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

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: **February 27, 2013**

SUBJECT: **3-Trifluoro-Methyl-4-Nitro-Phenol and Niclosamide. Revised** Human Health Risk Assessment Scoping Document in Support of Registration Review.

PC Code: 077401,036201
Decision No.: 475122
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D409179
Registration No.: 6704-45, 6704-86, 6704-91,6704-87
Regulatory Action: Registration Review
Case No.: 3082, 2455
CAS No.: 88-30-2
40 CFR: NA

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Attached is the Health Effects Division's (HED) human health risk assessment scoping Document (status update) for 3-trifluoro-methyl-4-nitro-phenol (TFM) and 2'5-dichloro-4'-nitrosalicylanilide (niclosamide) to support the registration review process.

Executive Summary

The Health Effects Division (HED) has considered the available human health risk assessments for 3-trifluoro-methyl-4-nitro-phenol (TFM) and 2'5-dichloro-4'-nitrosalicylanilide (niclosamide). HED performed this evaluation in order to determine the scope of work necessary to support the existing registrations during registration review. The primary sources of information for this evaluation were the 1998 risk assessments for TFM and niclosamide (D248544, D248546, D248563 and D248560).

Niclosamide and TFM are used by the U.S. Fish and Wildlife Service (USFWS) to control the sea lamprey population in the Great Lakes region of the United States. The USFWS is the primary registrant of these lampricide ingredients. TFM and niclosamide have been addressed in a single document since both compounds are typically used together (during stream treatments niclosamide is used to augment the efficacy of TFM applications). TFM is the primary control agent used.

TFM and niclosamide are formulated as either liquid or solid formulations although applications are predominantly applied as a liquid. Liquids may be applied by metered pump or backpack sprayers. TFM and niclosamide application methods and rates depend on the characteristics of the stream to be treated, sea lamprey populations, and the populations of non-target species. Extensive guidance on applications is provided by the USFWS lampricide application manual (EPA MRID 44003502). This manual also describes the USFWS program that closely governs the use of TFM and niclosamide. This feature is important as it contains stringent risk mitigation and monitoring components that are designed to minimize occupational exposures and exposures to the general population through direct contact or other use of treated waters.

There are no established food tolerances for niclosamide and TFM. Both chemicals are classified as low-volume and non-food use chemicals. Neither chemical is applied to areas where there is commercial fishing and, since residues degrade rapidly, there is no expectation that people would be exposed through consuming drinking water or through secondary residues in non-commercially caught fish. Dietary risk assessments are not needed for the TFM and niclosamide lampricide use.

There are no residential uses for niclosamide or TFM. In addition, the registered lampricide uses are not expected to result in any significant non-occupational exposures to the public. While the potential for postapplication exposure may exist for recreational activities (swimming, boating), that potential is minimal based on the use patterns and institutional risk mitigation measures associated with the use of niclosamide and TFM. Aggregate risk assessments are not needed.

No additional data related to human health risk assessment have been submitted to the Agency since the most recent risk assessments conducted in 1998 to support the Reregistration Eligibility Decision (RED) which was issued in November 1999.

In 1998 HED considered the toxicology database for TFM/niclosamide to be limited/incomplete but sufficient to assess the human health risk for the expected exposures and durations of exposure. However, based on the current 40 CFR Part 158 Toxicology Data requirements,

subchronic dermal toxicity, developmental toxicity, 2-generation reproductive toxicity, acute neurotoxicity, subchronic neurotoxicity, and immunotoxicity studies are required for non-food use chemicals. The HED Hazard and Science Policy Council (HASPOC) met on 11/7/12 and granted waivers to all the above requirements. This decision was based on the following considerations: an extensive level of risk mitigation for each application event, which is intended to protect those occupationally exposed and the public from exposure through drinking water sources and also from other uses of the treated waterways (e.g., swimming and boating) and a program that monitors the use of TFM and niclosamide by minimizing occupational exposures and other exposures to the general population through direct contact or other use of treated waters.

The only toxicity endpoint selected for the 1998 risk assessments was for assessing short-term dermal exposure to handlers of TFM. Quantitative assessments are not required for niclosamide or for other routes/ durations for TFM. For the TFM occupational assessment, HED selected an oral study for short-term dermal risk assessment, since no dermal toxicity study was submitted. The point of departure (POD) was selected from the developmental toxicity study in rats, with the NOAEL of 125 mg/kg/day.

In 1998 a screening level occupational risk assessment was performed for TFM handler exposure scenarios using conservative assumptions (J. Dawson, D248560). The resulting MOEs were above 100 (the level of concern) except for the high-end treatments using the metered pump applications which resulted in MOEs of 73 and 75. Those MOEs were not considered of concern given the very conservative nature of the assessment, i.e., it was assumed that the entire maximum treatment amount (7000 lbs) was handled in one day by a single mixer/loader/applicator.

As part of the registration review scoping process, HED has performed a revised screening level short-term dermal assessment for TFM handlers using updated unit exposures and body weights (see attachment 6). Assumptions regarding usage per day have been refined as well, and reflect more likely scenarios than those used in 1998.

The current screening assessment is based on the TFM liquid formulation which is expected to result in higher potential exposures than the solid bar applications and is the formulation used most often. Treatment rates reported in the 1997 USFWS data indicate that individual streams received anywhere from 33 lbs to 7000 lbs of TFM per the annual treatment. For mixing and applying via direct metering pump, very large treatments would typically be performed by multiple (3-5) workers over a multi- day (3-5 days) period. As such, it is not realistic to assume that one person would apply 7000 lbs in one day. For the purpose of this exercise, HED assumes that 7000 lbs is applied over a 3.5 day period (approximately 2000 lbs per day) by only two workers; thus each worker handles 1000 lbs TFM per day. Short-term dermal handler MOEs for this scenario are over 100 (the level of concern) and are not of concern. The handling assumption is conservative and represents the very high end of expected exposure using direct metering pump applications of TFM.

The handler screen for backpack applications considers the maximum that an individual could potentially apply with a typical 2 gallon backpack sprayer in a day. It is assumed that a maximum of 12 lbs of TFM could be applied in a day, taking into consideration the time it takes

to reload the tanks and apply each load. Short-term dermal handler MOEs are greater than 100 for this scenario and are not of concern. The handling assumption is conservative and represents the very high end of expected exposure using back pack sprayer applications of TFM.

There are no outstanding exposure or toxicity data requirements for TFM and niclosamide except for the immunotoxicity study (guideline 870.7800).

Introduction

TFM and niclosamide have been used to control larval sea lamprey (*Petromyzon marinus*) in tributaries of the Great Lakes since the early 1960s. The U.S. Fish and Wildlife Service (USFWS) is the primary registrant and user of these materials.

The nomenclature and physiochemical properties of TFM and niclosamide can be found in Attachment 1.

The following registered formulations are used: For niclosamide there is a 70% wettable powder formulation (EPA Reg. No.6704-87) and 3.2% granular formulations (EPA Reg. No. 6704-91). The public health mollusicide use of niclosamide against snails that carry vectors for swimmer's itch has been voluntarily canceled by the registrant. There are two formulations of TFM, which include a 38% liquid concentrate (EPA Reg. No. 6704-45) and a solid bar (23 % TFM embedded in an inert chemical matrix (EPA Reg. No. 6704-86).

Applications of liquid FTM and niclosamide, the most common form of application, may be made by direct metering pump and backpack sprayers. Solid formulations may be applied by hand.

TFM and niclosamide application methods and rates depend on the characteristics of the stream to be treated, sea lamprey populations, and the populations of non-target species. In order to obtain acceptable sea lamprey control and minimize effects on non-target species, a working concentration range is developed for each specific application according to guidance specified in the USFWS lampricide application manual (EPA MRID 44003502). This manual also describes the USFWS program that closely governs the use of TFM and niclosamide. A key feature of this program is the risk mitigation component that is designed to minimize occupational exposures and exposures to the general population through direct contact or other use of treated waters.

Hazard Identification/Toxicology

In 1999, a reduced set of toxicology studies was required to support registration of non-food use chemicals. Although these required studies were available for both niclosamide and TFM, most of the studies were classified unacceptable for various reasons. HED considered the database to be limited/incomplete but sufficient to assess the human health risk for the expected exposures and durations of exposure. Neither chemical appears to be acutely toxic by the dermal route of exposure and niclosamide by the oral route of exposure.TFM is in Toxicity Category II following oral exposure. There is no acute inhalation study for either chemical. The effects observed following subchronic oral exposure of rats and dogs to TFM were decreased body weight. No effects were observed in the subchronic rat and dog studies on niclosamide. In the

TFM rat developmental toxicity study, maternal toxicity consisted of mortality and salivation, but developmental toxicity was not observed. No effects (maternal or fetal) were observed in the rabbit developmental toxicity study on niclosamide. In a chronic cancer study on niclosamide conducted by the National Cancer Institute (NCI) with mice and rats, there was no evidence of carcinogenicity in rats (both sexes) and female mice; inconclusive for male mice due to inadequate survival. Niclosamide was negative in a dominant lethal test (only mutagenicity test available). TFM was negative in the Ames assay and in the *in vivo* mouse micronucleus assay but induced chromosomal aberrations in the *in vitro* cytogenetic assay both with and without S9 activation.

Based on the current 40 CFR Part 158 Toxicology Data requirements, subchronic dermal toxicity (870.3250), developmental toxicity (870.3700b), 2-generation reproductive toxicity (870.3800), acute neurotoxicity (870.6200a), subchronic neurotoxicity (870.6200b), and immunotoxicity (870.7800) studies are required for non-food use chemicals. The Hazard and Science Policy Council (HASPOC) met on 11/08/2012 to discuss toxicology data requirements to support the registered uses of niclosamide/TFM. HASPOC (TXR No. 0056516) granted waivers to all the above requirements. This decision was based on the following considerations: an extensive level of risk mitigation for each application event, which is intended to protect those occupationally exposed and the public from exposure through drinking water sources and also from other uses of the treated waterways (e.g., swimming and boating) and a program that monitors the use of TFM and niclosamide by minimizing occupational exposures and other exposures to the general population through direct contact or other use of treated waters. Although the toxicology database is not complete, the available studies indicate that both TFM and niclosomide show evidence for low toxicity and a critical study was available to assess risks via dermal exposure. Consequently, there are no other outstanding toxicity data requirements for TFM or niclosamide.

Toxicity endpoints were not selected for the 1998 risk assessment for niclosamide and only short-term dermal endpoints (for occupational workers) were selected for TFM. Endpoints for dietary exposure were not required because the registered uses were determined to be non-food (and this has not changed). Residential exposure assessments were not required for niclosamide or TFM and are not required under registration review. This decision was based on the low potential for exposure to persons entering treated sites following application because of restricted use designation and risk mitigation and monitoring requirements to protect the public from exposure. Quantitative occupational exposure assessments were not required for niclosamide because the Agency determined that there was low potential for exposure to occupational handlers based on no evidence of acute dermal toxicity, extremely low usage, and the risk mitigation measures such as the requirement to wear vapor respirators when handling niclosamide. An occupational risk assessment for TFM dermal exposure was conducted.

For the TFM occupational assessment, HED selected an oral study for short-term dermal risk assessment, since no dermal toxicity study was submitted. The endpoint and dose were selected from the developmental toxicity study in rats, with the NOAEL of 125 mg/kg/day based on clinical signs (salivation) and mortality in dams at the LOAEL of 250 mg/kg/day. The study was considered to be the most relevant for occupational dermal risk assessment and, although no male rats were evaluated, the endpoint has been applied to account for exposures to the general

population including males and females. In the absence of dermal absorption data, HED conservatively assumed 100% dermal absorption for TFM.

Dietary Exposure

There is no reasonable expectation of human exposures to TFM/niclosamide residues in the diet via water, fish, irrigated crops, and livestock due to the low use volume applied, the infrequency of use, infinite dilution as treated stream water enters the Great Lakes, and rapid and complete dissipation of TFM/niclosamide residues from treated streams.

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 patterns 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

Conclusions: There is no expectation of dietary exposure to TFM and niclosamide, therefore, they are considered to be non-food chemicals and acute and chronic dietary risk assessments are not required

Residential (Non-Occupational) Exposure

There are currently no products containing TFM or niclosamide that are marketed for homeowner or residential uses. In addition, the registered lampricide uses are not expected to result in any significant non-occupational exposures to the public. While the potential for postapplication exposure may exist for swimmers, boaters, or other riparian water users, that potential is minimal based on the use patterns and institutional risk mitigation measures associated with the use of niclosamide and TFM.

Conclusion: Because TFM and niclosamide are not registered for use in residential settings, there is currently no risk concern for residential exposure. If exposure data and methodologies for estimating exposure have changed for issues such as volatilization and spray drift, then a new exposure assessment may be required.

Aggregate Risk Assessment

Aggregate assessments consider exposures from food, drinking water, and residential uses. Since there are no residential uses or exposure from food or drinking water for either niclosamide or TFM, an aggregate risk assessment is not required.

Conclusion: no aggregate risk assessment is required

Occupational Exposure

There are potential occupational handler exposures associated with the lampricide uses of niclosamide and TFM. Any handler exposures would be short-term in duration based on the use

pattern. There are no post-application occupational exposures expected for niclosamide and TFM.

The two potential niclosamide exposure scenarios are mixing/loading/application of niclosamide wettable powder slurry and loading/application of niclosamide granules using powered backpack blowers applications. Toxicological endpoints were not selected for niclosamide and a quantitative occupational assessment has not been performed. That decision was based on no evidence of acute dermal toxicity, extremely low usage (<350 lbs/yr), the infrequency of use, and the risk mitigation measures already implemented by USFWS, such as the requirement to wear vapor respirators when handling niclosamide. A quantitative occupational risk assessment is not needed for niclosamide under registration review.

Similarly, TFM can result in potential exposures when mixing/loading/application of liquid TFM for direct metering pump and for backpack sprayers. Toxicological points of departure (based on oral studies) were previously selected only for assessing short-term dermal occupational exposures for handlers. Intermediate- and long-term dermal exposures are not expected based on TFM lampricide use. Inhalation toxicity endpoints were not selected for TFM and there are no inhalation studies available. However, the HASPOC waived the requirements for inhalation studies based on the extensive level of risk mitigation and monitoring required for the lampricide use. In addition, previous screens indicated that inhalation exposure to TFM is not a significant contributor to the overall risks associated with the use of TFM (J. Dawson, D259427).

In 1998 a screening level occupational risk assessment was performed for TFM handler exposure scenarios using conservative assumptions (J. Dawson, D248560). Use information provided by USFWS for the years 1994 through 1997 were used, with data from 1997 selected as being representative of TFM use patterns. Treatment rates reported in the 1997 USFWS data indicate that individual streams received anywhere from 33 lbs to 7000 lbs of TFM per the annual treatment. The range of rates were assessed and resulting MOEs were above 100 (the level of concern) except for the high-end treatments using the metered pump applications which resulted in MOEs of 73 and 75. Those MOEs were not considered of concern given the very conservative nature of the assessment, i.e., it was assumed that the entire treatment amount was handled in one day by a single mixer/loader/applicator. The USFWS informed the Agency that larger applications are made by a crew of 3-5 handlers over a period of 3-5 days.

Since the 1998 TFM handler assessment was completed, HED has updated the unit exposures used to assess handlers and assumptions for average body weights have been changed to reflect the most recent Exposure Factors Handbook. As part of the registration review scoping process, HED has performed a revised screening level short-term dermal assessment for TFM handlers using updated unit exposures and body weights (see attachment 6). Assumptions regarding usage per day have been refined as well, and reflect more likely scenarios than those used in 1998.

The current screening assessment is based on the TFM liquid formulation which is expected to result in higher potential exposures than the solid bar applications and is the formulation used most often. The scenarios assessed, as identified in the USFWS manual, were mixing/loading/application of liquid TFM via direct metering pump and

mixing/loading/application of TFM using backpack sprayers. The screen assumed the use of the recommended FWS PPE of double layer of clothing, rubber boots and chemical resistant gloves.

Treatments using direct metering pump are used for treating larger bodies of water. This method accounts for the vast majority of TFM use. Treatment rates reported in the 1997 USFWS data indicate that individual streams received anywhere from 33 lbs to 7000 lbs of TFM per the annual treatment. Very large treatments would typically be performed by multiple (3-5) workers over a multi- day (3-5 days) period. As such, it is not realistic to assume that one person would apply 7000 lbs in one day. For the purpose of this exercise, HED assumes that 7000 lbs is applied over a 3.5 day period (approximately 2000 lbs per day) by only two workers; thus each worker handles 1000 lbs TFM per day. Short-term dermal handler MOEs for this scenario are over 100 (the level of concern) and are not of concern. The handling assumption is conservative and represents the very high end of expected exposure using direct metering pump applications of TFM.

TFM treatments using a back pack sprayer are used less frequently than the metered pump applications and are typically used to treat small areas of stagnant water. This handler screen considers the maximum that an individual could potentially apply with a typical 2 gallon backpack sprayer in a day. It is assumed that 12 lbs of TFM could be applied in a day. This rate is derived by assuming that in an 8 hour day, an applicator could fill and apply 16 tank loads (32 gallons) based on 30 minutes per tank. Short-term dermal handler MOEs are greater than 100 for this scenario and are not of concern. The handling assumption is conservative and represents the very high end of expected exposure using back pack sprayer applications of TFM.

Conclusion: the revised screening level short-term dermal assessment for TFM handlers using conservative assumptions show acceptable risk of concern. HED will evaluate the new usage data during registration review. If there are significant changes in the use pattern a new occupational risk assessment will be required.

Tolerance Assessment and International Harmonization

Niclosamide and TFM are non-food use chemicals and there are no established tolerances.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.pdf). The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Because TFM and niclosamide are applied directly to water bodies, the potential for contamination of fish and shellfish was considered. However, because of the high dilution and rapid breakdown of these chemicals, contamination of fish and shellfish which might lead to residues in commercially-caught fish, or which might be consumed by recreational or subsistence fishers is unlikely.

Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), TFM/Niclosamide is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. TFM/Niclosamide are not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Accordingly, as part of registration review, EPA will issue future EDSP orders/data call-ins, requiring the submission of EDSP screening assays for TFM/Niclosamide. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Human Studies

TFM/Niclosamide human health risk assessments rely, in part, on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements.

Public Health and Pesticide Epidemiology Data

Updated reviews of TFM/Niclosamide incident reports were recently prepared by HED (S. Recore, D409182, 02/14/2013). For TFM this evaluation, the OPP Incident Data System (IDS) and NIOSH SENSOR-Pesticides indicated no incidents involving TFM. Low frequency and severity was reported for niclosamide in the IDS database. No cases reported for niclosamide to the NIOSH SENSOR-Pesticides database; and niclosamide not being included in the AHS.

The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Data Requirements

None.

References

Dawson, J., ORE Aspects of HED RED Chapter for Niclosamide & TFM, September 10, 1998. DP Barcodes D248563 & D248560.

William J. Hazel, Ph.D., Niclosamide, Human Health Risk Assessment for the Reregistration Eligibility
Decision September 30, 1998. DP Barcode D248544.

William J. Hazel, Ph.D., TFM, Human Health Risk Assessment for the Reregistration Eligibility Decision September 30, 1998. DP Barcode D248546.

USEPA, 11/1999, Reregistration Elegibility Decision (RED) 3-Trifluoro-Methyl-4-Nitro-Phenol and Niclosamide.

Dawson, J., 9/15/99**,** Response to USFWS Comments on the document entitled ORE *Aspects of HED RED Chapter for Niclosamide & TFM* [Case 819174, Chem. Code 077401, DP Barcode D259427]

Van Alstine, J. 2/xx/13, Niclosamide/TFM: Summary of Hazard and Science Policy Council (HASPOC) Meeting on November 8, 2012: Recommendations on the Waivers of Toxicity Data Required for Registration Review. TXR No. 0056516.

Manual for Application of Lampricides in the US Fish and Wildlife Service Sea Lamprey (Petromyzon marinus) Control Program Including Standard Operating Procedures (EPA MRID 440035-02);

Attachments

Attachments1. Chemical Identity Tables
Attachment 2. Summary of toxicological doses and endpoints for use in the most recent human health risk assessment for Niclosamide and TFM
Attachment 3. Toxicity Profile for Niclosamide and TFM
Attachment 4. TFM/Niclosamide Products and Use Sites
Attachment 5. Toxicology Data Requirements
Attachment 6. Scoping Occupational Assessment

Attachment 1

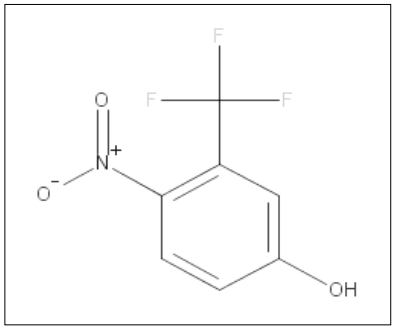
Table 1.1. Chemical Identity – TFM	
Common Name	TFM
Chemical Name (CAS)	α, α , α trifluoro-4-nitro-m-cresol,
IUPAC name	3-trifluoromethyl-4-nitrophenol
PC Code	036201
Chemical Abstracts No.	88-30-2
Chemical Class	Lampricide
Chemical structure	

Table 1.2. Physicochemical Properties of TFM		
Parameter	**Value**	**Reference**
Melting point/range	NA (Liquid)	NA
Boiling point/range	135-138 c	MRID 42295401
pH	3.15	MRID 42295401
Density	1.463 g/ml	MRID 42295401
Water solubility (25 °C)	0.498 g/100 g water	MRID 42295401
Vapor pressure (25 °C)	NA	NA
Dissociation constant, pK_a	Not Available	NA
Octanol/water partition coefficient, K_{OW} at 25 °C	NA (lampricide is a polar organic ai.)	MRID 42295401
UV/visible absorption spectrum	Not Available	NA

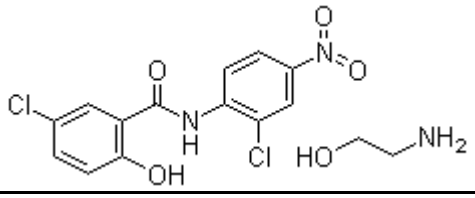
Table 1.3. Chemical Identity – Niclosamide	
Common Name	Niclosomide
Chemical Name (CAS)	2'5-dichloro-4'- nitrosalicylanilide
IUPAC name	5-chloro-N-(2-chloro-4-nitrophenyl)-2- hydroxybenzamide
PC Code	077401
Chemical Abstracts No.	1420-04-8
Chemical Class	Lampricide
Chemical structure	

Table 1.4. Physicochemical Properties of Niclosamide		
Parameter	**Value**	**Reference**
Boiling point/range	Not Available	NA
pH	Not Available	NA
Density	1.59 g/cm^3 at 22 C	MRID 42295401
Water solubility (25 °C)	1.05 x 10^{-5} g/100 mL	MRID 42295401
Vapor pressure (25 °C)	9.7 x 10^{-8} Pa	MRID 42295401
Dissociation constant, pK_a	Not Available	NA
Octanol/water partition coefficient, K_{OW} at 25 °C	NA (lampricide is a polar organic ai.)	MRID 42295401
UV/visible absorption spectrum	Not Available	NA

Attachment 2. Summary of toxicological doses and endpoints for use in the most recent human health risk assessment for Niclosamide and TFM

Table 2.1 Acute Toxicity of TFM Technical

Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute Oral Toxicity-Rat	40999204 41898102	LD 50 = 9.3 g/kg	II
870.1200 Acute Dermal Toxicity - Rabbit	40999205 41898103	LD50 > 20 g/kg	III
870.1300 Acute Inhalation Toxicity -Rat	no study	-	
870.2400 Acute Eye Irritation- Rabbit	40999207 41898104	No eye irritation	III
870.2500 Acute Dermal Irritation- Rabbit	40999206 41898105	No dermal irritation	IV
870.2600 Skin sensitization - Guinea pig	41898106	Not a dermal sensitizer	NA

Table 2.2 Acute Toxicity of Niclosamide

Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute Oral Toxicity-Rat	42552301*	LD 50 > 1000 mg/kg Single dose (no deaths or clinical signs)	III
870.1200 Acute Dermal Toxicity - Rabbit	42552301*	LD50 > 2000 mg/kg no mortality or clinical signs	III
870.1300 Acute Inhalation Toxicity - Rat		-	
870.2400 Acute Eye Irritation- Rabbit	42552305*	Evidence of eye irritation (iritis, corneal opacity, chemosis, redness at 72 hours)	Category not assigned because eyes not examined after 72 hours
870.2500 Acute Dermal Irritation- Rabbit	42552305	No dermal irritation	IV
870.2600 Skin sensitization - Guinea pig	42552306	Moderate dermal sensitizer	NA

- Submitted studies unacceptable to fulfill guideline but provide useful information for risk assessment

Table 2.3. Summary of Doses and Endpoints Used in the Human Health Risk Assessment for TFM

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-term dermal	NOAEL = 125 mkd Default 100% DAF	UF_A 10x UF_H 10x	Rat developmental toxicity LOAEL = 250 mkd, based on mortality (2/25) and salivation

Attachment 3. Toxicity Profile for Niclosamide and TFM

Table 3.1. Toxicity Profile of Niclosamide /TFM.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
NICLOSAMIDE		
870.3100 Subchronic oral toxicity (Sprague-Dawley rat)	MRID 42552307 (1974) Unacceptable (numerous parameters not monitored) 0, 30, 125, 500 mkd;	NOAEL=500 mkd LOAEL no treatment-related findings
870.3150 Subchronic oral toxicity (dog)	MRID 42552309 (1974) Unacceptable (3/sex; numerous parameters not monitored); 0, 1.6, 6.2, 25 mkd;	NOAEL= 25 mkd LOAEL not identified.
870.3100 Subchronic oral toxicity (Syrian hamster)	MRID 42552308 (1974) 0, 39, 177, 726 mkd	NOAEL = 177 mkd LOAEL = 726 mkd, based on decreased body weight/gain (both sexes)
870.3200b 21-day Dermal Toxicity (rabbit)	45256101 (1990) guinea pigs 45256102 (1990) rabbits	Not evaluated by HIARC
870.3700a Developmental Toxicity in rodents (rat)		
870.3700b Developmental Toxicity in non- rodents (rabbit)	MRID 42552310 (1975) MRID 42552311 (1074) RF Unacceptable/not upgradeable 0, 20, 60, 180 mkd GD 8-18	LOAELs not established. no maternal toxicity; no treatment-related findings in fetuses
870.3800 Reproduction and fertility effects (rats)	59380 (1975) unacceptable	Not evaluated by HIARC
870.4100 Chronic toxicity (dogs)	42552309 (1974) Unacceptable (3/sex; numerous parameters not monitored); 0, 1.6, 6.2, 25 mkd; for 180 days	NOAEL= 25 mkd LOAEL not identified.
870.4200 Chronic toxicity (rat)	42698001 (1982) unacceptable	Not evaluated by HIARC
870.4300 Chronic toxicity/ carcinogenicity in rodents (Osborne-Mendel rat)	NCI (1978) NIH 78-1341 0, 14216 ppm or 28433 ppm (0, 711, 1421 mkd) for 78 weeks;	no evidence of carcinogenicity in either sex
870.4200 Carcinogenicity study (B6C3F1 mice)	NCI (1978) NIH 78-1341 0, 274 ppm or 549 ppm (0, 39, 78 mkd) Unacceptable	inadequate survival of males; no evidence of carcinogenicity in females
870.5100 Mutagenicity: gene mutation (bacterial)		
870.5300 In vitro mammalian cell gene mutation test L5178Y mouse lymphoma cells	MRID 43677901 (1995) Acceptable/guideline -S9 (30-80 µg/mL cytotoxic); 2.5-25 µg/mL	No increase in mutant frequency at cytotoxic doses

Table 3.1. Toxicity Profile of Niclosamide /TFM.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
	+S9 (1.25-40 µg/mL)	
870.5375 Mutagenicity: *in vitro* chromosomal aberration	1996 Mutation Res 370 (1): 1-9	In vivo sister chromatid exchange (SCE) and chromosome aberration studies positive in both assays.
870.5385 *in vivo* cytogenetic mutagenicity assay (mammalian bone marrow chromosomal aberration test Crl:CD)ICR)BR mice)	MRID 43677902 (1995) Acceptable 1250, 2500, or 5000 mg/kg	No evidence of chromosome aberration in bone marrow cells
In Vivo Mammalian cell Assay	MRID 42552312 (1975) Unacceptable; 500 mkd;	dominant lethal; no effects seen but no + control data
870.5550 Mutagenicity: Unscheduled DNA synthesis		
TFM		
870.3100 Subchronic oral toxicity (rat)	MRID 00112726 /7(1971) 0, 500, 900, 1620, 2916, 5248 ppm MRID 00112727 (1971) 0, 500, 900, 1620, 2916, 5248 ppm	Study 1:NOAEL 525 mkd (5248 ppm) Study 2: NOAEL 162 mkd; LOAEL 292 mkd, based on↓BW
870.3150 Subchronic oral toxicity (dog)	MRID 00112725 (1973)	NOAEL 31 mkd; LOAEL 125 mkd, based on ↓BW/BWG
870.3700a Developmental Toxicity (COBS CD(SD) BR rat)	00131201 (1983) 0, 25, 125, or 250 mkd GD 6-15	Maternal NOAEL 125 mkd (2/25 salivation) Maternal LOAEL 250 mkd, based on mortality (1 on GD 6, 1 on GD 12) and salivation (22/25) Developmental NOAEL 250 mkd (HDT)
870.3700b Developmental Toxicity (rabbit)	00138481 (1975) 00150476 (1975) Unacceptable	not considered by HIARC
870.3800 Reproduction and fertility effects (rats)		
870.4100 Chronic toxicity (dogs)		
870.4200 Chronic toxicity (rat)		
870.4300 Chronic toxicity/ carcinogenicity (rat)	MRID 00112718 (1975)	Not evaluated by HIARC
870.4200 Carcinogenicity (mice)		
870.5100 Mutagenicity: gene mutation (bacterial)	MRID 42551801 (1977)	Negative

Table 3.1. Toxicity Profile of Niclosamide /TFM.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5375 Mutagenicity: *in vitro* chromosomal aberration	MRID 40999201 (1988) Chinese hamster ovary cell assay	Induced Chromosomal aberrations in Chinese hamster ovary cells; with and without metabolic activation
870.5395 *in vivo* Mammalian erythrocyte micronucleus test	MRID 42187101 (1989)	Negative
870.5550 Mutagenicity: Unscheduled DNA synthesis	MRID 40999202 (1988)	Negative in rat primary hepatocytes

Attachment 4. Niclosamide/TFM Products and Use Sites.

Table 4.1 Use Patterns for End-use Product Formulations of Niclosamide/TFM			
EPA Reg. No. & (Formul. types)	**% AI**	**Use sites & (Applicable ORE Review)**	**Application equipment**
Niclosamide (D248563&D248560)			
6704-87	70(WP)	Lampricide in Great Lakes, Finger Lakes, and Lake Champlain	Direct Metering Pump, Back pack Sprayer
6704-91	3.2(G)		
TFM(D248563&D248560)			
6704-45	36-38 (EC)	Lampricide in Great Lakes, Finger Lakes, and Lake Champlain	Direct Metering Pump, Back pack Sprayer
6704-86	23 (solid bar)		Hand

Abbreviations used: AI = active ingredient, EC = emulsifiable concentrate, NA = not applicable, G = granule, WP =Wettable Powder,

Attachment 5. Toxicology Data Requirements

Table 5.2 Summary of Toxicological Data Requirements for Niclosamide

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	Yes	No
870.1200 Acute Dermal Toxicity	Yes	No
870.1300 Acute Inhalation Toxicity	Yes	No
870.2400 Primary Eye Irritation	Yes	No
870.2500 Primary Dermal Irritation	Yes	Yes
870.2600 Dermal Sensitization	Yes	Yes
870.3100 Oral Subchronic (rodent)	CR	W[A]
870.3150 Oral Subchronic (nonrodent)	CR	W
870.3200 21-Day Dermal	NR	W
870.3250 90-Day Dermal	Yes	W
870.3465 90-Day Inhalation*	CR	W
870.3700a Developmental Toxicity (rodent)	Yes	W
870.3700b Developmental Toxicity (nonrodent)	Yes	W
870.3800 Reproduction	Yes	W
870.4100a Chronic Toxicity (rodent)	CR	W
870.4100b Chronic Toxicity (nonrodent)	CR	W
870.4200a Oncogenicity (rat)	CR	W
870.4200b Oncogenicity (mouse)	CR	W
870.4300 Chronic/Oncogenicity	CR	W
870.5100 Mutagenicity—Gene Mutation - bacterial	Yes	W
870.5300 Mutagenicity—Gene Mutation - mammalian	Yes	W
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosome Aberration Aberrations	Yes	W
870.5550 Mutagenicity—Unscheduled DNA Synthesis	yes	W
870.6200a Acute Neurotoxicity Screening Battery (rat)	Yes	W
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	Yes	W
870.6300 Developmental Neurotoxicity	CR	W
870.7485 General Metabolism	CR	W
870.7600 Dermal Penetration	CR	W
870.7800 Immunotoxicity	Yes	W

[A]Waived by HED HASPOC (TXR # 0056516)

Table 5.2 Summary of Toxicological Data Requirements for TFM		
Test	**Technical**	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	Yes	Yes
870.1200 Acute Dermal Toxicity	Yes	Yes
870.1300 Acute Inhalation Toxicity	Yes	No
870.2400 Primary Eye Irritation	Yes	Yes
870.2500 Primary Dermal Irritation	Yes	Yes
870.2600 Dermal Sensitization	Yes	Yes
870.3100 Oral Subchronic (rodent)	CR	W[A]
870.3150 Oral Subchronic (nonrodent)	CR	W
870.3200 21-Day Dermal	NR	W
870.3250 90-Day Dermal	Yes	W
870.3465 90-Day Inhalation*	CR	W
870.3700a Developmental Toxicity (rodent)	Yes	Yes
870.3700b Developmental Toxicity (nonrodent)	Yes	W
870.3800 Reproduction	Yes	W
870.4100a Chronic Toxicity (rodent)	CR	W
870.4100b Chronic Toxicity (nonrodent)	CR	W
870.4200a Oncogenicity (rat)	CR	W
870.4200b Oncogenicity (mouse)	CR	W
870.4300 Chronic/Oncogenicity	CR	W
870.5100 Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300 Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosome Aberration Aberrations	Yes	Yes
	Yes	W
870.5550 Mutagenicity—Unscheduled DNA Synthesis	yes	W
870.6200a Acute Neurotoxicity Screening Battery (rat)	Yes	W
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	Yes	W
870.6300 Developmental Neurotoxicity	CR	W
870.7485 General Metabolism	CR	W
870.7600 Dermal Penetration	CR	W
870.7800 Immunotoxicity	Yes	W

[A]Waived by HED HASPOC (TXR # 0056516)

Attachment 6. Screening Occupational Assessment

Table 6.1Occupational Handler Dermal Exposures and Risks For TFM			
Dermal Exposures (ug/lb ai)[1]	Usages estimate Lbs[2]	Dermal Doses (mg/kg/day)[3]	Short-term MOE
Mix/Load for metering pump			
29.1 (Double layer &glove)	1000	0.37	340
Mix/Load/Apply with a back pack sprayer			
4120 (Double layer &glove)	12	1.24	200

[1] Based on "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2012); includes data from PHED /AHETF.

[2] Usage estimates (lbs) used for scoping assessment.

[3] Dose (mg/kg/day) = Unit exposure (mg/lb ai) x Usage Estimate) x % Absorption (100% dermal) / Body weight. The body weight is 80 kg for dermal dose.

[4] Short-term MOE = short-term dermal NOAEL (125 mg/kg/day) / Dermal Doses (mg/kg/day)