B. Determination of Eligibility Decision

1. Eligibility Decision

Based on the reviews of the generic data for the active ingredients TFM and niclosamide, the Agency has sufficient information on the health effects of TFM and niclosamide and on its potential for causing adverse effects in fish and wildlife and the environment. Although the current database is limited, this finding of sufficient information is based on the limited use pattern, stringent use restrictions mandated by the USFWS and the PPE required on current labels. The Agency has determined that TFM and niclosamide products, labeled and used as specified in this Reregistration Eligibility Decision, will not pose unreasonable risks of adverse effects to humans or the environment. Therefore, the Agency concludes that products containing TFM and niclosamide for all uses are eligible for reregistration.

2. Eligible and Ineligible Uses

The Agency has determined that all uses of TFM and niclosamide for control of Sea Lamprey are eligible for reregistration under the conditions specified in this RED.

The niclosamide Special Local Needs labels for use in ornamental fish ponds should result in minimum exposure to humans and non-target organisms and are eligible for reregistration under the conditions specified in this RED assuming monitoring programs similar to those conducted by the U.S. Fish and Wildlife Service (USFWS) are instituted for these uses. These monitoring programs include medical monitoring for applicators, a routine industrial hygiene program, an incident reporting system, and comprehensive use records.

The Agency has determined that the mollusicide use of niclosamide for human health purposes is not eligible for reregistration due to lack of data on the use and potential non-occupational exposure of humans to niclosamide. According to the Public Health Service at the Centers for Disease Control and Prevention, there are currently no public health uses for niclosamide in the United States. The currently labeled public health use is the use of Bayluscide 70% Wettable Powder (EPA Registration Number 6704-87) in Puerto Rico against fresh water snails serving as the vector for schistosomiasis. Niclosamide has not been used in Puerto Rico since 1980. This use is ineligible for reregistration at this time. In order for this use to be eligible for reregistration, a minimum of use information, application methods summary, and a 21-28 day dermal toxicity study (OPPTS 870.3200) are required.

The USFWS has submitted a voluntary cancellation letter for Bayluscide 5% Granular (EPA Registration Number 6704-90) which was used to kill snails serving as the vector for swimmer's itch in MI, WI, and MN.

C. Regulatory Position

The Agency recognizes the efforts of the USFWS and the Great Lakes Fisheries Commission to lessen the risks posed by TFM and niclosamide, by the use of extensive monitoring, IPM measures, public notification and worker training. In order to support these efforts EPA is requiring the following clarification measures for TFM and niclosamide containing products.

- The manual for application must be cited on the label and must be available to all workers.
- The required PPE must be clearly stated on the label.
- The label must prohibit aerial applications.

There are currently two Special Local Needs (SLN) labels issued for niclosamide; both labels are for the Bayluscide 70% Wettable Powder formulation. These labels are for the use of Bayluscide in ornamental fish ponds in Florida (**SLN FL94000100**) and Arkansas **(SLN AR99000700**). This use is to kill fresh water snails which infect the fish. The empty pond is treated with Bayluscide at 1 lb formulated product per acre of surface area; the pond is then filled with water. Fish are usually added to the pond in four to seven days. The labels require an NPDES permit for discharging the water from the

pond, but in practical terms, the water is rarely released without treatment. There have been no fish toxicity incidents reported from this use.

The risk assessment calculations reported for risks to humans were made with the following assumptions:

(1) The manual developed for the use of TFM and niclosamide by the USFWS will be adopted by any user of these compounds (i.e., add it as a requirement on all labeling). *Manual for Application of Lampricides in the U.S. Fish and Wildlife Service Sea Lamprey Control Program including Standard Operating Procedures* (1993).

(2) The USFWS administers a comprehensive medical monitoring program for their employees engaged in any activities involving the use of TFM and niclosamide.

(3) A routine industrial hygiene monitoring program is conducted to quantify exposures for those occupationally exposed to TFM and niclosamide (in lieu of completing a comprehensive pesticide guideline exposure study)

(4) The USFWS will maintain an incident reporting system.

(5) A record keeping system to document the use of TFM and niclosamide will also be maintained by the USFWS. Such a system should be able to document chemical use, locations, dates, site-specific data (e.g., water concentrations and amount used), efficacy, incidents, and any postapplication follow-up required. This system could be used to assess a relationship between the use of TFM and niclosamide and incidents and illnesses should they occur.

The purpose of these monitoring and reporting systems is to verify that EPA's assumptions of low exposure are correct and to ensure that potentially exposed populations are adequately protected.

The following is a summary of the Agency's regulatory position and rationale for managing risks associated with the use of TFM/niclosamide. Where labeling revisions are imposed, specific language is set forth in Section V of this document.

1. Food Quality Protection Act Findings

a. Determination of Safety for U.S. Population

The Agency has determined that there is no reasonable expectation of humans being exposed to TFM or niclosamide residues in the diet via water, fish, irrigated crops, and livestock due to the low use volume, the infrequency of use and the tight control USFWS has over the use of TFM and niclosamide including 24-hr irrigation and potable water intake restrictions. There are no established tolerances for TFM or niclosamide.

There are no residential uses and residential exposure is expected to be neglible.

If the Agency determines, as a result of later implementation process of FQPA, that any of the determinations described in this RED are no longer appropriate, the Agency will consider itself free to pursue whatever action may be appropriate, including but not limited to, reconsideration of any portion of this RED.

b. Endocrine Disruptor Effects

TFM treatments have been associated with induction of hepatic mixed function oxygenase activity and altered levels of circulating steroids in fish and induced hepatic vitellogenesis in primary cultures of rainbow trout hepatocytes (Hewitt et al. 1998). As such, TFM acts as an estradiol agonist and has a demonstrated endocrine disrupting effect.

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. EPA may require further testing of TFM active ingredient and end use products for endocrine disruptor effects when this program is in place.

2. Tolerance Reassessment

TFM has been classified as a low-volume and nonfood use chemical based on the quantity used, the method of application, and the rapid dissipation of any possible residues in fish and water. Therefore, a dietary risk assessment is not required for TFM and there are no tolerances.

3. Benefits from Use of TFM/Niclosamide

Although no formal benefits analysis was conducted for TFM and niclosamide, an informal analysis was provided by the USFWS. Sea Lampreys were introduced to the Great Lakes when the Welland Canal opened in 1829. These parasitic organisms are very destructive to commercial and sport

fish species in the Great Lakes. A variety of IPM measures including traps, weirs and a sterilized male program are in place to try to control the adult sea lamprey population; however, these measures are only partially successful. The TFM/niclosamide treatment program managed by the Great Lakes Fisheries Commission is necessary to protect commercial and sport fish populations in the Great Lakes.

4. Human Health Risk Mitigation

Worker Mitigation

Risk From Handler Exposure: Based on two worker exposure scenarios for TFM, workers are not at unreasonable risk from TFM use. The exposure assessments indicate that workers are primarily at risk to dermal, rather than inhalation exposure. The exposure scenarios were calculated using application information from 41 applications made in tributaries to the Great Lakes in 1997. The backpack application scenarios were calculated assuming that 1% of the total applied could be applied by backpack spray. The margins of exposure (MOE) were calculated taking into account the PPE required in the Fish and Wildlife Services Manual for Pesticide Application which is a double layer of clothing, rubber boots, chemical resistant gloves for TFM, and a respirator. However, respirators are only required in poorly ventilated areas and are not required for general (open air) applications. MOEs calculated with double layers of clothing, rubber boots and chemical resistant gloves, but with no respirators are still above 100 except for three large application scenarios which have MOEs of 66, 68, and 96. These applications would not be made by one person during one day; therefore, the Agency has determined that the MOEs for TFM are above the level of concerns and a respirator is not required for workers handling or applying TFM.

The TFM and niclosamide labels must be updated to clarify the double layer clothing and to ensure that the labels are consistent with the Manual for Lampricide Applications.

No risk assessment was conducted for niclosamide based on the low volume of use; therefore, the Agency is recommending to retain the PPE and use restrictions which are currently on the niclosamide labels.

Table 12 outlines the handler PPE required on the various TFM and niclosamide labels. No engineering controls are required. Although EPA has no data to specifically assess the exposure reduction to mixers/loaders afforded by a chemical-resistant apron, the Agency is persuaded that the exposure reduction would be significant for this chemical. Available data indicate that the preponderance of non-hand exposure to mixers/loaders/applicators and other handlers is to the front torso. Therefore, for mixers/loaders/applicators and other handlers the use of a chemical-resistant apron is probably approximately equivalent to double-layer body protection.

Table 12. Summary of Worker Protection Requirements for TFM and Niclosamide	
Exposure Scenario	**PPE Required**
TFM	
Mixing/Loading	face shield, double layer of clothing, rubber boots, and chemical resistant gloves
Applying with metered pump.	face shield, double layer of clothing, rubber boots, and chemical resistant gloves
Applying with backpack sprayer	face shield, double layer of clothing, rubber boots, and chemical resistant gloves.
Niclosamide	
Mixing/Loading/Applying 70% Wettable Powder Formulation	face shield, double layer of clothing, rubber boots, chemical resistant gloves, NIOSH approved PF-10 respirator
Mixing/Loading/Applying 3.2% Granular applications	face shield, double layer of clothing, rubber boots, chemical resistant gloves, NIOSH approved PF-10 respirator.

Other Risks: No residential exposures or occupational post-application exposures are expected from the approved registered uses of TFM and niclosamide given compliance with the USFWS regulations.

5. Ecological Risk Mitigation

Mammalian and Avian Mitigation

Aerial applications are to be prohibited on all new labels in order to lessen chances of exposures to nontarget terrestrial animals. Several of the fish kills reported to the Agency were the result of aerial applications of the product which is being voluntarily canceled.

There should be very limited exposure to terrestrial animals and, therefore, low risk to most birds and mammals. The USFWS limits applications in order to avoid disturbing nesting osprey. No further mitigation is necessary for terrestrial systems.

Aquatic Species Mitigation

Although application rates are carefully monitored and adjusted to minimize impact to nontarget aquatic organisms, the analysis of the environmental fate and ecotoxicity indicates that current application rates will impact non-target aquatic organisms. When the combination of TFM and niclosamide are applied, the toxic effects of TFM are potentiated. The extent or degree of adverse effects in the treatment area depends on stream/river discharge rate, pH, hardness and water temperature. Although TFM is likely to have an immediate effect on the aquatic community in the treatment area, the data suggest that most organisms recover quickly and the treatment area community structure returns to pre-

treatment conditions within approximately 6 months (Kolton et al.,1986). Additionally, a genuine effort is made to document where sensitive populations reside and steps are undertaken to avoid treatments at concentrations known to be toxic to these organisms. Some areas are not treated because of the sensitive or endangered species concerns. The long-term effects to more sensitive species, *e. g.*, indigenous lampreys, lake sturgeon and Mayflies, and to aquatic communities downstream from the treatment sites where chronic effects are more likely, remain uncertain.

The goal of The Great Lakes Fishery Commission is to control the sea lamprey populations and not to eradicate the sea lamprey. The Commission has targeted that the reliance on lampricides be reduced by 50%. Through a combination of physical barriers, sterile male release and fine tuning of lampricide applications, lampricide use has been reduced by 35% compared to levels used in the 1980's. To further reduce chemical reliance while controlling the lamprey populations, the Commission has recommended that additional research be conducted on the use of pheromones to serve as attractants to traps and treatment areas, the use of TFM/niclosamide mix, and the use of lampricide formulations that better direct treatments to habitats favored by larval sea lamprey.

6. Labeling Rationale

a. Occupational Risk Mitigation

The Worker Protection Standard (WPS)

At this time none of the registered uses of TFM and niclosamide are within the scope of the Worker Protection Standard for Agricultural Pesticides (WPS).

(1) Personal Protective Equipment for Handlers (Mixers, Loaders, Applicators, etc.)

For each end-use product, PPE requirements for pesticide handlers are set during reregistration in one of two ways:

1. If EPA determines that no regulatory action must be taken as the result of the acute effects or other adverse effects of an active ingredient, the PPE for pesticide handlers will be based on the acute toxicity of the end-use product. For occupational-use products, PPE must be established using the process described in PR Notice 93-7 or more recent EPA guidelines.

2. If EPA determines that regulatory action on an active ingredient must be taken as the result of very high acute toxicity or certain other adverse effects, such as allergic effects or systemic effects (cancer, developmental toxicity, reproductive effects, etc.):

- In the RED for that active ingredient, EPA may establish minimum or "baseline" handler PPE requirements that pertain to all or most end-use products containing that active ingredient.

- # These minimum PPE requirements must be compared with the PPE that would be designated on the basis of the acute toxicity of the end-use product.
- # The more stringent choice for each type of PPE (i.e., bodywear, hand protection, footwear, eyewear, etc.) must be placed on the label of the end-use product.

The Agency concurs with the PPE requirements for TFM and niclosamide which are currently specified in the USFWS manual for application. For TFM, the requirements are two layers of clothing, rubber boots, and chemical resistant gloves. For niclosamide, the requirements are two layers of clothing, rubber boots, chemical resistant gloves, a face shield and an approved organic vapor resistant respirator. Although EPA has no data to specifically assess the exposure reduction to mixers/loaders afforded by a chemical-resistant apron, the Agency is persuaded that the exposure reduction would be significant for this chemical. Available data indicate that the preponderance of non-hand exposure to mixers/loaders/applicators and other handlers is to the front torso. Therefore, for mixers/loaders/applicators and other handlers the use of a chemical-resistant apron is probably approximately equivalent to double-layer body protection.

b. Occupational-Use Products

NonWPS Uses: EPA's evaluation of the dermal and inhalation toxicity of TFM indicates that significant toxicity from either route of exposure is unlikely with the PPE specified by the USFWS manual for application of lampricides. Only very large applications (greater than 1500 kg/treatment) yielded MOEs less than 100; and it is unlikely these large applications would be made by one applicator during one day.

No toxicity endpoints were chosen for niclosamide based on the low volume of use; therefore, so no worker risk assessment was done. The Agency concurs with the PPE currently required on the niclosamide labels.

4. Post-Application/Entry Restrictions

a. Occupational-Use Products

Restricted-Entry Interval: Due to the nature of the TFM and niclosamide use patterns, no significant occupational postapplication exposure scenarios are thought to exist. There are no specified worker re-entry intervals.

b. Other Labeling Requirements

The Agency is also requiring other use and safety information to be placed on the labeling of all end-use products containing TFM/niclosamide. For the specific labeling statements, refer to Section V of this document.

c. Endangered Species Statement

Currently, the Agency is developing a program ("The Endangered Species Protection Program") to identify all pesticides whose use may cause adverse impacts on endangered and threatened species and to implement mitigation measures that will eliminate the adverse impacts. The program would require use restrictions to protect endangered and threatened species at the county level. Consultations with the Fish and Wildlife Service may be necessary to assess risks to newly listed species or from proposed new uses. In the future, the Agency plans to publish a description of the Endangered Species Program in the Federal Register and have available voluntary county-specific bulletins. Because the Agency is taking this approach for protecting endangered and threatened species, it is not imposing label modifications at this time through the RED. Rather, any requirements for product use modifications will occur in the future under the Endangered Species Protection Program.

V. ACTIONS REQUIRED OF REGISTRANTS

This section specifies the data requirements, responses and labeling changes 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 TFM and niclosamide for the eligible uses has been reviewed and determined to be complete enough to make an assessment for the limited use pattern and low volume usage of these restricted use compounds. The following data gaps remain and these confirmatory data are still required:

Table 13: Data gaps for TFM and Niclosamide.

	New Guideline #	Old Guideline #	Description
TFM	835-2240	161-2	Photodegradation in water.
Niclosamide	835-2240	161-2	Photodegradation in water.
	835-4300	162-4	Aerobic aquatic metabolism
	835-4400	162-3	Anaerobic aquatic metabolism

The chronic ecotoxicity data requirements listed below are data gaps, but the requirements are being held in reserve pending the results of a currently ongoing monitoring study which the USFWS is conducting.

Table 14: Data requirements held in reserve for TFM and Niclosamide.			
	New Guideline #	Old Guideline #	Description
TFM	850.1300	72-4b	Aquatic invertebrate life cycle
	850.1500	72-5	Fish full life cycle
Niclosamide	850-1790	---	Chronic sediment toxicity testing
TFM/Niclosamide mixture	850.1500	72-5	Fish full life cycle
	850.1300	72-4b	Aquatic invertebrate life cycle

Additionally, EPA may require further testing of this active ingredient and end use products for endocrine disruptor effects when the endocrine disruptor test program is in place.

2. Labeling Requirements for Manufacturing-Use Products

To remain in compliance with FIFRA, manufacturing use product (MP) labeling must be revised to comply with all current EPA regulations, PR Notices and applicable policies. The MP labeling must bear the labeling contained in the table at the end of this section.

In addition, one of the following statements may be added to a label to allow reformulation of the product for a specific use or all additional uses supported by a formulator or user group.

> "This product may be used to formulate products for specific use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)."

> "This product may be used to formulate products for any additional use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)."

If included, this statement should be placed in the Directions for Use section of the label.

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. Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria 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

Label changes are necessary to implement mitigation measures outlined in Section IV above. Specific language to implement these changes is specified in the following table.

C. Required Labeling Changes Table Summary (Following Page)

Table 15: Summary of Required Labeling Changes for TFM		
Description	**Required Labeling**	**Placement on Label**
End Use Products Intended for Occupational Use (Non-WPS))		
Restricted Use Pesticide is Triggered by Active Ingredient	"RESTRICTED USE PESTICIDE due to acute hazards to the eye, nontarget aquatic organisms, and to the need for highly specialized applicator training." "Only for sale to and application by certified applicators of the U.S. Fish and Wildlife Service, Fisheries and Oceans Canada, and Provincial and State fish and game employees or persons under their direct supervision."	Top of Front Panel and enclosed in a box.
	"RESTRICTED USE PESTICIDE"	Immediately under the heading Directions for Use.
[1]PPE Requirements Established by the RED Based on the Active Ingredient.	"Personal Protective Equipment (PPE) Some materials that are chemical-resistant to this product are listed below. If you want more options, follow the instructions for category [insert A,B,C,D,E,F,G,or H] on an EPA chemical-resistance category selection chart." "Mixers, loaders, applicators and other handlers must wear: Long sleeved shirt and long pants Rubber boots and socks Chemical resistant gloves such as (registrant inserts correct glove type) Chemical Resistant aprons or coveralls Face shield."	Precautionary Statements: Hazards to Humans and Domestic Animals
User Safety Requirements	"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washable exist, use detergent and hot water. Keep and wash PPE separately from other laundry."	Precautionary Statements: Hazards to Humans and Domestic Animals immediately following the PPE requirements

Table 15: Summary of Required Labeling Changes for TFM		
Description	**Required Labeling**	**Placement on Label**
User Safety Recommendations	"User Safety Recommendations" "Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet." "Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing." "Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)
Environmental Hazards	"Environmental Hazards" "This chemical is toxic to fish and aquatic invertebrates. Nontarget aquatic organisms may be killed at rates recommended on this label." "Directions for Use must be strictly followed to minimize hazards to nontarget organisms. Do not contaminate water when cleaning equipment or disposing of equipment washwaters." "Local, State, and Provincial Fish and Game Agencies must be contacted before product is applied. Municipalities that use streams requiring treatment as potable water sources must be notified of the impending treatment at least 24 hours prior to application. Agricultural irrigators that use streams requiring treatment as a source of irrigation water must be notified of the impending treatment at least 24 hours prior to application. Agricultural irrigators must turn off their irrigation systems for a 24-hour period during and after treatment." "May not be used by unauthorized personnel."	Precautionary Statements under Environmental Hazards
Application Restrictions	"Do not apply this product in a way that will contact workers or other persons, either directly or through drift"	Directions for Use
Other Use/Application Restrictions	"Applicators must follow the instructions provided in the "Manual for Application of Lampricides in the U.S. Fish and Wildlife Service Sea Lamprey (*Petromyzon marinus*) Control Program" for correct rates of application. Prior to and during the application of this chemical, take all appropriate actions to notify public water users including notification actions specified in this manual."	Directions for Use under Application Instructions and/or General Precautions and Restrictions

Table 15: Summary of Required Labeling Changes for TFM		
Description	**Required Labeling**	**Placement on Label**
Other Use/Application Restrictions	"Aerial applications of this product are prohibited."	Directions for Use under Application Instructions and/or General Precautions and Restrictions

[1]PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

Table 16: Summary of Required Labeling Changes for Niclosamide		
Description	**Required Labeling**	**Placement on Label**
Manufacturing Use Products		
Formulation Instructions required on all MUPs	"Only for formulation into a lampricide for use in tributaries to the Great Lakes, Lake Champlain or the Finger Lakes or into a mollusicide for use against fresh water snails.	Directions for Use
Environmental Hazards Statements Required by the RED and Agency Label Policies	"This chemical is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your state Water Board or Regional Office of the EPA."	
End Use Products Intended for Occupational Use (Non-WPS)		
Restricted Use Pesticide is Triggered by Active Ingredient	"RESTRICTED USE PESTICIDE due to:" *For Bayluscide 70% WP insert:* "acute inhalation toxicity, aquatic organism toxicity and to the need for highly specialized applicator training." *For Bayluscide 3.2% Granular:* "to acute hazards to the eye, nontarget aquatic organisms, and to the need for highly specialized applicator training."	Top of Front Panel and enclosed in a box.
	"RESTRICTED USE PESTICIDE"	Immediately under the heading Directions for Use.

Table 16: Summary of Required Labeling Changes for Niclosamide		
Description	**Required Labeling**	**Placement on Label**
PPE Requirements Established by the RED Based on the Active Ingredient.[1]	"Personal Protective Equipment (PPE) Some materials that are chemical-resistant to this product are listed below. If you want more options, follow the instructions for category [insert A,B,C,D,E,F,G,or H] on an EPA chemical-resistance category selection chart." "Mixers, loaders, applicators and other handlers must wear: Long sleeved shirt and long pants Rubber boots & socks Chemical resistant gloves such as (registrant inserts correct glove type) Chemical resistant aprons or coveralls Face shield NIOSH approved respirator with: - an organic-vapor removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or - a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G), or a NIOSH approved respirator with an (OV) cartridge, or - a canister with any N,R,P or HE prefilter NIOSH approved organic vapor resistant respirator."	Precautionary Statements: Hazards to Humans and Domestic Animals
User Safety Requirements	"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washable exist, use detergent and hot water. Keep and wash PPE separately from other laundry."	Precautionary Statements: Hazards to Humans and Domestic Animals immediately following the PPE requirements

Table 16: Summary of Required Labeling Changes for Niclosamide		
Description	**Required Labeling**	**Placement on Label**
User Safety Recommendations	"User Safety Recommendations" "Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet." "Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing." "Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)
Environmental Hazards	"Environmental Hazards" "This chemical is toxic to fish and aquatic invertebrates. Nontarget aquatic organisms may be killed at rates recommended on this label." "Directions for use must be strictly followed to minimize hazards to non-target organisms. Do not contaminate water when cleaning equipment or disposing of equipment washwaters." "Local, State, and Provincial Fish and Game Agencies must be contacted before product is applied. Municipalities that use streams requiring treatment as potable water sources must be notified of the impending treatment at least 24 hours prior to application. Agricultural irrigators that use streams requiring treatment as a source of irrigation water must be notified of the impending treatment at least 24 hours prior to application. Agricultural irrigators must turn off their irrigation systems for a 24-hour period during and after treatment." "May not be used by unauthorized personnel."	Precautionary Statements under Environmental Hazards
Application Restrictions	"Do not apply this product in a way that will contact workers or other persons, either directly or through drift"	Directions for Use
Other Use/Application Restrictions	"Applicators must follow the instructions provided in the "Manual for Application of Lampricides in the U.S. Fish and Wildlife Service Sea Lamprey (*Petromyzon marinus*) Control Program" for correct rates of application. Prior to and during the application of this chemical, take all appropriate actions to notify public water users including notification actions specified in this manual."	Directions for Use under Application Instructions and/or General Precautions and Restrictions

Table 16: Summary of Required Labeling Changes for Niclosamide		
Description	**Required Labeling**	**Placement on Label**
Other Use/Application Restrictions	"Aerial applications of this product are prohibited."	Directions for Use under Application Instructions and/or General Precautions and Restrictions

[1] PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

D. Existing Stocks

Registrants may generally distribute and sell products bearing old labels/labeling for 26 months from the date of the issuance of this Reregistration Eligibility Decision (RED). Persons other than the registrant may generally distribute or sell such products for 50 months from the date of the issuance of this RED. However, existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors. Refer to "Existing Stocks of Pesticide Products; Statement of Policy"; Federal Register, Volume 56, No. 123, June 26, 1991.

In accordance with the above policy, the Agency has determined that registrants may distribute and sell TFM and niclosamide products bearing old labels/labeling for 26 months from the date of issuance of this RED. Persons other than the registrant may distribute or sell such products for 50 months from the date of the issuance of this RED. Registrants and persons other than registrants remain obligated to meet pre-existing Agency imposed label changes and existing stocks requirements applicable to products they sell or distribute.

VI. APPENDICES

Appendix A. TABLE OF USE PATTERNS ELIGIBLE FOR REREGISTRATION

Report Run Date: 11/25/98) Time 08:30 LUIS 5.2 - Page: 1
PRD Report Date: 06/05/98

APPENDIX A REPORT

Case 3082 [Lamprecide (*)] Chemical 036201 [a,a,a-Trifluoro-4-nitro-meta-cresol]

SITE Application Type, Application Timing, Application Equipment) Surface Type (Antimicrobial only) & Efficacy Influencing Factor (Antimicrobial only)	Form(s)	Min. Appl. Rate (AI unless noted otherwise)	Max. Appl. Rate (AI unless noted otherwise)	Soil Tex.	Max. # Apps @ Max. Rate /crop	/year cycle	Max. Dose [(AI unless noted otherwise)/A] /crop	/year cycle	Min. Interv (days)	Re-Entry Intv.	Geographic Limitations Allowed	Disallowed	Use Limitations Codes
USES ELIGIBLE FOR REREGISTRATION													
FOOD/FEED USES													
LAKES/PONDS/RESERVOIRS (WITH HUMAN OR WILDLIFE USE)			Use Group: AQUATIC FOOD CROP										
Water application, When needed, Pump	IMPR	NA	UC	*	NS	NS	NS	NS	NS	NS			CWH, CWL
	SC/L	NA	UC	*	NS	NS	NS	NS	NS	NS			CWH, CWJ, CWL

APPENDIX A REPORT

Case 3082 [Lamprecide (*)] Chemical 036201 [a,a,a-Trifluoro-4-nitro-meta-cresol]

LEGEND

Sort: Uses Eligible or Ineligible for Re-registration, Food/Feed or Non-Food/Non-Feed Uses, Alpha Site Name, Use Group Name, Alpha Application Type/Timing/Equipment Description, Formulation, Maximum Application Rate Unit/Area Quantity, Minimum Application Rate

HEADER ABBREVIATIONS

Min. Appl. Rate (AI unless noted otherwise)	Minimum dose for a single application to a single site. System calculated. Antimicrobial claims only.
Max. Appl. Rate (AI unless noted otherwise)	Maximum dose for a single application to a single site. System calculated.
Soil Tex. Max. Dose	Maximum dose for a single application to a single site as related to soil texture (Herbicide claims only).
Max. # Apps @ Max. Rate	Maximum number of Applications at Maximum Dosage Rate. Example: "4 applications per year" is expressed as "4/1 yr"; "4 applications per 3 years" is expressed as "4/3 yr"
Max. Dose [(AI unless noted otherwise)/A]	Maximum dose applied to a site over a single crop cycle or year. System calculated.
Min. Interv (days)	Minimum Interval between Applications (days)
Re-Entry Intv.	Reentry Intervals
PRD Report Date	LUIS contains all products that were active or suspended (and that were available from OPP Document Center) as of this date. Some products registered after this date may have data included in this report, but LUIS does not guarantee that all products registered after this date have data that has been captured.

SOIL TEXTURE FOR MAX APP. RATE

*	Non-specific
C	Coarse
M	Medium
F	Fine
O	Others

FORMULATION CODES

IMPR	IMPREGNATED MATERIAL
SC/L	SOLUBLE CONCENTRATE/LIQUID

ABBREVIATIONS

AN	As Needed
NA	Not Applicable
NS	Not Specified (on label)
UC	Unconverted due to lack of data (on label), or with one of following units: bag, bait, bait block, bait pack, bait station, bait station(s), block, briquet, briquets, bursts, cake, can, canister, capsule, cartridges, coil, collar, container, dispenser, drop, eartag, grains, lure, pack, packet, packets, pad, part, parts, pellets, piece, pieces, pill, pumps, sec, sec burst, sheet, spike, stake, stick, strip, tab, tablet, tablets, tag, tape, towelette, tray, unit, --

APPLICATION RATE

DCNC	Dosage Can Not be Calculated
No Calc	No Calculation can be made
W	PPM calculated by weight
V	PPM Calculated by volume
U	Unknown whether PPM is given by weight or by volume

APPENDIX A REPORT

Case 3082 [Lamprecide (*)] Chemical 036201 [a,a,a-Trifluoro-4-nitro-meta-cresol]

APPLICATION RATE (CONT.)
cwt : Hundred Weight
nnE-xx : nn times (10 power -xx); for instance, "1.234E-04" is equivalent to ".0001234"

USE LIMITATIONS CODES
CWH : Do not contaminate water by cleaning of equipment or disposal of equipment wash waters.
CWJ : This pesticide is toxic to aquatic invertebrates.
CWL : Do not contaminate water, food, or feed by storage or disposal.
* NUMBER IN PARENTHESES REPRESENTS THE NUMBER OF TIME UNITS (HOURS,DAYS, ETC.) DESCRIBED IN THE LIMITATION.

SELECTED PRODUCTS
006704-00045 006704-00086

APPENDIX A REPORT

Case 2455 [Niclosamide] Chemical 077401 [2-Aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide]

SITE Application Type, Application Timing, Application Equipment) Surface Type (Antimicrobial only) & Efficacy Influencing Factor (Antimicrobial only)	Form(s)	Min. Appl. Rate (AI unless noted otherwise)	Max. Appl. Rate (AI unless noted otherwise)	Soil Tex.	Max. # Apps @ Max. Rate /crop /year cycle	Max. Dose [(AI unless noted otherwise)/A] /crop /year cycle	Min. Interv (days)	Re-Entry Intv.	Geographic Limitations Allowed	Geographic Limitations Disallowed	Use Limitations Codes
USES ELIGIBLE FOR REREGISTRATION											
FOOD/FEED USES											
LAKES/PONDS/RESERVOIRS (WITH HUMAN OR WILDLIFE USE)				Use Group: AQUATIC FOOD CROP							
Water treatment, Not on label, Not on label	G	NA	5 lb A	*	NS	NS	NS	NS	1	NS	MI, MN, WI
	G	NA	5 lb A	*	NS	NS	NS	NS	NS	NS	013
Geo.013: Lake Champlain and the waters of the Great Lakes Basin.											CAL, CWD, CWH, CWJ, CWL
Water treatment, When needed, Pump	WP	NA	UC	*	NS	NS	NS	NS	AN	NS	PR
											C40, C62, CAL, CAT, CWC, CWH, CWJ, CWL
NON-FOOD/NON-FEED											
ORNAMENTAL PONDS/AQUARIA				Use Group: AQUATIC NON-FOOD RESIDENTIAL							
Spray, When needed, Sprayer	WP	NA	.7 lb A	*	NS	1/1 yr	NS	NS	NS	NS	FL
											C23, C40, CAL, CAT, CWD, CWH, CWJ, CWL
STREAMS/RIVERS/CHANNELED WATER				Use Group: AQUATIC NON-FOOD OUTDOOR							
Water treatment, Not on label, Metering pump	WP	NA	UC	*	NS	NS	NS	NS	AN	NS	PR
											C40, C62, CAL, CAT, CWC, CWH, CWJ, CWL

APPENDIX A REPORT

Case 2455 [Niclosamide] Chemical 077401 [2-Aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide]

LEGEND

Sort: Uses Eligible or Ineligible for Re-registration, Food/Feed or Non-Food/Non-Feed Uses, Alpha Site Name, Use Group Name, Alpha Application Type/Timing/Equipment Description, Formulation, Maximum Application Rate Unit/Area Quantity, Minimum Application Rate

HEADER ABBREVIATIONS

Min. Appl. Rate (AI unless noted otherwise)	Minimum dose for a single application to a single site. System calculated. Antimicrobial claims only.
Max. Appl. Rate (AI unless noted otherwise)	Maximum dose for a single application to a single site. System calculated.
Soil Tex. Max. Dose	Maximum dose for a single application to a single site as related to soil texture (Herbicide claims only).
Max. # Apps @ Max. Rate	Maximum number of Applications at Maximum Dosage Rate. Example: "4 applications per year" is expressed as "4/1 yr"; "4 applications per 3 years" is expressed as "4/3 yr"
Max. Dose [(AI unless noted otherwise)/A]	Maximum dose applied to a site over a single crop cycle or year. System calculated.
Min. Interv (days)	Minimum Interval between Applications (days)
Re-Entry Intv.	Reentry Intervals
PRD Report Date	LUIS contains all products that were active or suspended (and that were available from OPP Document Center) as of this date. Some products registered after this date may have data included in this report, but LUIS does not guarantee that all products registered after this date have data that has been captured.

SOIL TEXTURE FOR MAX APP. RATE

*	Non-specific
C	Coarse
M	Medium
F	Fine
O	Others

FORMULATION CODES

G	GRANULAR
WP	WETTABLE POWDER

ABBREVIATIONS

AN	As Needed
NA	Not Applicable
NS	Not Specified (on label)
UC	Unconverted due to lack of data (on label), or with one of following units: bag, bait, bait block, bait pack, bait station, bait station(s), block, briquet, briquets, bursts, cake, can, canister, capsule, cartridges, coil, collar, container, dispenser, drop, eartag, grains, lure, pack, packet, packets, pad, part, parts, pellets, piece, pieces, pill, pumps, sec, sec burst, sheet, spike, stake, stick, strip, tab, tablet, tablets, tag, tape, towelette, tray, unit, --

APPLICATION RATE

DCNC	Dosage Can Not be Calculated
No Calc	No Calculation can be made
W	PPM calculated by weight
V	PPM Calculated by volume
U	Unknown whether PPM is given by weight or by volume

APPENDIX A REPORT

Case 2455 [Niclosamide] Chemical 077401 [2-Aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide]

APPLICATION RATE (CONT.)
cwt : Hundred Weight
nnE-xx : nn times (10 power -xx); for instance, "1.234E-04" is equivalent to ".0001234"

USE LIMITATIONS CODES
C23 : NPDES license restriction.
C40 : Do not apply by aircraft.
C62 : Do not use on surfaces that may contact food, feed, potable water, livestock or dairy animals.
CAL : Do not contaminate water, food or feed.
CAT : Do not place in locations accessible to children, pets or domestic animals.
CWC : Shrimp and crab may be killed at application rates recommended on this label. Do not apply where these are important resources.
CWD : Shrimp and crab will be killed at application rates recommended on this label. Do not apply where these are important resources.
CWH : Do not contaminate water by cleaning of equipment or disposal of equipment wash waters.
CWJ : This pesticide is toxic to aquatic invertebrates.
CWL : Do not contaminate water, food, or feed by storage or disposal.
* NUMBER IN PARENTHESES REPRESENTS THE NUMBER OF TIME UNITS (HOURS,DAYS, ETC.) DESCRIBED IN THE LIMITATION.

GEOGRAPHIC CODES
013 : Other
FL : Florida
MI : Michigan
MN : Minnesota
PR : Puerto Rico
WI : Wisconsin

UNIT DESCRIPTIONS
A : acre
lb : pound

Appendix B. TABLE OF GENERIC DATA REQUIREMENTS AND STUDIES USED TO MAKE THE REREGISTRATION DECISION

GUIDE TO APPENDIX B

Appendix B contains listings of data requirements which support the reregistration for active ingredients within case 3082 (TFM) and case 2455 (Niclosamide) covered by this Reregistration Eligibility Decision Document. It contains generic data requirements that apply to TFM and Niclosamide 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) 605-6000.

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–TFM

Data Supporting Guideline Requirements for the Reregistration of TFM.

REQUIREMENT		USE PATTERN	CITATION(S)
PRODUCT CHEMISTRY			
61-1	**Chemical Identity**	ALL	41507102
61-2A	**Start. Mat. & Mnfg. Process**	ALL	41507102
61-2B	**Formation of Impurities**	ALL	41507102
62-1	**Preliminary Analysis**	ALL	41507102
62-2	**Certification of limits**	ALL	41507102
62-3	**Analytical Method**	ALL	41507101, 93135002
63-2	**Color**	ALL	41507102
63-3	**Physical State**	ALL	41507102
63-4	**Odor**	ALL	41507102
63-5	**Melting Point**	ALL	41507102
63-6	**Boiling Point**	ALL	41507102
63-7	**Density**	ALL	41507102
63-8	**Solubility**	ALL	41507102
63-9	**Vapor Pressure**	ALL	41507102
63-10	**Dissociation Constant**	ALL	41507102
63-12	**pH**	ALL	41507102
63-13	**Stability**	ALL	41507102
63-14	**Oxidizing/Reducing Action**	ALL	41507102
63-15	**Flammability**	ALL	41507102

Data Supporting Guideline Requirements for the Reregistration of TFM.

REQUIREMENT		USE PATTERN	CITATION(S)
ECOLOGICAL EFFECTS			
71-1A	**Acute Avian Oral - Quail/Duck**	E	43677702
71-2A	**Avian Dietary - Quail**	E	00067314,93135005
71-2B	**Avian Dietary - Duck**	E	Heath et al, 1972.
71-3	**Wild Mammal Toxicity**		40999204, 41898102
72-1A	**Fish Toxicity Bluegill**	E	44186901, Bills and Marking, 1976
72-1C	**Fish Toxicity Rainbow Trout**	E	44186902 Bills and Marking, 1976
72-2A	**Invertebrate Toxicity**	E	40094602 Maki et al, 1975.
72-4A	**Early Life Stage Fish**	E	00070314
72-4B	**Life Cycle Invertebrate**	E	Reserved
72-5	**Life Cycle Fish**	E	Reserved
122-1B	**Vegetative Vigor**		00070732
122-2	**Aquatic Plant Growth**		Maki et al, 1975
TOXICOLOGY			
81-1	**Acute Oral Toxicity - Rat**	ALL	40999204,41898102
81-2	**Acute Dermal Toxicity - Rabbit/Rat**	ALL	40999205, 41898103
81-4	**Primary Eye Irritation - Rabbit**	ALL	40999207, 41898104
81-5	**Primary Dermal Irritation - Rabbit**	ALL	40999206,41898105
81-6	**Dermal Sensitization - Guinea Pig**	ALL	41898106

Data Supporting Guideline Requirements for the Reregistration of TFM.

REQUIREMENT		USE PATTERN	CITATION(S)
82-1A	**90-Day Feeding - Rodent**	ALL	00112726, 00112727
82-1B	**90-Day Feeding - Non-rodent**	ALL	00112725[a]
83-1A	**Chronic Feeding Toxicity - Rodent**	ALL	00081184[b]
83-3A	**Developmental Toxicity - Rat**	ALL	00131201
84-2A	**Gene Mutation (Ames Test)**	ALL	42551801
84-2B	**Structural Chromosomal Aberration**	ALL	40999201
84-4	**Other Genotoxic Effects**	ALL	42187101,40999202
ENVIRONMENTAL FATE			
161-1	**Hydrolysis**	ALL	44429501
161-2	**Photodegradation - Water**	E	data gap
162-3	**Anaerobic Aquatic Metabolism**	E	43887601
162-4	**Aerobic Aquatic Metabolism**	E	43781801
163-1	**Leaching/Adsorption/Desorption**	E	Dawson, 1986 Carey, Fox, and Schleen, 1988
165-4	**Bioaccumulation in Fish**		44666501

a No 90-day feeding study was available for non-rodents. A 6-month feeding study for dogs was substituted.

b. No study was required, but study was submitted, if it is upgraded, this study could substitute for subchronic study.

APPENDIX B–NICLOSAMIDE

Data Supporting Guideline Requirements for the Reregistration of NICLOSAMIDE.

REQUIREMENT		USE PATTERN	CITATION(S)
PRODUCT CHEMISTRY			
61-1	**Chemical Identity**	ALL	43667101
61-2A	**Start. Mat. & Mnfg. Process**	ALL	43667101
61-2B	**Formation of Impurities**	ALL	43667101
62-1	**Preliminary Analysis**	ALL	43667102
62-2	**Certification of limits**	ALL	43667101
62-3	**Analytical Method**	ALL	43667102, 41616301
63-2	**Color**	ALL	43667103
63-3	**Physical State**	ALL	43667103
63-4	**Odor**	ALL	43667103
63-5	**Melting Point**	ALL	43667103
63-6	**Boiling Point**	ALL	43667103
63-7	**Density**	ALL	43667103
63-8	**Solubility**	ALL	43667103
63-9	**Vapor Pressure**	ALL	43667103
63-10	**Dissociation Constant**	ALL	43044901
63-11	**Octanol/Water Partition**	ALL	43667103
63-12	**pH**	ALL	43667103
63-13	**Stability**	ALL	41616302

Data Supporting Guideline Requirements for the Reregistration of NICLOSAMIDE.

REQUIREMENT		USE PATTERN	CITATION(S)
ECOLOGICAL EFFECTS			
71-1A	**Acute Avian Oral - Quail/Duck**	E	43677701, 43677702, 44180301,
71-2A	**Avian Dietary - Quail**	E	44180302
71-2B	**Avian Dietary - Duck**	E	44180303
71-3	**Wild Mammal Toxicity**		42552301
72-1A	**Fish Toxicity Bluegill**	E	43679302
72-1C	**Fish Toxicity Rainbow Trout**	E	44206101
72-2A	**Invertebrate Toxicity**	E	44174804
72-4A	**Early Life Stage Fish**	E	reserved
72-4B	**Life Cycle Invertebrate**	E	reserved
72-5	**Life Cycle Fish**		reserved
72-7B	**Actual Field - Aquatic Organisms**		42552317
122-2	**Aquatic Plant Growth**		43679310[a]
TOXICOLOGY			
81-1	**Acute Oral Toxicity - Rat**	ALL	425522301[a]
81-2	**Acute Dermal Toxicity - Rabbit/Rat**	ALL	42552301[a]
81-4	**Primary Eye Irritation - Rabbit**	ALL	42552305[a]
81-5	**Primary Dermal Irritation - Rabbit**	ALL	42552301
81-6	**Dermal Sensitization - Guinea Pig**	ALL	42552306
82-1A	**90-Day Feeding - Rodent**	ALL	42552307[a,] 42552308[a]
82-1B	**90-Day Feeding - Non-rodent**	ALL	42552309[a]

Data Supporting Guideline Requirements for the Reregistration of NICLOSAMIDE.

REQUIREMENT		USE PATTERN	CITATION(S)
83-1A	**Chronic Feeding Toxicity - Rodent**	ALL	42698001[a]
83-3B	**Developmental Toxicity - Rabbit**	ALL	42552310[a]
84-2B	**Structural Chromosomal Aberration**	ALL	43677901, 43677902,
ENVIRONMENTAL FATE			
161-1	**Hydrolysis**	ALL	42552313
161-2	**Photodegradation - Water**	E	data gap
162-3	**Anaerobic Aquatic Metabolism**	E	data gap
162-4	**Aerobic Aquatic Metabolism**		data gap
163-1	**Leaching/Adsorption/Desorption**	E	42552315, 42552316, 42552317
164-2	**Aquatic Field Dissipation**	E	42552317
165-4	**Bioaccumulation in Fish**		44128201, 42552317

a: The submitted study did not fulfill guidelines, but provided some information for the assessment of Niclosamide. No new data are required.

Appendix C. CITATIONS CONSIDERED TO BE PART OF THE DATA BASE SUPPORTING THE REREGISTRATION DECISION (BIBLIOGRAPHY)

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 the 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 used 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 identifier. These entries are listed after all MRID entries. This 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 an 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.

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 defaulted 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.

BIBLIOGRAPHY

MRID CITATION

BIBLIOGRAPHY for TFM

Bills, T. D. and L. L. Marking. 1976. Toxicity of 3-trifluoromethyl-4-nitrophenol (TFM), 2',5-Dichloro-4'-nitrosalicylanide (Bayer 73), and 98.2 Mixture to Fingerlings of Seven Fish Species and to Eggs and Fry of Coho Salmon. US Fish and Wildlife Service, Investigations in Fish Control No.69 .pgs 1-9.

Carey, J. and Fox, M. Photodegradation of the Lampricide TFM- Pathway of the Direct Photolysis in Solution. J. Great Lakes Res. 7(3):234-241, Internat. Assoc. Great Lakes Res. 1981. Acc. # 109279.

Dawson, V.K. Adsorption/Desorption of ^{14}C-TFM by Bottom Sediments. U.S. Fish and Wildlife Service. 1986. 158888/262165.

Dawson, V. K., D. A. Johnson, and J. L. Allen. 1986. Loss of lampricides by adsorption on bottom sediments. Canadian Journal of Fisheries and Aquatic Sciences. Vol 43, No. 8: pp 1515 - 1520.

Fletcher, J.S., J.E. Nellessen, and T.G. Pfleeger. 1994. Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. Environ. Tox. Chem. 13:1383-1391.

Gilderhus, P. A. and Johnson, B.G.H. 1980. Effects of sea lamprey (*Petromyzon marinus*) control in the Great Lakes on aquatic plants, invertebrates and amphibians. Can. J. Fish. Aquat. Sci. 37: 1895-1905.

Heath, R. G., J.W. Spann, E.F. Hill, and J Kreitzer. 1972. Comparative dietary toxicities of Pesticides to birds. U.S. Fish and Wildlfie Service, Special Scientific Report-- Wildlife No. 152. 57.

Henrich,J.W, J.G. Weise and B.R. Smith. 1979. Changes in biological characteristics of the sea lamprey (*Petromyzon marinus*) as related to lamprey abundance, prey abundance, and sea lamprey control. Canadian Journal of Fisheries and Aquatic Science 27: 1861-1871.

BIBLIOGRAPHY

MRID CITATION

Hewitt, L. M., L. Treblay, G. J Van Der Kraak, K. R. Solomon, and M.. R. Servos. 1998. Identification of the lampricide 3-trifluoromethyl-4-nitrophenol as a agonist for the rainbow trout estrogen receptor. Environmental Toxicology and Chemistry. Vol 17. No. 3: pp 425 - 432.

Hoerger. F.D. and E.E. Kenaga. 1972. Pesticide residues on plants: correlation of representative data as a basis for estimation of their magnitude in the environment. Environmental Quality. Academic Press, New York, I: 9-28.

Maki, A.W., Geissel, L. and Johnson, H.E. 1975. Toxicity of the lampricides 3-trifluoromethyl-4-nitrophenol (TFM) to 10 species of algae. U.S. Fish and Wildlife Serv., Invest, Fish Control 56:3-17.

NRCC. 1985. TFM and Bayer 73 in the Aquatic Environment. Envir. Sec. Publ. NRCC 22488, Otawa, Ontario, 203 pp.

Piavis, G. W. and J. H. Howell. 1975. Effects of 3-trifluoromethyl-4-nitrophenol (TFM) on developmental stages of the sea lamprey. Investigations in Fish Control Technical Report 64. U. S. Fish and Wildlife Service, pp 3 - 8.

00067314 Bodden, R.M. (1976) Report: WARF Institute No. 6120293. (Unpublished study received Feb 10, 1978 under 6704-45; prepared by WARF Institute, Inc., submitted by U.S. Dept. of Interior, Fish & Wildlife Service, Washington, D.C.; CDL:243965-A)

00070314 Olson, L.E.; Marking, L.L. (1973) Toxicity of Four Toxicants to Green Eggs of Salmonids. (U.S. Fish and Wildlife Service, Fish Control Laboratory; unpublished study; CDL:223650-H)

00070732 Maki, A.W.; Johnson, H.E. (1977) Kinetics of Lampricide (TFM, 3-Trifluoromethyl-4-nitrophenol) Residues in Model Stream Communities. (Unpublished study received Feb 10, 1978 under 6704-45; prepared by Michigan State Univ., Dept. of Fisheries and Wildlife, submitted by U.S. Fish and Wildlife Service, Washington,D.C.; CDL:244417-D)

BIBLIOGRAPHY

MRID CITATION

00081184 WARF Institute, Incorporated (1975) Two Year Chronic Feeding Study in Hamsters: Contract No. 14-16-0008-620. Final rept. (For U.S. Dept. of the Interior, Bureau of Sport Fisheries and Wildlife; unpublished study; CDL:097875-A; 097876; 097874; 097930)

00112725 Harris, D. (1973) TFM (85.6%): Chronic Study in Dog for Safety Evaluation: Contract No. 14-16-0008-620. Final rept. (WARF Institute, Inc. for U.S. Fish and Wildlife Service; unpublished study; CDL:097969-B)

00112726 Harris, D. (1971) TFM (82.4%) ...: 90 Day Rat Toxicity Feeding Study: Contract No. 14-16-0008-620. Final rept. (WARF Institute, Inc. for U.S. Fish and Wildlife Service; unpublished study; CDL:097969-C)

00112727 Harris, D. (1971) TFM (HB) ...: Rat 90 Day Toxicity Feeding Study: Contract 14-16-0008-620. Final rept. (WARF Institute, Inc. for U.S. Fish and Wildlife Service; unpublished study; CDL: 097869-A)

00131201 MacKenzie, K.; Dickie, S. (1983) Teratology Study with TFM in Rats: Study No. 6115-102. Final rept. (Unpublished study received Oct 3, 1983 under 6704-45; prepared by Hazleton Raltech, Inc., submitted by U.S. Fish and Wildlife Service, Washington, DC; CDL:071977-A)

40094602 Johnson, W. and Finley, M. 1980. Handbook of Acute Toxicity of Chemical to Fish and Aquatic Invertebrates. USDI Publication 137, Washington, D.C.

40999201 Murli, H. (1988) Mutagenicity Test on ","-Trifluoro-4-nitro-m-cresol in an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: HLA Study No.: 10414- 0-437. Unpublished study prepared by Hazleton Laboratories America, Inc. 27 p.

40999202 Cifone, M. (1988) Mutagenicity Test on ","-Trifluoro-4-nitro-m-cresol in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay: HLA Study No.: 10414-0-447. Unpublished study prepared by Hazleton Laboratories America, Inc. 19 p.

BIBLIOGRAPHY

MRID CITATION

40999204 Lemen, J. (1988) Acute Oral Toxicity Study in Rats ","-trifluoro-4-nitro-m-cresol, sodium salt: Laboratory Project ID: 2497-100. Unpublished study prepared by Hazleton Laboratories America, Inc. 18 p.

40999205 Lemen, J. (1988) Acute Dermal Toxicity Study in Rabbits with ","-trifluoro-4-nitro-m-cresol, sodium salt: Laboratory Project ID: 2497-101. Unpublished study prepared by Hazleton Laboratories America, Inc. 12 p.

40999206 Murli, H. (1988) Mutagenicity Test on ","-Trifluoro-4-nitro-m-cresol in an *in vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: Final Report: HLA Study No.: 10414-0-437. Unpublished study prepared by Hazleton Laboratories America, Inc. 12 p.

40999207 Lemen, J. (1988) Primary Eye Irritation Study in Rabbits with ","-trifluoro-4-nitro-m-cresol, sodium salt:HLA 2497-103. Unpublished study prepared by Hazleton Laboratories America, Inc. 14 p.

41507101 Bartsch,(1990) Analytical Method for Determination of Hoe 02770 in Formulations: Lab Project Number: A11095. Unpublished study prepared by Hoechst Aktiengesellschaft. 7 p.

41507102 Rexer, Frisch, and Maier, (1989) Material Safety Data Sheet ","-trifluoro-4-nitro-m-cresol and isopropanol with Documents on Colour, Physical Form, Odour, Density, Vapour Pressure, pH-value, Flash Point and Stability: Lab Project Nos. A41583: A41593. Unpublished study prepared by Hoechst Aktien-gesellschaft. 15 p.

41898102 Glaza, S. (1990) Acute Oral Toxicity Study of a,a,a-triflouro-nitro -m-creosol (TFM), Technical Grade in Rats: Final Report: Lab Project Number: HLA 00504436. Unpublished study prepared by Hazleton Labs America, Inc. 38 p.

41898103 Glaza, S. (1990) Acute Dermal Toxicity Study of a,a,a,-trifluoronitro-m-creosol (TFM), Technical Grade in Rabbits: Final Report: Lab Project Number: HLA 00504437. Unpublished study prepared by Hazleton Labs America, Inc. 39 p.

BIBLIOGRAPHY

MRID CITATION

41898104 Glaza, S. (1990) Primary Eye Irritation Study of a,a,a-trifluoronitro-m-creosol (TFM) Technical Grade in Rabbits: Final Report: Lab Project Number: HLA 00504439. Unpublished study prepared by Hazleton Labs America, Inc. 33 p.

41898105 Glaza, S. (1990) Primary Dermal Irritation Study of a,a,a-trifluoro -nitro-m-creosol (TFM) Technical Grade in Rabbits: Final Report: Lab Project Number: HLA 00504438. Unpublished study prepared by Hazleton Labs America, Inc. 22 p.

41898106 Glaza, S. (1990) Dermal Sensitization Study of ","-trifluoro-nitro-m-creosol (TFM) Technical Grade in Guinea Pigs--Closed Patch Technique: Final Report: Lab Project Number: HLA 00504440. Unpublished study prepared by Hazleton Labs America, Inc. 32 p.

42187101 Ivett, J. (1989) Mutagenicity Test on a,a,a-Trifluro-4-nitro-m-creosol: In vivo Mouse Micronucleus Assay: Final Report: Lab Project Number: HLA 10414-0-455. Unpublished study prepared by Hazleton Labs America, Inc. 39 p.

42551801 Nitze, W. (1977) TFM: Ames Test: Lab Project Number: 7043135. Unpublished study prepared by WARF Institute, Inc. 6 p.

42551806 Thingvold, D. Adsorption, Degradation and Persistence of 3-Trifluoromethyl-4-nitrophenyl (TFM) in Aquatic Environments. Ph.D. Thesis, Univ. of Wisconsin, 1975.

42551807 Thingvold, D. and Lee, G. Persistence of TFM in Aquatic Environments. Environmental Science and Technology, vol. 15, no. 11, p. 1335-1340. 1981.

42551808 Carey, J., Fox, M., and Schleen, L. Photodegradation of the Lampricide TFM- Field Confirmation of Direct Photolysis and Persistence of Formulation Impurities in a Stream during Treatment. J. Great Lakes Res. 14(3):338-346, Internat. Assoc. Great Lakes Res. 1988.

43677702 Hudson, R. (1979) Toxicites of the lampricides 3-trifluoromethyl-4-nitrophenol (TFM) and the 2-aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide (Bayer 73) to four bird species. Investigations in Fish Control 89:1-5.

BIBLIOGRAPHY

MRID CITATION

43781801 Fathulla, R. (1995) Aerobic Aquatic Metabolism of (carbon 14) Labeled 3-Trifluoromethyl-4-Nitrophenol ((carbon 14)-TFM): Final Report: Lab Project Number: HWI-6293-133. Unpublished study prepared by Hazleton Wisconsin, Inc. 118 p.

43887601 Fathulla, R. (1996) Anaerobic Aquatic Metabolism of (carbon 14)-Labeled 3-Trifluoromethyl-4-Nitrophenol ((carbon 14)-TFM): Final Report: Lab Project Number: HWI 6293-135: EF-F-21. Unpublished study prepared by Hazleton Wisconsin, Inc. 124 p.

44186901 Drottar, K.; Swigert, J. (1996) Mixture of TFM and Bayer 73: A 96-Hour Flow-Through Acute Toxicity Test with the Bluegill (Lepomis macrochirus): Final Report: Lab Project Number: 433A-109. Unpublished study prepared by Wildlife International Ltd. 61 p.

44186902 Drottar, K.; Swigert, J. (1996) Mixture of TFM and Bayer 73: A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss): Final Report: Lab Project Number: 433A-108. Unpublished study prepared by Wildlife International Ltd. 61 p.

44429501 Reynolds, Joanne. Hydrolysis of [^{14}C] TFM. Performed by XenoBiotic Laboratories, Inc. Submitted by Great Lakes Fishery Commission, Ann Arbor, Michigan. 1997.

44666501 Hubert, T. (1997) Uptake and Elimination of Lampricide TFM by Rainbow Trout: Lab Project Number: CAP-97-00079-01: CAP-97-0079-01-FFS00. Unpublished study prepared by Upper Mississippi Science Center. 677 p.

93135002 Schnick, R. (1991) U.S. Department of Interior, Fish and Wildlife Phase 3 Summary of MRID 41507101. Analytical Method for Determination of Hoe 02770 in Formulations. Prepared by Hoechst Aktiengesellschaft. 5 p.

93135005 Schnick, R. (1991) U.S. Department of Interior, Fish and Wildlife Phase 3 Summary of MRID 00067314. Dietary LC50 Determination in Bobwhite Quail. Prepared by WARF Institute, Inc. 6 p.

BIBLIOGRAPHY

MRID CITATION

BIBLIOGRAPHY for NICLOSAMIDE

Bills, T. D. and L. L. Marking. 1976. Toxicity of 3-trifluoromethyl-4-nitrophenol (TFM), 2',5-Dichloro-4'-nitrosalicylanide (Bayer 73), and 98.2 Mixture to Fingerlings of Seven Fish Species and to Eggs and Fry of Coho Salmon. US Fish and Wildlife Service, Investigations in Fish Control No.69 .pgs 1-9.

Dawson, V. K., D. A. Johnson, and J. L. Allen. 1986. Loss of lampricides by adsorption on bottom sediments. Canadian Journal of Fisheries and Aquatic Sciences. Vol 43, No. 8: pp 1515 - 1520.

Fletcher, J.S., J.E. Nellessen, and T.G. Pfleeger. 1994. Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. Environ. Tox. Chem. 13:1383-1391.

Hoerger. F.D. and E.E. Kenaga. 1972. Pesticide residues on plants: correlation of representative data as a basis for estimation of their magnitude in the environment. Environmental Quality. Academic Press, New York, I: 9-28.

41616301 Talbott, T. (1990) Product Chemistry of Bayluscide: Lab Project Number: C-33.1: C-33.3: C-33.10. Unpublished study prepared by Mobay Corp. 16 p.

41616302 Talbott, T. (1990) Product Chemistry of Bayluscide [Chemical and Physical Properties]: Lab Project Number: 99885: 98383: 98007. Unpublished study prepared by Mobay Corp. 42 p.

42552301 Nelson, D.; Bauman, E. (1969) The Acute [Oral] Toxicity of Bayluscide (Bay 73) 70% Wettable Powder: Lab Project Number: 24859. Unpublished study prepared by Chemagro Corp. 5 p.

42552305 Crawford, C.; Roney, D. (1971) The Skin and Eye Irritation Properties of Bayluscide 70% Wettable Powder to Rabbits: Lab Project Number: 30699. Unpublished study prepared by Farbenfabriken Bayer A.G. 8 p.

BIBLIOGRAPHY

MRID CITATION

42552306 Frost, D.; et al. (1988) Dermal Sensitization Potential of Niclosamide in Guinea Pigs. Unpublished study prepared by Letterman Army Institute of Research. 38 p.

42552307 Harris, D. (1974) Bayer 73: 90 Day Subacute Feeding Study--Rat: Lab Project Number: 14-16-0008-620. Unpublished study prepared by WARF Institute, Inc. 168 p.

42552308 Harris, D. (1974) Bayer 73: 90 Day Subacute Feeding Study--Hamster: Lab Project Number: 14-16-0008-620. Unpublished study prepared by WARF Institute, Inc. 142 p.

42552309 Procter, B.; Dussault, P.; Rona, G.; et al. (1974) A Study of the Chronic Toxicity of Bayer 73 in Dog: Lab Project Number: 6425. Unpublished study prepared by Bio-Research Labs Ltd. 87 p.

42552310 Dyck, M.; Chappel, C. (1975) A Study of the Potential Teratological Effects of Bayer 73 in Rabbit: Lab Project Number: 3. Unpublished study prepared by Bio-Research Labs Ltd. 45 p.

42552313 Schultz, D.; Harman, P. (1978) Hydrolysis and Photolysis of the Lampricide Bayer 73: Lab Project Number: 85. Unpublished study prepared by US Fish and Wildlife Service. 8 p.

42552315 Dawson, V.; Johnson, D.; Allen, J. (1986) Loss of Lampricides by Adsorption on Bottom Sediments. Canadian Journal of Fish. Aquat. Science 43:1515-1520.

42552316 Dawson, V. (1986) Adsorption-Desorption of [carbon 14]-Bayer 73 by Bottom Sediments. Unpublished study prepared by US Fish and Wildlife Service. 110 p.

42552317 Ho, K.; Gloss, S. (1987) Distribution and Persistence of the Lampricide Bayer 73 following a Control Application. Can. J. Fish. Aquat. Sci. 44:112-119.

42698001 Bomhard, E.; Loser, E.; Janda, B. (1982) SR 73: Chronic Toxicological Study with Rats (Feeding Study Over Two Years; Niclosamide, Bayluscide--Active Ingredient):

BIBLIOGRAPHY

MRID CITATION

Lab Project Nos.: 10989; 82382. Unpublished study prepared by Bayer AG, Dept. of Toxicology. 504 p.

43044901 Williams, M.; Heim, L. (1993) Dissociation Constant (for Niclosamide): Lab Project Number: 41223: FIFRA-D-63-10. Unpublished study prepared by ABC Labs, Inc. 31 p.

43667101 Riekena, C. (1995) Product Identity and Composition of 3.2% Bayluscide Granular: Lab Project Number: FIS/0594/C142. Unpublished study prepared by Bell Labs, Inc. 64 p.

43667102 Riekena, C. (1995) Analysis and Certification of Product Ingredients of 3.2% Bayluscide Granular: Lab Project Number: FIS/0594/C142. Unpublished study prepared by Bell Labs, Inc.34 p.

43667103 Riekena, C. (1995) Physical and Chemical Characteristics of 3.2% Bayluscide Granular: Lab Project Number: FIS/0594/C142. Unpublished study prepared by Bell Labs, Inc. 15 p.

43677701 Schafer, E.; Bowles, W.; Hurlbut, J. (1983) The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. Arch. Environmental Contam. Toxicol. 12:355-382.

43677702 Hudson, R. (1979) Toxicites of the lampricides 3-trifluoromethyl-4-nitrophenol (TFM) and the 2-aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide (Bayer 73) to four bird species. Investigations in Fish Control 89:1-5.

43677901 Cifone, M. (1995) Mutagenicity Test on Niclosamide in the L5178Y TK+/Mouse Lymphoma Forward Mutation Assay: Final Report: Lab Project Number: 16403-0-431: 20989: 431. Unpublished study prepared by Corning Hazleton Inc. 71 p.

43677902 Murli, H. (1995) Mutagenicity Test on Niclosamide (2',5-Dichloro-4'-Nitrosalicylanilide) Measuring Chromosomal Aberrations in vivo in

BIBLIOGRAPHY

MRID CITATION

Mouse Bone Marrow Cells: Final Report: Lab Project Number: 16403-0-451: 22202: 451. Unpublished study prepared by Hazleton Washington, Inc. 70 p.

43679302 Farringer, J. (1972) The Determination of the Acute Toxicity of Rotenone and Bayer 73 to Selected Aquatic Organisms: Master's Thesis. Unpublished study prepared by University of Wisconsin at La Crosse, Wisconsin. 42 p.

43679310 Ibrahim, A. (1984) Effect of growth rate of the microscopic algae Ankistrodesmus falcatus (Corda) ralfs, Scenedesmus quadricauda (Turp.) breb. and Phaeodactylum tricornutum (bohlin). Aqua 5:303-306.

44128201 Hubert, T. (1996) Accumulation of the Lampricide Niclosamide by Rainbow Trout: Pilot Study: Lab Project Number: CAP-94-00083-01: UMSC CAP-94-00083-01. Unpublished study prepared by Upper Mississippi Science Center, NBS. 317 p.

44174804 Drottar, K.; Swigert, J. (1996) Niclosamide Ethanolamine Salt TEP (Bayluscide 70% Wettable Powder): A 96-Hour Flow-Through Acute Toxicity Test with the Cladoceran (Daphnia magna): Final Report: Lab Project Number: 433A-103. Unpublished study prepared by Wildlife International, Ltd. 50 p.

44180301 Palmer, S.; Beavers, J. (1996) Niclosamide Ethanolamine Salt TGAI: An Acute Oral Toxicity Study with the Mallard: Lab Project Number: 433-103: 433/110295/MLDC/CHP102. Unpublished study prepared by Wildlife International Ltd. 47 p.

44180302 Palmer, S.; Beavers, J. (1996) Niclosamide Ethanolamine Salt TGAI: (Bayer 73 Technical): A Dietary LC50 Study with the Northern Bobwhite: Lab Project Number: 433-101: 433/110295/QLCSDT.WC/CHP102. Unpublished study prepared by Wildlife International Ltd. 72 p.

44180303 Palmer, S.; Beavers, J. (1996) Niclosamide Ethanolamine Salt TGAI: (Bayer 73 Technical): A Dietary LC50 Study with the Mallard: Lab Project Number: 433-102: 433/110295/MLCSDT.WC/CHP102. Unpublished study prepared by Wildlife International Ltd. 71 p.

BIBLIOGRAPHY

MRID CITATION

44206101 Drottar, K.; Swigert, J. (1997) Niclosamide Ethanolamine Salt TGAI (Bayer 73 Technical): A 96-Hour Flow-Through Acute Toxicity Test with the Bluegill (Lepomis macrochirus): Amended Final Report: Lab Project Number: 433A-104. Unpublished study prepared by Wildlife International Ltd. 51 p.

Appendix D. COMBINED GENERIC AND PRODUCT SPECIFIC DATA CALL-IN

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

GENERIC AND PRODUCT SPECIFIC DATA CALL-IN NOTICE

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 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 1 through 6; or

2. Why you believe you are exempt from the requirements listed in this Notice and in Attachment 3 (for both generic and product specific data), the Requirements Status and Registrant's Response Form, (see section III-B); or

3. Why you believe EPA should not require your submission of 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 2. All products are listed on both the

generic and product specific Data Call-In Response Forms. Also included is a list of all registrants who were sent this Notice (Attachment 5).

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 and 2070-0057 (expiration date 3-31-99).

This Notice is divided into six sections and six 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:

1 - Data Call-In Chemical Status Sheet
2 - Generic Data Call-In and Product Specific Data Call-In Response Forms (Insert A) with Instructions
3 - Generic Data Call-In and Product Specific Data Call-In Requirements Status and Registrant's Response Forms (Insert B) with Instructions
4 - EPA Batching of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration
5 - List of Registrants Receiving This Notice

SECTION I. WHY YOU ARE RECEIVING THIS NOTICE

The Agency has reviewed existing data for this active ingredient(s) and reevaluated the data needed to support continued registration of the subject active ingredient(s). This reevaluation identified additional data necessary to assess the health and safety of the continued use of products containing this active ingredient(s). You have been sent this Notice because you have product(s) containing the subject active ingredient(s).

SECTION II. DATA REQUIRED BY THIS NOTICE

II-A. DATA REQUIRED

The data required by this Notice are specified in the Requirements Status and Registrant's Response Forms (Insert B) (for both generic and product specific data requirements). Depending on the results of the studies required in this Notice, additional studies/testing may be required.

II-B. SCHEDULE FOR SUBMISSION OF DATA

You are required to submit the data or otherwise satisfy the data requirements specified in the Requirements Status and Registrant's Response Forms (Insert B) within the time frames 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 (Telephone number: 703-605-6000).

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, 2001 L Street, N.W., Washington, D.C. 20036 (Telephone number 202-785-6323; Fax telephone number 202-785-0350).

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].

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

You must use the correct forms and instructions when completing your response to this Notice. The type of Data Call-In you must comply with (Generic or Product Specific) is specified in item number 3 on the four Data Call-In forms (Attachments 2 and 3).

III-A. SCHEDULE FOR RESPONDING TO THE AGENCY

The appropriate responses initially required by this Notice for generic and 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 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

1. Generic Data Requirements

The options for responding to this Notice for generic data requirements are: (a) voluntary cancellation, (b) delete use(s), (c) claim generic data exemption, (d) agree to satisfy the generic data requirements imposed by this Notice or (e) request a data waiver(s).

A discussion of how to respond if you choose the Voluntary Cancellation option, the Delete Use(s) option or the Generic Data Exemption option is presented below. A discussion of the various options available for satisfying the generic 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.

Two forms apply to generic data requirements, one or both of which must be used in responding to the Agency, depending upon your response. These two forms are the Data-Call-In Response Form (Insert A), and the Requirements Status and Registrant's Response Form (Insert B).

The Data Call-In Response Forms (Insert A) must be submitted as part of every response to this Notice. The Requirements Status and Registrant's Response Forms (Insert B) also must be submitted if you do not qualify for a Generic Data Exemption or are not requesting voluntary cancellation of your registration(s). Please note that the company's authorized representative is required to sign the first page of both Data Call-In Response Forms (Insert A) and the Requirements Status and Registrant's Response Forms (Insert B) 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 1.

a. 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 completed Generic and Product Specific Data Call-In Response Forms (Insert A), indicating your election of this option. Voluntary cancellation is item number 5 on both Data Call-In Response Form(s). If you choose this option, these are the only forms 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.

b. Use Deletion -

You may avoid the requirements of this Notice by eliminating the uses of your product to which the requirements apply. If you wish to amend your registration to delete uses, you must submit the Requirements Status and Registrant's Response Form (Insert B), a completed application for amendment, a copy of your proposed amended labeling, and all other information required for processing the application. Use deletion is option number 7 under item 9 in the instructions for the Requirements Status and Registrant's Response Forms (Insert B). You must also complete a Data Call-In Response Form (Insert A) by signing the certification, item number 8. Application forms for amending registrations may be obtained from the Registration Support Branch, Registration Division, Office of Pesticide Programs, EPA, by calling (703) 308-8358.

If you choose to delete the use(s) subject to this Notice or uses subject to specific data requirements, further sale, distribution, or use of your product after one year from the due date of your 90 day response, is allowed only if the product bears an amended label.

c. Generic Data Exemption -

Under section 3(c)(2)(D) of FIFRA, an applicant for registration of a product is exempt from the requirement to submit or cite generic data concerning an active ingredient if the active ingredient in

the product is derived exclusively from purchased, registered pesticide products containing the active ingredient. EPA has concluded, as an exercise of its discretion, that it normally will not suspend the registration of a product which would qualify and continue to qualify for the generic data exemption in section 3(c)(2)(D) of FIFRA. To qualify, all of the following requirements must be met:

(i). The active ingredient in your registered product must be present solely because of incorporation of another registered product which contains the subject active ingredient and is purchased from a source not connected with you;

(ii). Every registrant who is the ultimate source of the active ingredient in your product subject to this DCI must be in compliance with the requirements of this Notice and must remain in compliance; and

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

To apply for the Generic Data Exemption you must submit a completed Data Call-In Response Form (Insert A), Attachment 2 and all supporting documentation. The Generic Data Exemption is item number 6a on the Data Call-In Response Form (Insert A). If you claim a generic data exemption you are not required to complete the Requirements Status and Registrant's Response Form (Insert A). Generic Data Exemption cannot be selected as an option for responding to product specific data requirements.

If you are granted a Generic Data Exemption, you rely on the efforts of other persons to provide the Agency with the required data. If the registrant(s) who have committed to generate and submit the required data fail to take appropriate steps to meet requirements or are no longer in compliance with this Data Call-In Notice, the Agency will consider that both they and you are not compliance and will normally initiate proceedings to suspend the registrations of both your and their product(s), unless you commit to submit and do submit the required data within the specified time. In such cases the Agency generally will not grant a time extension for submitting the data.

d. Satisfying the Generic Data Requirements of this Notice

There are various options available to satisfy the generic data requirements of this Notice. These options are discussed in Section III-C.1. of this Notice and comprise options 1 through 6 of item 9 in the instructions for the Requirements Status and Registrant's Response Form (Insert B) and item 6b on the Data Call-In Response Form (Insert A). If you choose item 6b (agree to satisfy the generic data requirements), you must submit the Data Call-In Response Form (Insert A) and the Requirements Status and Registrant's Response Form (Insert B) as well as any other information/data pertaining to the option chosen to address the data requirement. Your response must be on the forms marked "GENERIC" in item number 3.

e. Request for Generic Data Waivers.

Waivers for generic data are discussed in Section III-D.1. of this Notice and are covered by options 8 and 9 of item 9 in the instructions for the Requirements Status and Registrant's Response Form (Insert B). 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.

2. Product Specific Data Requirements

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 choose 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.2. A discussion of options relating to requests for data waivers is contained in Section III-D.2.

Two forms apply to the product specific data requirements one or both of which must be used in responding to the Agency, depending upon your response. These forms are the Data-Call-In Response Form (Insert A), and the Requirements Status and Registrant's Response Form (Insert B), for product specific data. The Data Call-In Response Form (Insert A) must be submitted as part of every response to this Notice. In addition, one copy of the Requirements Status and Registrant's Response Form (Insert B) also must be submitted for each product listed on the Data Call-In Response Form (Insert A) unless the voluntary cancellation option is selected. Please note that the company's authorized representative is required to sign the first page of the Data Call-In Response Form (Insert A) and Requirements Status and Registrant's Response Form (Insert B) (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 1.

a. 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 (Insert A), indicating your election of this option. Voluntary cancellation is item number 5 on both the Generic and Product Specific Data Call-In Response Forms (Insert B). If you choose this option, you must complete both Data Call-In response forms. These are the only forms that you are required to complete.

If you choose 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.

b. 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 of item 9 in the instructions for the product specific Requirements Status and Registrant's Response Form (Insert B) and item numbers 7a and 7b (agree to satisfy the product specific data requirements for an MUP or EUP as applicable) on the product specific Data Call-In Response Form (Insert A). Note that the options available for addressing product specific data requirements differ slightly from those options for fulfilling generic data requirements. Deletion of a use(s) and the low volume/minor use option are not valid options for fulfilling product specific data requirements. It is important to ensure that you are using the correct forms and instructions when completing your response to the Reregistration Eligibility Decision document.

c. Request for Product Specific Data Waivers.

Waivers for product specific data are discussed in Section III-D.2. of this Notice and are covered by option 7 of item 9 in the instructions for the Requirements Status and Registrant's Response Form (Insert B). If you choose this option, you must submit the Data Call-In Response Form (Insert A) and the Requirements Status and Registrant's Response Form (Insert B) as well as any other information/data pertaining to the option chosen to address the data requirement. Your response must be on the forms marked "PRODUCT SPECIFIC" in item number 3.

III-C SATISFYING THE DATA REQUIREMENTS OF THIS NOTICE

1. Generic Data

If you acknowledge on the Generic Data Call-In Response Form (Insert A) that you agree to satisfy the generic data requirements (i.e. you select item number 6b), then you must select one of the six options on the Generic Requirements Status and Registrant's Response Form (Insert B) 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 you 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 ungradable (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 guidelines 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. In addition, certain studies require Agency approval of test protocols in advance of study initiation. Those studies for which a protocol must be submitted have been identified in the Requirements Status and Registrant's Response Form (Insert B) and/or footnotes to the form. If you wish to use a protocol which differs from the options discussed in Section II-C of this Notice, you must submit a detailed description of the proposed protocol and your reason for wishing to use it. The Agency may choose to reject a protocol not specified in Section II-C. If the Agency rejects your protocol you will be notified in writing, however, you should be aware that rejection of a proposed protocol will not be a basis for extending the deadline for submission of data.

A progress report must be submitted for each study within 90 days from the date you are required to commit to generate or undertake some other means to address that study requirement, such as making an offer to cost share or agreeing to share in the cost of developing that study. This 90-day progress report must include the date the study was or will be initiated and, for studies to be started within 12 months of commitment, the name and address of the laboratory(ies) or individuals who are or will be conducting the study.

In addition, if the time frame for submission of a final report is more than 1 year, interim reports must be submitted at 12 month intervals from the date you are required to commit to generate or otherwise address the requirement for the study. In addition to the other information specified in the preceding paragraph, at a minimum, a brief description of current activity on and the status of the study must be included as well as a full description of any problems encountered since the last progress report.

The time frames in the Requirements Status and Registrant's Response Form (Insert B) are the time frames that the Agency is allowing for the submission of completed study reports or protocols. 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

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

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 unsuccessful, you may request EPA (by selecting this option) to exercise its discretion not to suspend your registration(s), although you did 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 the 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 Certification with Respect to Citations of Data (in PR Notice 98-5) (EPA Form 8570-34) . In addition, you must demonstrate that the other registrant to whom the offer was made has not accepted your offer to enter into a cost-sharing 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 to 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 (Insert A) and a Requirements Status and Registrant's Response Form (Insert B) 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 burden 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 normally will 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.

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

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, *Raw 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, 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 also must certify at the time of submission of 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 documents 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 usually are not available for such studies.

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

If EPA has previously reviewed a protocol for a study you are submitting, you must identify any action taken by the Agency on the protocol and must indicate, as part of your certification, the manner in which all Agency comments, concerns, or issues were addressed in the final protocol and study.

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 a 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 entitled "Standard Format for Data Submitted under FIFRA".

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 1. 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 entitled "Standard Format for Data Submitted under FIFRA."

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 also should 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 toxicology studies generally will have been classified as "core-guideline" or "core-minimum." For ecological effects studies, the classification generally would be a rating of "core." 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 No. 8570-34, Certification with Respect to Citations of Data.

2. Product Specific Data

If you acknowledge on the product specific Data Call-In Response Form (Insert A) that you agree to satisfy the product specific data requirements (i.e. you select option 7a or 7b), then you must select one of the six options on the Requirements Status and Registrant's Response Form (Insert B) 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 (Insert B). 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 time-frame (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 -- The requirements for developing product specific data are the same as those described for generic data (see Section III.C.1, Option 1) except that normally no protocols or progress reports are required.

Option 2. Agree to Share in Cost to Develop Data -- If you enter into an agreement to cost share, the same requirements apply to product specific data as to generic data (see Section III.C.1, Option 2). However, 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.

Option 3. Offer to Share in the Cost of Data Development --The same requirements for generic data (Section III.C.I., Option 3) apply to this option. This option only applies to acute toxicity and certain efficacy data as described in option 2 above.

Option 4. Submitting an Existing Study -- The same requirements described for generic data (see Section III.C.1., Option 4) apply to this option for product specific data.

Option 5. Upgrading a Study -- The same requirements described for generic data (see Section III.C.1., Option 5) apply to this option for product specific data.

Option 6. Citing Existing Studies -- The same requirements described for generic data (see Section III.C.1., Option 6) apply to this option for product specific data.

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 (Insert A) and the Requirements Status and Registrant's Response Form (Insert B), and in the generic data requirements section (III.C.1.), as appropriate.

III-D. REQUESTS FOR DATA WAIVERS

1. Generic Data

There are two types of data waiver responses to this Notice. The first is a request for a low volume/minor use waiver and the second is a waiver request based on your belief that the data requirement(s) are not appropriate for your product.

a. Low Volume/Minor Use Waiver

Option 8 under item 9 on the Requirements Status and Registrant's Response Form (Insert B). Section 3(c)(2)(A) of FIFRA requires EPA to consider the appropriateness of requiring data for low volume/minor use pesticides. In implementing this provision, EPA considers low volume pesticides to be only those active ingredients whose total production volume for all pesticide registrants is small. In determining whether to grant a low volume, minor use waiver, the Agency will consider the extent, pattern and volume of use, the economic incentive to conduct the testing, the importance of the pesticide, and the exposure and risk from use of the pesticide. If an active ingredient is used for both high volume and low volume uses, a low volume exemption will not be approved. If all uses of an active ingredient are low volume and the combined volumes for all uses are also low, then an exemption may be granted, depending on review of other information outlined below. An exemption will not be granted if any registrant of the active ingredient elects to conduct the testing. Any registrant receiving a low volume/minor use waiver must remain within the sales figures in their forecast supporting the waiver request in order to remain qualified for such waiver. If granted a waiver, a registrant will be required, as a condition of the waiver, to submit annual sales reports. The Agency will respond to requests for waivers in writing.

To apply for a low volume/minor use waiver, you must submit the following information, as applicable to your product(s), as part of your 90-day response to this Notice:

(i). Total company sales (pounds and dollars) of all registered product(s) containing the active ingredient. If applicable to the active ingredient, include foreign sales for those products that are not registered in this country but are applied to sugar (cane or beet), coffee, bananas, cocoa, and other such crops. Present the above information by year for each of the past five years.

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

(iii) Total direct production cost of product(s) containing the active ingredient by year for the past five years. Include information on raw material cost, direct labor cost, advertising, sales and marketing, and any other significant costs listed separately.

(iv) Total indirect production cost (e.g. plant overhead, amortized plant and equipment) charged to product(s) containing the active ingredient by year for the past five years. Exclude all non-recurring costs that were directly related to the active ingredient, such as costs of initial registration and any data development.

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

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

(vii) For each of the next ten years, a year-by-year forecast of company sales (pounds and dollars) of the active ingredient, direct production costs of product(s) containing the active ingredient (following the parameters in item 2 above), indirect production costs of product(s) containing the active ingredient (following the parameters in item 3 above), and costs of data development pertaining to the active ingredient.

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

Failure to submit sufficient information for the Agency to make a determination regarding a request for a low volume/minor use waiver will result in denial of the request for a waiver.

b. Request for Waiver of Data

Option 9, under Item 9, on the Requirements Status and Registrant's Response Form. This option may be used if you believe that a particular data requirement should not apply because the requirement is inappropriate. You must submit a rationale explaining why you believe the data requirements should not apply. You also must submit the current label(s) of your

product(s) and, if a current copy of your Confidential Statement of Formula is not already on file you must submit a current copy.

You will be informed of the Agency's decision in writing. If the Agency determines that the data requirements of this Notice are not appropriate to your product(s), you will not be required to supply the data pursuant to section 3(c)(2)(B). If EPA determines that the data are required for your product(s), you must choose a method of meeting the requirements of this Notice within the time frame provided by this Notice. Within 30 days of your receipt of the Agency's written decision, you must submit a revised Requirements Status and Registrant's Response Form indicating the option chosen.

2. Product Specific Data

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 product specific Requirements Status and Registrant's Response Form (Insert B). 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.

SECTION 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:

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 (Insert A) and a Requirements Status and Registrant's Response Form (Insert B).

   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 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 generally would 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 also must 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.

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 a 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 1, the Data Call-In Chemical Status Sheet.

All responses to this Notice must include completed Data Call-In Response Forms (Insert A) and completed Requirements Status and Registrant's Response Forms (Insert B), for both (generic and product specific data) and any other documents required by this Notice, and should be submitted to the contact person(s) identified in Attachment 1. If the voluntary cancellation or generic data exemption option is chosen, only the Generic and Product Specific Data Call-In Response Forms (Insert A) need be submitted.

The Office of Compliance (OC) of the Office of Enforcement and Compliance Assurance (OECA), EPA, will be monitoring the data being generated in response to this Notice.

Sincerely yours,

Lois A. Rossi, Director
Special Review and
Reregistration Division

Attachments

The Attachments to this Notice are:

1 - Data Call-In Chemical Status Sheet
2 - Generic Data Call-In and Product Specific Data Call-In Response Forms with Instructions
3 - Generic Data Call-In and Product Specific Data Call-In Requirements Status and Registrant's Response Forms with Instructions
4 - EPA Batching of End-Use Products for Meeting Acute Toxicology Data Requirements for Reregistration
5 - List of Registrants Receiving This Notice

1. Chemical Status Sheets

TFM AND NICLOSAMIDE DATA CALL-IN CHEMICAL STATUS SHEET

INTRODUCTION

You have been sent this Product Specific Data Call-In Notice because you have product(s) containing TFM or Niclosamide.

This Product Specific Data Call-In Chemical Status Sheet, contains an overview of data required by this notice, and point of contact for inquiries pertaining to the reregistration of cases 3082 and 2455. 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 2), (3) the Requirements Status and Registrant's Form (Attachment 3), (4) EPA's Grouping of End-Use Products for Meeting Acute Toxicology Data Requirement (Attachment 4), and (5) a list of registrants receiving this DCI (Attachment 5). Instructions and guidance accompany each form.

DATA REQUIRED BY THIS NOTICE

The additional data requirements needed to complete the databases for TFM and Niclosamide are contained in the Requirements Status and Registrant's Response, Attachment 3. The Agency has concluded that additional data on TFM and Niclosamide are needed for specific products. These data are required to be submitted to the Agency within the time frame listed. These data are needed to fully complete the reregistration of all eligible TFM and Niclosamide products.

INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding this product specific data requirements and procedures established by this Notice, please contact Bonnie Adler at (703) 308-8523.

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

Bonnie Adler
Chemical Review Manager
Product Reregistration Branch
Special Review and Reregistration Branch 7508C
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

RE: **TFM AND NICLOSAMIDE**

TFM AND NICLOSAMIDE DATA CALL-IN CHEMICAL STATUS SHEET

INTRODUCTION

You have been sent this Generic Data Call-In Notice because you have product(s) containing TFM or Niclosamide.

This Generic Data Call-In Chemical Status Sheet, contains an overview of data required by this notice, and point of contact for inquiries pertaining to the reregistration of TFM and Niclosamide. This attachment is to be used in conjunction with (1) the Generic Data Call-In Notice, (2) the Generic Data Call-In Response Form (Attachment 2), (3) the Requirements Status and Registrant's Form (Attachment 3), and (4) a list of registrants receiving this DCI (Attachment 5). Instructions and guidance accompany each form.

DATA REQUIRED BY THIS NOTICE

The additional data requirements needed to complete the generic database for TFM and Niclosamide are contained in the Requirements Status and Registrant's Response, Attachment 3. The Agency has concluded that additional product chemistry data on TFM and Niclosamide are needed. These data are needed to fully complete the reregistration of all eligible TFM and Niclosamide products.

INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding the generic data requirements and procedures established by this Notice, please contact Laura Parsons at (703) 305-5776.

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

Laura Parsons, Chemical Review Manager
Special Review Branch
Special Review and Registration Division (H7508C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

RE: **TFM and Niclosamide**

2. Combined Generic and Product Specific DCI Response Forms (Insert A) Plus Instructions

Instructions For Completing The "Data Call-In Response Forms" For The Generic And Product Specific Data Call-In

INTRODUCTION

These instructions apply to the Generic and Product Specific "Data Call-In Response Forms" (Insert A) and are to be used by registrants to respond to generic and product specific Data Call-Ins as part of EPA's Reregistration Program under the Federal Insecticide, Fungicide, and Rodenticide Act. If you are an end-use product registrant only and have been sent this DCI letter as part of a RED document you have been sent just the product specific "Data Call-In Response Forms." (Insert A) Only registrants responsible for generic data have been sent the generic data response form. **The type of Data Call-In (generic or product specific) is indicated in item number 3 ("Date and Type of DCI") on each form.**

Although the form is the same for both generic and product specific data, instructions for completing these forms are different. Please read these instructions carefully before filling out the forms.

EPA has developed these forms individually for each registrant, and has preprinted these forms with a number of items. DO NOT use these forms for any other active ingredient.

Items 1 through 4 have been preprinted on the form. Items 5 through 7 must be completed by the registrant as appropriate. Items 8 through 11 must be completed by the registrant before submitting a response to the Agency.

The public reporting burden for this collection of information is estimated to average 15 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, Mail Code 2137, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, D.C. 20460; and to the Office of Management and Budget, Paperwork Reduction Project 2070-0107, Washington, D.C. 20503.

INSTRUCTIONS FOR COMPLETING THE DATA CALL-IN RESPONSE FORMS (INSERT A)

Generic and Product Specific Data Call-In

Item 1. **ON BOTH FORMS**: This item identifies your company name, number and address.

Item 2. **ON BOTH FORMS:** This item identifies the case number, case name, EPA chemical number and chemical name.

Item 3. **ON BOTH FORMS:** This item identifies the type of Data Call-In. The date of issuance is date stamped.

Item 4. **ON BOTH FORMS:** This item identifies the EPA product registrations relevant to the data call-in. Please note that you are also responsible for informing the Agency of your response regarding any product that you believe may be covered by this Data Call-In but that is not listed by the Agency in Item 4. You must bring any such apparent omission to the Agency's attention within the period required for submission of this response form.

Item 5. **ON BOTH FORMS:** Check this item for each product registration you wish to cancel voluntarily. If a registration number is listed for a product for which you previously requested voluntary cancellation, indicate in Item 5 the date of that request. Since this Data Call-In requires both generic and product specific data, you must complete item 5 on both Data Call-In response forms. You do not need to complete any item on the Requirements Status and Registrant's Response Forms (Insert B)

Item 6a. **ON THE GENERIC DATA FORM:** Check this Item if the Data Call-In is for generic data as indicated in Item 3 and you are eligible for a Generic Data Exemption for the chemical listed in Item 2 and used in the subject product. By electing this exemption, you agree to the terms and conditions of a Generic Data Exemption as explained in the Data Call-In Notice.

If you are eligible for or claim a Generic Data Exemption, enter the EPA registration Number of each registered source of that active ingredient that you use in your product.

Typically, if you purchase an EPA-registered product from one or more other producers (who, with respect to the incorporated product, are in compliance with this and any other outstanding Data Call-In Notice), and incorporate that product into all your products, you may complete this item for all products listed on this form. If, however, you produce the active ingredient yourself, or use any unregistered product (regardless of the fact that some of your sources are registered), you may not claim a Generic Data Exemption and you may not select this item.

INSTRUCTIONS FOR COMPLETING THE DATA CALL-IN RESPONSE FORMS (INSERT B)

Generic and Product Specific Data Call-In

Item 6b. **ON THE GENERIC DATA FORM:** Check this Item if the Data Call-In is for generic data as indicated in Item 3 and if you are agreeing to satisfy the generic data requirements of this Data Call-In. Attach the Requirements Status and Registrant's Response Form (Insert B) that indicates how you will satisfy those requirements.

NOTE: **Item 6a and 6b are not applicable for Product Specific Data.**

Item 7a. **ON THE PRODUCT SPECIFIC DATA FORM:** 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."

FOR BOTH MUP and EUP products

You should also respond "yes" to this item (7a for MUP's and 7b for EUP's) if your product is identical to another product and you qualify for a data exemption. You must provide the EPA registration numbers of your source(s); do 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.

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.

NOTE: **Item 7a and 7b are not applicable for Generic Data.**

Item 8. **ON BOTH FORMS:** This certification statement must be signed by an authorized representative of your company and the person signing must include his/her title. Additional pages used in your response must be initialed and dated in the space provided for the certification.

Item 9. **ON BOTH FORMS:** Enter the date of signature.

Item 10. **ON BOTH FORMS:** Enter the name of the person EPA should contact with questions regarding your response.

Item 11. **ON BOTH FORMS:** Enter the phone number of your company contact.

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

Insert Generic and Product Specific DCI Sample page here–4 pages

3. Generic and Product Specific Requirements Status and Registrants' Response Forms (Insert B) and Instructions

Instructions For Completing The "Requirements Status and Registrant's Response Forms" (Insert B) For The Generic and Product Specific Data Call-In

INTRODUCTION

These instructions apply to the Generic and Product Specific "Requirements Status and Registrant's Response Forms" and are to be used by registrants to respond to generic and product specific Data Call-In's as part of EPA's reregistration program under the Federal Insecticide, Fungicide, and Rodenticide Act. If you are an end-use product registrant only and have been sent this DCI letter as part of a RED document you have been sent just the product specific "Requirements Status and Registrant's Response Forms." Only registrants responsible for generic data have been sent the generic data response forms. **The type of Data Call-In (generic or product specific) is indicated in item number 3 ("Date and Type of DCI") on each form.**

Although the form is the same for both product specific and generic data, instructions for completing the forms differ slightly. Specifically, options for satisfying product specific data requirements do not include (1) deletion of uses or (2) request for a low volume/minor use waiver. Please read these instructions carefully before filling out the forms.

EPA has developed these forms individually for each registrant, and has preprinted these forms to include certain information unique to this chemical. DO NOT use these forms for any other active ingredient.

Items 1 through 8 have been preprinted on the form. Item 9 must be completed by the registrant as appropriate. Items 10 through 13 must be completed by the registrant before submitting a response to the Agency.

The public reporting burden for this collection of information is estimated to average 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, Mail Code 2137, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, D.C. 20460; and to the Office of Management and Budget, Paperwork Reduction Project 2070-0107, Washington, D.C. 20503.

INSTRUCTIONS FOR COMPLETING THE "REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE FORMS" (Insert B)

Generic and Product Specific Data Call-In

Item 1. **ON BOTH FORMS:** This item identifies your company name, number and address.

Item 2. **ON THE GENERIC DATA FORM:** This item identifies the case number, case name, EPA chemical number and chemical name.

ON THE PRODUCT SPECIFIC DATA FORM: This item identifies the case number, case name, and the EPA Registration Number of the product for which the Agency is requesting product specific data.

Item 3. **ON THE GENERIC DATA FORM:** This item identifies the type of Data Call-In. The date of issuance is date stamped.

ON THE PRODUCT SPECIFIC DATA FORM: This item identifies the type of Data Call-In. The date of issuance is also date stamped. Note the unique identifier number (ID#) assigned by the Agency. This ID number must be used in the transmittal document for any data submissions in response to this Data Call-In Notice.

Item 4. **ON BOTH FORMS:** This item identifies the guideline reference number of studies required. These guidelines, in addition to the requirements specified in the Data Call-In 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. **ON BOTH FORMS:** This item identifies the study title associated with the guideline reference number and whether protocols and 1, 2, or 3-year progress reports are required to be submitted in connection with the study. As noted in Section III of the Data Call-In Notice, 90-day progress reports are required for all studies.

If an asterisk appears in Item 5, EPA has attached information relevant to this guideline reference number to the Requirements Status and Registrant's Response Form (Insert B).

Item 6. **ON BOTH FORMS:** This item identifies the code associated with the use pattern of the pesticide. In the case of efficacy data (product specific requirement), the required study only pertains to products which have the use sites and/or pests indicated. A brief description of each code follows:

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 crop
J	Forestry
K	Residential
L	Indoor food
M	Indoor non-food
N	Indoor medical
O	Indoor residential

Item 7. **ON BOTH FORMS:** This item identifies the code assigned to the substance that must be used for testing. A brief description of each code follows:

EUP	End-Use Product
MP	Manufacturing-Use Product
MP/TGAI	Manufacturing-Use Product and Technical Grade Active Ingredient
PAI	Pure Active Ingredient
PAI/M	Pure Active Ingredient and Metabolites
PAI/PAIRA	Pure Active Indredient or Pute Active Ingredient Radiolabelled
PAIRA	Pure Active Ingredient Radiolabelled
PAIRA/M	Pure Active Ingredient Radiolabelled and Metabolites
PAIRA/PM	Pure Active Ingredient Radiolabelled and Plant Metabolites
TEP	Typical End-Use Product
TEP ___%	Typical End-Use Product, Percent Active Ingredient Specified
TEP/MET	Typical End-Use Product and Metabolites
TEP/PAI/M	Typical End-Use Product or Pure Active Ingredient and Metabolites
TGAI	Technical Grade Active Ingredient
TGAI/PAI	Technical Grade Active Ingredient or Pure Active Ingredient
TGAI/PAIRA	Technical Grade Active Ingredient or Pure Active Ingredient Radiolabelled
TGAI/TEP	Technical Grade Active Ingredient or Typical End-Use Product
MET	Metabolites
IMP	Impurities
DEGR	Degradates
*	See: guideline comment

Item 8. This item completed by the Agency identifies the time frame allowed for submission of the study or protocol identified in item 5.

ON THE GENERIC DATA FORM: The time frame runs from the date of your receipt of the Data Call-In notice.

ON THE PRODUCT SPECIFIC DATA FORM: The due date for submission of product specific studies begins from the date stamped on the letter transmitting the Reregistration Eligibility Decision document, and not from the date of receipt. However, your response to the Data Call-In itself is due 90 days from the date of receipt.

Item 9. **ON BOTH FORMS:** Enter the appropriate Response Code or Codes to show how you intend to comply with each data requirement. Brief descriptions of each code follow. The Data Call-In Notice contains a fuller description of each of these options.

Option 1. **ON BOTH FORMS:** (Developing Data) I will conduct a new study and submit it within the time frames specified in item 8 above. 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 and that I will provide the protocols and progress reports required in item 5 above.

Option 2. **ON BOTH FORMS:** (Agreement to Cost Share) I have entered into an agreement with one or more registrants to develop data jointly. By indicating that I have chosen this option, I certify that I will comply with all the requirements pertaining to sharing in the cost of developing data as outlined in the Data Call-In Notice.

However, for Product Specific Data, I understand that this option is available for acute toxicity or certain efficacy data **ONLY** if the Agency indicates in an attachment to this notice that my 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 may be subject to suspension.

Option 3. **ON BOTH FORMS:** (Offer to Cost Share) I have made an offer to enter into an agreement with one or more registrants to develop data jointly. I am also submitting a completed "Certification of offer to Cost Share in the Development of Data" form. 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 including a copy of my offer and proof of the other registrant's receipt of that offer. I am identifying the party which is committing to submit or provide the required 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 apply as well.

However, for Product Specific Data, I understand that this option is available only for acute toxicity or certain efficacy data and only if the Agency indicates in an attachment to this Data Call-In Notice that my product is similar enough to another product to qualify for this option.

Option 4. **ON BOTH FORMS:** (Submitting Existing Data) I will submit an existing study by the specified due date that has never before been submitted to EPA. By indicating that I have chosen this option, I certify that this study meets all the requirements pertaining to the conditions for submittal of existing data outlined in the Data Call-In Notice and I have attached the needed supporting information along with this response.

Option 5. **ON BOTH FORMS:** (Upgrading a Study) I will submit by the specified due date, or will cite data to upgrade a study that EPA has classified as partially acceptable and potentially upgradeable. By indicating that I have chosen this option, I certify that I have met all the requirements pertaining to the conditions for submitting or citing existing data to upgrade a study described in the Data Call-In Notice. I am indicating on attached correspondence the Master Record Identification Number (MRID) that EPA has assigned to the data that I am citing as well as the MRID of the study I am attempting to upgrade.

Option 6. **ON BOTH FORMS:** (Citing a Study) I am citing an existing study that has been previously classified by EPA as acceptable, core, core minimum, or a study that has not yet been reviewed by the Agency. If reviewed, I am providing the Agency's classification of the study.

However, for Product Specific Data, 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 the Agency 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 case, I will provide the MRID or Accession number (s). If I cite another registrant's data, I will submit a completed "Certification With Respect To Data Compensation Requirements" form.

FOR THE GENERIC DATA FORM ONLY: The following three options (Numbers 7, 8, and 9) are responses that apply only to the "Requirements Status and Registrant's Response Form" (Insert B) for generic data.

Option 7. (Deleting Uses) I am attaching an application for amendment to my registration deleting the uses for which the data are required.

Option 8. (Low Volume/Minor Use Waiver Request) I have read the statements concerning low volume-minor use data waivers in the Data Call-In Notice and I request a low-volume minor use waiver of the data requirement. I am attaching a detailed justification to support this waiver request including, among other things, all information required to support the request. I understand that, unless modified by the Agency in writing, the data requirement as stated in the Notice governs.

Option 9. (Request for Waiver of Data) I have read the statements concerning data waivers other than lowvolume minor-use data waivers in the Data Call-In Notice and I request a waiver of the data requirement. I am attaching a rationale explaining why I believe the data requirements do not apply. I am also submitting a copy of my current labels. (You must also submit a copy of your Confidential Statement of Formula if not already on file with EPA). I understand that, unless modified by the Agency in writing, the data requirement as stated in the Notice governs.

FOR PRODUCT SPECIFIC DATA: The following option (number 7) is a response that applies to the "Requirements Status and Registrant's Response Form" (Insert B) for product specific data.

Option 7. (Waiver Request) I request a waiver for this study because it is inappropriate for my product. 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 required 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" form specifying the option chosen. I also understand that the deadline for submission of data as specified by the original Data Call-In notice will not change.

Item 10. **ON BOTH FORMS:** This item must be signed by an authorized representative of your company. The person signing must include his/her title, and must initial and date all other pages of this form.

Item 11. **ON BOTH FORMS:** Enter the date of signature.

Item 12. **ON BOTH FORMS:** Enter the name of the person EPA should contact with questions regarding your response.

Item 13. **ON BOTH FORMS:** Enter the phone number of your company contact.

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

Insert Generic and Product Specific “Requirements Status and registrants” response Forms Here, including footnotes and definitions–page 1 of 10

4. EPA's Batching of TFM and Niclosamide 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 products containing **TFM or Niclosamide** as the active ingredient, 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.

Using available information, batching has been accomplished by the process described in the preceding paragraph. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual product should the need arise.

Registrants of 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 registrants' option to participate in the process with all 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 attached), 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. If more than one confidential statement of formula (CSF) exists for a product, the registrant must indicate the formulation actually tested by identifying the corresponding CSF.

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 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.

Two products were found which contain TFM as the active ingredient. These products have been placed into two batches. Five products were found to contain Niclosamide as the active ingredient and these products have been placed in three batches in accordance with the active and inert ingredients and type of formulation.

NOTE: The technical acute toxicity values included in this document are for informational purposes only. The data supporting these values may or may not meet the current acceptance criteria.

EPA'S BATCHING OF **TFM** 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 products containing **TFM** as the active ingredient, 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.

Using available information, batching has been accomplished by the process described in the preceding paragraph. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual product should the need arise.

Registrants of 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 registrants' option to participate in the process with all 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 attached), 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. If more than one Confidential Statement of Formula (CSF) exists for a product, the registrant must indicate the formulation actually tested by identifying the corresponding CSF.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In (DCI) 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 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.

Two products were found which contain TFM as the active ingredient. These products have been placed into two batches, in accordance with the active and inert ingredients and type of formulation. Based on the existing acute toxicity data available to the Agency, and based on the differences between the formulation types of the two batches, the Agency is requiring that data for each batch be submitted separately.

NOTE: The technical acute toxicity values included in this document are for informational purposes only. The data supporting these values may or may not meet the current acceptance criteria.

Batch	EPA Reg. No.	% Active Ingredient	Formulation Type
1	6704-45	38.8	liquid

Batch	EPA Reg. No.	% Active Ingredient	Formulation Type
2	6704-86	23.0	solid block

EPA'S BATCHING OF **NICLOSAMIDE** 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 products containing **NICLOSAMIDE** as the active ingredient, 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.

Using available information, batching has been accomplished by the process described in the preceding paragraph. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual product should the need arise.

Registrants of 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 registrants' option to participate in the process with all 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 attached), 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 are generated or existing data are referenced, registrants must clearly identify the test material by EPA Registration Number. If more than one Confidential Statement of Formula (CSF) exists for a product, the registrant must indicate the formulation actually tested by identifying the corresponding CSF.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In (DCI) 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 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.

Five products were found which contain NICLOSAMIDE as the active ingredient. These products have been placed into three batches, in accordance with the active and inert ingredients and type of formulation.

NOTE: The technical acute toxicity values included in this document are for informational purposes only. The data supporting these values may or may not meet the current acceptance criteria.

Batch	EPA Reg. No.	% Active Ingredient on most-recent label	Formulation Type
1	6704-88	96%	technical; solid

Batch	EPA Reg. No.	% Active Ingredient	Formulation Type
2	6704-87	70%	wettable powder
	6704-89	70%	wettable powder

Batch	EPA Reg. No.	% Active Ingredient on most-recent label	Formulation Type
3	6704-90	5%	granular
	6704-91	3.2%	granular

5. List of All Registrants Sent This Data Call-In Notice

page 1 of 1--Insert list of registrants here

Appendix E. LIST OF AVAILABLE RELATED DOCUMENTS AND ELECTRONICALLY AVAILABLE FORMS

Pesticide Registration Forms are available at the following EPA internet site:

http://www.epa.gov/opprd001/forms/.

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

Instructions

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)

2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.

3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the address below for the Document Processing Desk.

   DO NOT fax or e-mail any form containing 'Confidential Business Information' or 'Sensitive Information.'

   If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at williams.nicole@epamail.epa.gov.

The following Agency Pesticide Registration Forms are currently available via the internet: at the following locations:

8570-1	Application for Pesticide Registration/Amendment	http://www.epa.gov/opprd001/forms/8570-1.pdf.
8570-4	Confidential Statement of Formula	http://www.epa.gov/opprd001/forms/8570-4.pdf.
8570-5	Notice of Supplemental Registration of Distribution of a Registered Pesticide Product	http://www.epa.gov/opprd001/forms/8570-5.pdf.
8570-17	Application for an Experimental Use Permit	http://www.epa.gov/opprd001/forms/8570-17.pdf.
8570-25	Application for/Notification of State Registration of a Pesticide To Meet a Special Local Need	http://www.epa.gov/opprd001/forms/8570-25.pdf.
8570-27	Formulator's Exemption Statement	http://www.epa.gov/opprd001/forms/8570-27.pdf.

8570-28	Certification of Compliance with Data Gap Procedures	http://www.epa.gov/opprd001/forms/8570-28.pdf.
8570-30	Pesticide Registration Maintenance Fee Filing	http://www.epa.gov/opprd001/forms/8570-30.pdf.
8570-32	Certification of Attempt to Enter into an Agreement with other Registrants for Development of Data	http://www.epa.gov/opprd001/forms/8570-32.pdf.
8570-34	Certification with Respect to Citations of Data (in PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf.
8570-35	Data Matrix (in PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf.
8570-36	Summary of the Physical/Chemical Properties (in PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf.
8570-37	Self-Certification Statement for the Physical/Chemical Properties (in PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf.

Pesticide Registration Kit www.epa.gov/pesticides/registrationkit/.

Dear Registrant:

For your convenience, we have assembled an online registration kit which contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices

    a. 83-3 Label Improvement Program--Storage and Disposal Statements
    b. 84-1 Clarification of Label Improvement Program
    c. 86-5 Standard Format for Data Submitted under FIFRA
    d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)
    e. 87-6 Inert Ingredients in Pesticide Products Policy Statement
    f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement
    g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments
    h. 98-1 Self Certification of Product Chemistry Data with Attachments (This document is in PDF format and requires the Acrobat reader.)

Other PR Notices can be found at http://www.epa.gov/opppmsd1/PR_Notices.

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader.)

    a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment
    b. EPA Form No. 8570-4, Confidential Statement of Formula
    c. EPA Form No. 8570-27, Formulator's Exemption Statement
    d. EPA Form No. 8570-34, Certification with Respect to Citations of Data
    e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader.)

    a. Registration Division Personnel Contact List
    b. Biopesticides and Pollution Prevention Division (BPPD) Contacts
    c. Antimicrobials Division Organizational Structure/Contact List
    d. 53 F.R. 15952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)
    e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)

f.. 40 CFR Part 158, Data Requirements for Registration (PDF format)
g.. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)

Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' Web Site

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

   National Technical Information Service (NTIS)
   5285 Port Royal Road
   Springfield, VA 22161

   The telephone number for NTIS is (703) 605-6000. Please note that EPA is currently in the process of updating this booklet to reflect the changes in the registration program resulting from the passage of the FQPA and the reorganization of the Office of Pesticide Programs. We anticipate that this publication will become available during the Fall of 1998.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their Web site.

4. The National Pesticide Telecommunications Network (NPTN) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPTN by telephone at (800) 858-7378 or through their Web site: ace.orst.edu/info/nptn.

   The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

   Date of receipt
   EPA identifying number
   Product Manager assignment

   Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying File Symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.

To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a CAS number if one has been assigned.

Documents Associated with this RED

The following documents are part of the Administrative Record for this RED document and may included in the EPA's Office of Pesticide Programs Public Docket. Copies of these documents are not available electronically, but may be obtained by contacting the person listed on the respective Chemical Status Sheet.

a. Health and Environmental Effects Science Chapters.
b. Detailed Label Usage Information System (LUIS) Report.