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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: November 9, 2015

SUBJECT: **Pronamide.** Human Health Risk Assessment for Registration Review and to Support New Section 3 Use on Leaf Lettuce **(Revised)**.

PC Code: 101701
Decision No.: D493477
Petition No.: 4F8301
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: see References

DP Barcode: D422207, D410291
Registration No.: 62719-578
Regulatory Action: Registration Review/Section 3
Case No.: 0082
CAS No.: 23950-58-5
40 CFR: 40 CFR §180.317

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1.0 Executive Summary

Background

Pronamide, also called propyzamide, [3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide], is a selective, systemic, pre-and post-emergence herbicide registered for the control of grasses and broadleaf weeds in several food and feed crops as well as woody ornamentals, Christmas trees, grasses grown for seed or turf (sod), golf course turf, recreational area turf, and fallow land. This assessment has been conducted for the purpose of addressing two separate regulatory actions: (1) Section 3 registration for leaf lettuce, and (2) reassessment of all currently registered uses to support the Draft Risk Assessment (DRA) for Registration Review.

Exposure and Use Profile

There are five end-use products registered with pronamide as the active ingredient. These include liquid and wettable powder in Water Soluble Package (WSP) formulations. The registered use sites include various agricultural sites, Christmas tree farms, golf courses, seedling nurseries, landscape ornamentals, non-crop use sites (such as railroad, highway, roadside, pipeline and utility rights-of-way, and industrial areas), residential/commercial turf, and sod farms. Most of the uses are soil-directed, and are applied either via aerial, chemigation, groundboom, or handheld equipment. The application rates for all uses range from 0.5 to 4 lb ai/A. The re-entry interval (REI) for the registered uses is 24 hours. All of the pronamide registered labels require handlers to wear a double layer of clothing (long sleeved shirt and long pants) with either waterproof or chemical-resistant gloves.

There is a proposed new Section 3 use on leaf lettuce. The liquid formulation (EPA REG # 62719-578) may be applied via aerial, chemigation, and groundboom equipment. The proposed single maximum application rates and PHIs range from 0.5 lbs ai/A (25 days) to 2.0 lbs ai/A (55 days). Two broadcast applications can be made per year.

Hazard Assessment

The primary target organ for pronamide is the liver. Effects include elevated levels of enzymes associated with liver damage and histopathology of liver cells. There are other target organs as well, including the thyroid, testes and pituitary, but effects to these organs are typically secondary to primary effects on the liver. The liver is affected in all species tested.

Pronamide is a carcinogen in rats and mice, causing liver tumors in mice, thyroid tumors in male rats and testicular tumors in rats. Mode of action (MOA) data have been submitted to the Agency and accepted for all three tumor types. All of the cancer modes of action focus on the liver as the site of the molecular initiating events for carcinogenicity.

Neurotoxicity was observed in the acute neurotoxicity study (ACN) at a lowest observed effect level (LOAEL) of 40 mg/kg, and is the basis for the point of departure (POD) of 4 mg/kg/day to assess acute dietary risk. Since there are no effects observed in any of the pronamide toxicity studies below 4 mg/kg/day, this point of departure from the ACN study also serves as a convenient reference point to assess chronic dietary risk, inhalation risk and short and intermediate incidental oral risk to young children.

Residue Chemistry

Several residue chemistry data deficiencies were identified in the scoping document of pronamide (D363904, 06/17/2009). New data has been submitted and evaluated in support of Registration Review and there is a proposed new use on leaf lettuce. The chemistry database of pronamide is adequate to support Registration Review and the proposed new use in leaf lettuce provided that data needs, recommended tolerances and label modifications described in Section 2.0 are considered. The nature of the residue is adequately understood for alfalfa and lettuce, rotational crops, livestock, and drinking water. The terminal residues of concern in plants, livestock commodities, and drinking water, are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety. Adequate enforcement methods for residues of pronamide on plants and livestock are available. To support the use on peas, field trial data from two additional field trials for pea vines and hay and four additional field trials for pea seed are required.

Dietary Exposure and Risk

Unrefined acute and chronic dietary assessments were performed. Tolerance level residues of pronamide were used for the registered uses and proposed new use on leaf lettuce. Default processing factors and 100% crop treated (CT) assumptions were utilized. Drinking water was incorporated directly in the dietary assessment using the Tier II acute and chronic estimated drinking water concentrations (EDWC) for surface water generated by the Surface Water Concentration Calculator (SWCC). Acute and chronic dietary (food and water) risks from the existing and proposed use of pronamide are ≤ 46% of the aPAD and ≤ 11% of the cPAD, respectively. These are not of concern for the general population and the regulated population subgroups, i.e. < 100% of the aPAD and cPAD.

Residential (Non-Occupational) Exposure and Risk

Residential handler exposures are not expected as pronamide is a Restricted Use Pesticide and as such can only be applied by Certified Applicators. However, there is the potential for post-application exposure from currently registered turf uses (e.g., residential turf, golf courses) and these uses have been reassessed to reflect updates to HED's 2012 Residential SOPs.

All dermal and incidental oral risk estimates for post-application exposure are not of concern (i.e., dermal MOEs ≥ 100 and all incidental oral MOEs ≥ 1000).

Aggregate Exposure and Risk

There was a single scenario assessing aggregate risk to children from post application exposure to pronamide from treated turf. Aggregate hand-to-mouth and chronic food and water exposure is not of concern since the aggregate MOE of 1700 is greater than the LOC of 1000.

Spray Drift

A quantitative spray drift assessment for pronamide is not required because the turf post-application MOEs are protective for any potential exposures related to spray drift.

Occupational Exposure and Risk

Occupational handler exposure and risk estimates indicate that short- and intermediate-term dermal MOEs are not of concern to HED (i.e., MOEs $\geq$100) for any of the end-use products as long as label-required personal protective equipment (PPE) of double layer clothing and gloves are worn during mixing/loading of liquid formulation for aerial application to high-acreage crops (corn, soybeans and wheat).

To assess inhalation risk an inhalation study is normally required, or, in the absence of an inhalation study, an appropriate oral study may be used as a surrogate for risk assessment provided the MOEs are $\geq$1000 for inhalation exposure. In 2003 a waiver of the requirement to perform an inhalation study was granted because the MOEs based on an oral study exceeded 1000. Unit exposures and exposure assessment procedures have evolved since 2003 based on new data, nevertheless at this time, all short and intermediate-term scenarios have adequate MOEs in excess of 3000 (see Appendix E). Accordingly the requirement to perform an inhalation study continues to be waived.

Occupational post-application dermal exposure and risk estimates were assessed for the registered uses that are not soil-directed (e.g., turf), and resulted in acceptable MOE's $\geq$100 on the day of application, ranging from 100 to 79,000. Based on quantitative post-application assessment, the labeled REI of 24 hours is required to protect workers from exposures to pronamide.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this 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://www3.epa.gov/environmentaljustice/resources/policy/exec_order_12898.pdf

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the PHED 1.1, the AHETF database, and the ARTF database are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

Dislodgeable Foliar Residue (DFR): Since the MOE associated with the highest estimated occupational post-application exposure using default DFR values for pronamide is equal to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 100 compared to the LOC of 100); the DFR data under 40 CFR is needed.

Residue Chemistry. Additional field trials for pea vines and hay and pea seed are needed. Storage stability data will be required if samples to be collected from the requested field pea field trials are stored frozen longer than the intervals for which residues have been demonstrated to be stable (I. Negrón-Encarnación, D383372).

The standards of pronamide and methyl-3,5-dichlorobenzoate will expire in September 2015. In addition, the standard of 3,5-dichlorobenzoic acid is needed to support the residue measured in the new enforcement method for livestock commodities. The registrant should submit these standards to the EPA National Pesticide Standards Repository.

2.2 Tolerance Considerations

Tolerances have been previously established in 40 CFR §180.317 for the combined residues of pronamide and its metabolites (containing the 3,5-dichlorobenzoyl moiety and calculated as 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide). The terminal residues of concern in plants and

[1] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html

livestock commodities, and in drinking water, are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety.

2.2.1 Enforcement Analytical Method

Plant: An adequate residue analytical method is available for tolerance enforcement of residues in/on plant commodities. The PAM II lists a GLC/ECD method, designated as Method I, which converts residues of pronamide and its metabolites to methyl 3,5-dichlorobenzoate (MDCB). Method I was successfully radiovalidated using aged samples from the alfalfa and lettuce metabolism studies.

Livestock: Modifications to the livestock enforcement method were required previously (02/28/2002; D275536). An Independent Laboratory Validation (ILV) of a new method was submitted and considered acceptable. Based on this a gas chromatography method with negative-ion chemical ionization mass spectrometry detection (GC/MS), Method GRM 02.21, for the determination of residues of pronamide and metabolites containing the 3,5-dichlorobenzoyl moiety converted to 3,5-dichlorobenzoic acid (3,5-DCBA) in milk, bovine liver, kidney, muscle, and fat, and eggs and poultry muscle and fat is available for enforcement of tolerances for livestock commodities.

2.2.2 Recommended Tolerances

The current tolerance expression for pronamide (40CFR §180.317) is adequate for plant commodities, and includes both coverage and compliance statements for enforcement purposes. HED recommends a tolerance of 1 ppm to support the use of pronamide on leaf lettuce in order to harmonize with the Canadian MRL for lettuce (I. Negrón-Encarnación, D424598, 01/15/2015, I. Negrón-Encarnación, D429782, 10/26/2015 and discussion below). Moreover, based on limited field trial data to support the use of pronamide on field pea, HED recommends increasing the tolerance for field pea seed from 0.05 ppm to 0.10 ppm, and establishing tolerances of 1.5 ppm and 3.0 ppm for field pea vines and dry pea hay, respectively (I. Negrón-Encarnación, D383372, 09/17/2015).

The current tolerance expression is not adequate to enforce tolerances in livestock commodities as the tolerance enforcement method converts residues of pronamide to 3,5-dichlorobenzoic acid instead of methyl-3,5-dichlorobenzoate. Based on this, HED recommends modification of 40 CFR § 180.317 (a) General in two sections, (1) and (2). The first section may include the current tolerance expression for plants followed by a table with the tolerances for plant commodities while the second section may contain the tolerance expression below followed with a table with the tolerances for livestock commodities.

The recommended tolerance expression for section (2) is: “Tolerances are established for residues of the herbicide propyzamide, including its metabolites and degradates, in or on the commodities in the following table. Compliance with the tolerance levels specified in the table below is to be determined by measuring only those propyzamide residues convertible to 3,5-

dichlorobenzoic acid, expressed as the stoichiometric equivalent of propyzamide, 3,5-dichloro-N-(1,1-dimethyl-2-propynyl)benzamide, in or on the commodity."

Table 2.2.2. Tolerance Reassessment Summary for Pronamide			
Commodity	Established / Proposed* Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Tolerance to be Listed Under 40 CFR §180.317(a)(1)			
Alfalfa, seed	10.0	10.0	
Animal feed, nongrass, group 18	10.0	10.0	
Apple	0.1	0.1	
Artichoke, globe	0.01	0.01	
Blackberry	0.05	0.05	
Blueberry	0.05	0.05	
Boysenberry	0.05	0.05	
Endive	1.0	1.0	
Fruit, stone, group 12	0.1	0.1	
Grape	0.1	0.1	
Lettuce, head	1.0	1.0	
Lettuce, leaf	1.0	1	
Pear	0.1	0.1	
Radicchio	2.0	2.0	
Raspberry	0.05	0.05	
Tolerance to be Listed Under 40 CFR §180.317(a)(2)			
Cattle, fat	0.2	0.2	
Cattle, kidney	0.4	0.4	
Cattle, liver	0.4	0.4	
Cattle, meat	0.02	0.02	
Cattle, meat byproducts, except kidney and liver	0.02	0.02	
Egg	0.02	0.02	
Goat, fat	0.2	0.2	
Goat, kidney	0.4	0.4	
Goat, liver	0.4	0.4	
Goat, meat	0.02	0.02	
Goat, meat byproducts, except kidney and liver	0.02	0.02	
Hog, fat	0.2	0.2	
Hog, kidney	0.4	0.4	
Hog, liver	0.4	0.4	
Hog, meat	0.02	0.02	
Hog, meat byproducts, except kidney and liver	0.02	0.02	

Horse, fat	0.2	0.2	
Horse, kidney	0.4	0.4	
Horse, liver	0.4	0.4	
Horse, meat	0.02	0.02	
Horse, meat byproducts, except kidney and liver	0.02	0.02	
Milk	0.02	0.02	
Poultry, fat	0.02	0.02	
Poultry, liver	0.2	0.2	
Poultry, meat	0.02	0.02	
Poultry, meat byproducts, except liver	0.02	0.02	
Sheep, fat	0.2	0.2	
Sheep, kidney	0.4	0.4	
Sheep, liver	0.4	0.4	
Sheep, meat	0.02	0.02	
Sheep, meat byproducts, except kidney and liver	0.02	0.02	
Tolerance Listed Under 40 CFR §180.317(c)			
Pea, field, seed	0.05	0.10[1]	
Tolerances To Be Listed Under 40 CFR §180.317(c)			
Pea, field, hay	--	3.0[1]	
Pea, field, vines	--	1.5[1]	

[1] To be re-evaluated upon submission of adequate magnitude of residue studies.

2.2.3 Revisions to Petitioned-For Tolerances

The registrant had proposed a tolerance of 1.0 ppm for leaf lettuce. The recommended US tolerance was estimated following the Organisation for Economic Co-operation and Development (OECD) calculation procedures using field trial data that supports the intended use pattern. The data of the 2009 decline trials was organized in the following four sets: 0.5 lb ai/A (25 day-PHI), 1.0 lb ai/A (35-day PHI), 1.5 lb ai/A (45-day PHI), and 2.0 lb ai/A (55-day PHI). All data sets result in a rounded MRL of 2 ppm with the exception of the 0.5 lb ai/A which results in a rounded MRL of 1.5 ppm. Based on these calculations, the tolerance suggested by the OECD calculation procedures is 2 ppm. Canada has an MRL of 1 ppm for residues of pronamide on lettuce. The highest residue obtained from the crop field trial data with leaf lettuce was 1.0 ppm which is at the tolerance level. Because substantial data is available for pronamide on leaf lettuce (18 crop field trials in the US; 8 of those with 4 different use patterns), residues decline significantly within days (e.g. mean residues observed in the 2009 decline trials decrease by a factor of 0.6 in comparison to those from samples harvested 10 days before), and MRLs established by most countries are at 1 ppm or below, HED recommends in favor of a tolerance of 1 ppm for leaf lettuce.

2.2.4 International Harmonization

Where possible, EPA encourages the harmonization of US Tolerances and Maximum Residue Limits (MRLs) in key export markets. A table with US tolerances, and Canadian and Codex MRLs for pronamide is provided in Appendix G. Currently, Mexican or Codex MRLs for pronamide have not been established. The US and Canadian tolerance expressions are harmonized for measurement of pronamide, including metabolites containing the 3,5-dichlorobenzoate moiety. Canadian MRLs for apple, blueberry and pear are harmonized with US tolerances. The Canadian MRL for lettuce is 1 ppm. In order to harmonize with the Canadian MRL for lettuce, HED recommends that the US tolerance for leaf lettuce be established at 1 ppm.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The current labels for pronamide include plant back intervals for other crops than those recommended in the 2002 TRED. Rotation to crops other than leafy vegetables (crop group 4), root and tuber vegetables (crop group 1), and cereal grains is allowed by following a 365-day plant-back interval (PBI), refer to Section 3.3.

Feeding/grazing restrictions on the labels can be removed as potential residues of pronamide in/on field pea feedstuff and livestock commodities have been evaluated, and these restrictions are generally considered impractical and/or unenforceable.

For the new use on leaf lettuce, it is recommended that detailed instructions for split applications be included in the supplemental label. The maximum allowable total rates and corresponding PHIs for split applications should follow the recommendations currently proposed for regular applications.

2.3.2 Recommendations from Occupational Assessment

The current PPE for registered uses and the proposed use are coveralls over short-sleeved shirt and short pants, waterproof gloves and chemical-resistant footwear plus socks. The PPE are adequate and no extra PPE is required.

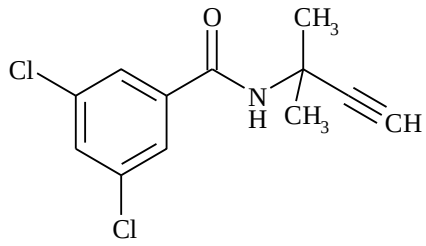
2.3.3 Recommendations from Residential Assessment

None at this time.

3.0 Introduction

Pronamide is a selective, systemic, pre-and post-emergence herbicide registered for the control of grasses and broadleaf weeds in several food and feed crops as well as woody ornamentals, Christmas trees, nursery stocks, lawns, turf, and fallow land.

3.1 Chemical Identity

Table 3.1 Pronamide Nomenclature.	
Compound	
Empirical Formula	$C_{12}H_{11}Cl_2NO$
Molecular weight	256.13
Common name	pronamide or propyzamide
Company experimental name	Not applicable
IUPAC name	3,5-dichloro-*N*-(1,1-dimethylpropynyl)benzamide
CAS name	3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide
CAS registry number	23950-58-5
Chemical Class	Amide herbicide (Pesticide Manual, 11th edition)

3.2 Physical/Chemical Characteristics

Pronamide is slightly soluble in water (15 mg/L) and is not expected to volatilize significantly due to the compound's relatively low vapor pressure of $8.5x10^{-5}$ torr. The log Kow for pronamide is 3.43. A table of physico-chemical properties for pronamide may be found in Appendix C.

3.3 Pesticide Use Pattern

There are five end-use product labels registered with pronamide as the active ingredient. These include liquid, and wettable powder formulations. Pronamide, may be applied using ground spray equipment, by soil incorporation, or by aircraft. The single application rates for agricultural uses range from 0.5 to 4 lb ai/A, and the maximum application rate per year range from 1 to 6 lbs ai/A. The 2002 residue chemistry chapter in support of the Tolerance Reassessment Eligibility Decision (TRED) recommended plant back intervals of 30-day for leafy vegetables (except Brassica vegetables) (Crop Group 4); 90-day for root and tuber vegetables (Crop Group 1); 360-day for cereal grains (Crop Group 15) and the forage, fodder, and straw of cereal grains (Crop Group 16) (D275536, 02/28/2002). Currently, extensive rotational crop restrictions, dependent on application rates, are established on the product labels. The restrictions for root and tuber vegetables, leafy vegetables crop group 4, and cereal grains are considered

adequate. However, restrictions for other crops such as legume vegetables and cotton (90 to 150-day PBI), and brassica leafy vegetables, cucurbit vegetables, fruiting vegetables, and bulb vegetables (90 to 210-day PBIs) are included in the labels. As indicated in the 2002 TRED, these rotational crop restrictions are inappropriate based on the results of the reviewed confined and limited rotational field studies.

Conclusions: Several label modifications are recommended with respect to the established plant back intervals, split applications for leaf lettuce, and feeding/grazing restrictions for pea feedstuff commodities.

(1) Appropriate plant back intervals are established for leafy vegetables crop group 4, root and tuber vegetables crop group 1, and cereal grains in the Dow labels for Kerb® (EPA Reg. Nos. 62719-578, and 62719-397) and those from Willowood (EPA Reg. Nos. 87290-22, 87290-9 and 87290-3). However, rotation to other crops than those was not recommended in the 2002 TRED. Rotation to other crops is allowed by following a 365-day PBI. Based on this, the rotation instructions for legume vegetables and cotton (90 to 150-day PBI), and brassica leafy vegetables, cucurbit vegetables, fruiting vegetables, and bulb vegetables (90 to 210-day PBIs) currently included in the labels should be deleted.

(2) For the new use on leaf lettuce, it is recommended that detailed instructions for split applications are included in the supplemental label, e.g. for split applications part of the maximum allowable application rate can be initially applied and the balance of the maximum allowable application rate can be made up to 10 days later. The maximum allowable total rates and corresponding PHIs for split applications for leaf lettuce should be 0.5, 0.75, 1.5, and 2.0 lbs ai/A with corresponding PHIs of 25, 35, 45, and 55 days, respectively.

(3) For the established use on field pea, the registrant may delete the existing feeding/grazing restrictions on the label since they are impractical and/or unenforceable.

3.4 Anticipated Exposure Pathways

The Registration Division and Pesticide Re-evaluation Division have requested an assessment of human health risk to support the proposed new use of pronamide for a Section 3 registration for leaf lettuce, and assessment of all currently registered uses to support the Preliminary Risk Assessment (PRA) for Registration Review. Humans may be exposed to pronamide in food and drinking water, since pronamide may be applied directly to growing crops and application may result in pronamide reaching surface and ground water sources of drinking water. There are residential uses of pronamide, so there is likely to be exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pronamide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields to dislodgeable pesticide residues from treated surfaces. The proposed use pattern is for preemergence or early postemergence application. As a result, there are few, if any, agricultural activities that might be necessary in the days closely

following application. The most likely activity is scouting for herbicide efficacy. Unlike scouting for insects or mites, there is little expected foliar contact, other than possibly walking in a treated field several days after application.

Risk assessments have been previously prepared for the existing uses of pronamide. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of pronamide, but also considers the existing uses as well, particularly for the dietary exposure assessment.

Based on the proposed and registered use patterns, it has been determined that the potential exposure scenarios that will need to be assessed include short- and intermediate-term occupational (handler and post-application) and residential exposures (post-application only).

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this 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://www3.epa.gov/environmentaljustice/resources/policy/exec_order_12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

Based on the proposed use pattern, the database for pronamide is complete. The data from the following acceptable studies were used to evaluate the hazard potential of pronamide:

- Oral subchronic toxicity study in the rat

- Dermal subchronic toxicity study in the rat
- Prenatal developmental toxicity study in the rabbit
- Multi-generation reproduction study in the rat
- Chronic toxicity studies in the rat and dog
- Carcinogenicity studies in the rat and mouse
- Mutagenicity battery
- Acute and subchronic neurotoxicity screening batteries in the rat
- Metabolism with pharmacokinetic studies in the rat
- Dermal absorption studies *in vivo* and *in vitro*
- Immunotoxicity study in the mouse
- Carcinogenicity MOA studies, including
    - a study designed to determine the induction pattern of hepatic metabolizing enzymes (CYPs) in male mice,
    - a study designed to determine molecular, cellular, and biochemical changes in the livers of male rats related to Leydig cell tumor formation,
    - a thyroid function and hepatic clearance study in male rats
    - Bromodeoxyuridine (BrdU) labeling index to explore patterns of hepatic cell proliferation in mice
    - a 90-day study to evaluate the MOA of pronamide-induced Leydig tumors in older male rats,
    - a study to determine if there is a surge in LH (luteinizing hormone) levels in the blood of rats after administration of pronamide in male rats.

The Hazard and Science Policy Council (HASPOC) determined that a new rat developmental toxicity study is not required since rabbits are the most sensitive species for developmental toxicity and a repeat developmental toxicity study in rats will not impact the risk assessment (TXR# 0056955). Also, the HASPOC granted a waiver to the comparative thyroid assay since the available mode of action studies show no direct interaction with the thyroid pathway and the thyroid effects are mediated through alterations in liver enzymes (TXR#0057211).

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

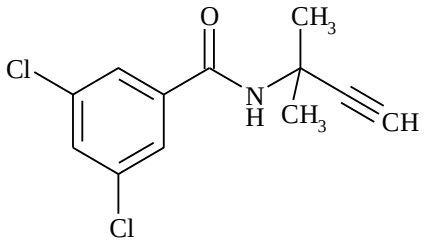
Orally administered pronamide is quickly absorbed from the g.i. tract and rapidly eliminated. In an ADME study with ^{14}C-pronamide (MRIDs 41801801, 41929901 and 42858001) radiolabel was recovered (total = 93-103%) in the urine (40-61%), feces (40-60%), tissues and carcass (0.08-2.4%) over a 7 day period. No bioaccumulation was apparent. The half-life of elimination of radioactivity from plasma of low dose (2 mg/kg) rats was biphasic with a rapid phase = 13 hrs (males and females) and a slow phase of 37 hours in males and 45 hours in females; and that of high dose (100 mg/kg) rats was monophasic with a half-life of 24hrs (males and females).

Very little pronamide per se was recovered in the urine and no significant difference in urinary metabolite profile was observed between doses or sexes. In the urine, there were 27 unidentified

metabolites and none exceeded 3.3% of the dose. Few metabolites were identified in the feces, and nearly all of them were less than 1% of the dose.

Data from dermal absorption studies discussed below (MRIDs 41117201 and 40256701) are also relevant to oral absorption. One satellite group of rats in the dermal studies was dosed i.v. with 1.3 mg/kg a.i. and urine and feces were collected over a 7-day period. Nearly 100% of the administered dose was recovered with 63% of the label in the urine and 36% in the feces. Fecal excretion of an i.v. dose indicates biliary clearance and the same pattern of urinary and fecal excretion is seen in the oral studies discussed above, suggesting that nearly all orally administered pronamide (at least up to 100 mg/kg) is absorbed from the g.i. tract.

Pronamide is an amide of 3,5-dichlorobenzoic acid. In metabolic studies in rats no alteration of



the halogenated benzene ring took place, but the alkyl (1,1-dimethyl-2-propynyl) group was extensively metabolized. The methyl groups and the triple bond were readily oxidized to hydroxyl and carboxyl groups and these were in turn conjugated with glucose and malonic acid. Appendix B contains structures of rat metabolites and a proposed metabolic pathway for pronamide in rats.

4.2.1 Dermal Absorption

Two formulations of radiolabeled pronamide (^{14}C-Kerb 50W and ^{14}C-Kerb 3.3F) were evaluated for dermal absorption in the rat (MRIDs 41117201 and 40256701). Each formulation was tested at a low dose of 1.2 mg ai/kg (0.08 mg ai/cm^2) or a high dose of 66 mg ai/kg (4.4 mg ai/cm^2). After 6 hours of exposure the treated areas of the rats were wiped with a soap solution followed by water. Dermal absorption was compared with oral uptake of 68 mg/kg ^{14}C- pronamide administered by gavage in corn oil, or an i.v. dose of 1.3 mg/kg of ^{14}C- pronamide in DMSO. Quantitation of uptake was based primarily on radiolabel recovered from excreta.

A total of 19% and 17% of recovered ^{14}C-pronamide was eliminated in the excreta following the low and high dose of ^{14}C-Kerb 50W, respectively. A total of 15% and 5% of the recovered ^{14}C-1abel was eliminated in the excreta following the low and high dose of ^{14}C- Kerb 3.3F, respectively. Based on the available data, the low dose of the 50W formulation was selected for risk assessment as it represents the highest dermal absorption potential. However, a low total mass balance recovery was obtained at this dose (78%), compared to the high dose (122%). Therefore, the data were normalized to give a dermal absorption factor of 23%. Furthermore, the

total absorbed dose reported in the study did not include the radioactivity remaining in the carcass. At this dose level 2 of the 4 carcasses were analyzed and found that 1.2 and 0.7% of the dose remained. Therefore, a 1% correction factor was applied to yield a final DAF of 24% for pronamide.

4.3 Toxicological Effects

Pronamide is a selective, systemic, pre-and post-emergence herbicide, that inhibits root and shoot growth from seedlings. Its mode of action in plants is to interfere with cell division in the root systems of a select group of annual grasses and broadleaf weeds.

In mammals, pronamide is primarily a liver toxicant. Liver-related effects included increases in absolute and relative liver weight, hypertrophy, and increases in serum enzymes associated with liver toxicity such as alkaline phosphatase and alanine aminotransferase, and/or histopathology. Adverse liver findings were consistently observed in every animal species studied with progression towards more severe effects over time ultimately leading to tumorigenesis in rats and mice. Based on the studies submitted, the rat is the most sensitive species. In most studies there is no gender sensitivity in response to pronamide.

Pronamide causes liver tumors in mice and thyroid tumors and testicular Leydig cell tumors in rats. In mice, cancer mode of action data clearly show rapid induction of CYP2B1 associated with the constitutive androstane nuclear receptor (CAR), as well as induction of peroxisomes and peroxisomal enzymes associated with a second nuclear receptor, PPAR-α. Induction of the nuclear receptors is followed by hepatocellular proliferation and eventually, liver tumors.
In rats tumor precursor effects such as decreases in T4 levels, increases in liver weight, liver hypertrophy, and elevated testosterone metabolism have been shown to occur at pronamide doses below or equivalent to the tumorigenic dose. For example, in rat pubertal studies submitted to fulfill EDSP testing requirements, there were effects on blood T4 levels at doses 2- to 4-fold lower than doses resulting in thyroid tumors. Based on mode of action studies, tumorigenesis for all three tumor types has been shown to be mediated by liver enzymes induced in response to treatment with pronamide. In rats, pronamide induces CYP2B1 200 fold over background levels, but has no effect on other CYPs commonly associated with carcinogenic modes of action. CYP2B1 is a biological marker for the constitutive androstane nuclear receptor (CAR) which interacts with pronamide to produce thyroid tumors in male rats and Leydig cell tumors of the testes. The CAR pathway is associated with the activation of uridine diphosphate glucuronyl transferase (UGT) which catalyzes the condensation of glucuronic acid with thyroxine (T4), leading to enhanced biliary excretion of T4. In male rats, the tumorigenic dose of pronamide for both thyroid tumors and Leydig cell tumors is 1000 ppm in the diet (34-75 mg/kg/day based on age of the rats) (12/02/2014, TXR 0057037).

There was no evidence of quantitative or qualitative increased susceptibility in the fetuses or the offspring of rats or rabbits following pre- and/or postnatal exposure to pronamide. In the prenatal developmental toxicity study in rabbits and the multi-generation reproduction study in

rats, any observed toxicity to the fetuses or offspring occurred at equivalent or higher doses than effects to parental animals.

In nearly every oral repeated dose study of pronamide there are dose-related decreases of body weight, body weight gain and food consumption also seen in the 28-day dermal toxicity study in rats. Typically, these effects on body weight occur at or above effects on the liver such as hypertrophy or increases in liver weight. The only exceptions to the co-occurrence of negative effects on body weight and increased liver weight and hypertrophy were in the subchronic neurotoxicity (SCN) and dermal toxicity studies where there were no effects at all on the liver. It should be noted, however, that the liver is not one the tissues examined within the SCN study design.

In contrast with the SCN where only body weight effects were reported at the LOAEL, in the acute neurotoxicity (ACN) study the LOAEL was based on an increase in landing foot splay in female rats and a decrease in motor activity seen in both genders on Day 1. The NOAEL was not determined in this study.

In the immunotoxicity study with pronamide in mice, there was no evidence of immunotoxicity nor significant systemic toxicity.

Pronamide has a low order of acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category III or IV), produces mild irritation to the eyes and skin (Toxicity Category IV), and is not a dermal sensitizer.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The toxicology and exposure data bases for pronamide are complete and the toxicology studies are adequate for assessing increased susceptibility under FQPA. There was no evidence of quantitative or qualitative susceptibility in the developing organism and evidence for neurotoxicity was limited to effects seen following a single gavage dosing in the acute neurotoxicity study. There was no evidence of neurotoxicity in the subchronic neurotoxicity study. Therefore, there is no concern for developmental neurotoxicity.

4.4.1 Completeness of the Toxicology Database

The toxicity database for pronamide is complete.

4.4.2 Evidence of Neurotoxicity

In the acute neurotoxicity study following oral (gavage) administration, there was an increase in landing foot splay in female rats and a decrease in motor activity seen in both genders on Day 1. There was no evidence of neurotoxicity in the subchronic neurotoxicity study following dietary administration. There was no evidence of neurotoxicity in the rest of the toxicology database across other species or other strains of rat.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There was no evidence of quantitative or qualitative increased susceptibility in developing fetuses or in offspring of rats or rabbits following pre- and/or postnatal exposure to pronamide.

4.4.4 Residual Uncertainty in the Exposure Database

Non-dietary exposure. The residential post-application exposure assessments are based upon the 2012 Residential Standard Operating Procedures (SOPs). These assessments of exposure are not likely to underestimate the resulting estimates of risk from exposure to pronamide.

Dietary exposure. There is no residual uncertainty in the exposure database for pronamide with respect to dietary exposure. An adequate database with respect to both the nature and magnitude of residues expected in food and water has been provided.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PoDs) for assessment of risks from exposure to pronamide are summarized below. Detailed descriptions of the studies used as a basis for the selected endpoints are presented in Appendix A. Toxicological endpoints were established for all relevant exposure scenarios.

Acute Dietary Endpoint (General Population): The acute neurotoxicity study in rats (MRID 48599202) was selected for this exposure scenario. The LOAEL of 40 mg/kg is the Point of Departure (POD) and is based on the increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1. This endpoint is appropriate for both the exposure duration (acute/single dose) and the population of concern (general population).

An acute RfD of 0.04 mg/kg/day is derived using the LOAEL of 40 mg/kg/day and 1000X Uncertainty Factor which included 10X for inter-species extrapolation, 10X for intra-species variation and a 10X for the use of a LOAEL (UF_L).

Acute Dietary Endpoint (Females 13-49 years old and infants and children): An endpoint of concern attributable to a single exposure was not identified from the database. In the developmental rabbit study, abortions were noted and could possibly be a result of fetal toxicity; however, as the abortions occurred very late (on or after GD 22), this finding was not considered to be a result of single dose of pronamide.

Chronic Dietary Endpoint, Incidental Oral (short and intermediate term), and Inhalation Endpoint (short and intermediate term): The database for pronamide contains subchronic and

chronic toxicity, carcinogenicity and reproductive toxicity studies conducted in CD rats and neurotoxicity studies (acute and subchronic) conducted in Fischer 344 rats.

In CD rats, the target organs were liver, thyroid and the testes. In the chronic toxicity/carcinogenicity study with CD rats, pronamide caused increased relative liver weight and histopathological lesions in the liver, thyroid, and ovaries at 43 mg/kg/day, the same dose that induced thyroid and testicular tumors in rats. The registrant has submitted mode of action studies for each of the tumor types and the available MOA studies clearly identify the sequence of key events, dose-response concordance and temporal relationship to effects seen in these target organs. For example, absolute and relative liver weights of rats dosed with 43 mg/kg/day were increased 29% and 36% after 4 weeks of treatment, and pronamide effects on T4 levels occurred at doses as low as 10 mg/kg/day after 4 weeks of dosing.

In Fischer 344 rats, minimal neurotoxicity was seen after a single gavage dose of 40 mg/kg in the ACN study but no neurotoxicity was evident following dietary administration in F344 rats in the 90-day SCN study in which systemic toxicity was manifested as decreases in body weight, body weight gain, and food consumption) at 12 mg/kg/day. There was no evidence of neurotoxicity in the rest of the toxicology database across other species or other strains of rat.

The LOAEL of 40 mg/kg in the ACN study in Fischer rats is also appropriate for assessing risk from chronic dietary and non-dietary (short/intermediate term incidental oral and inhalation exposures). The lowest LOAEL in the conventional toxicity database for pronamide is 12 mg/kg/day from the SCN, also carried out in Fischer rats. The NOAEL for the study was 2.4 mg/kg/day. The Fischer rat may therefore be a more sensitive model for human toxicity than the CD rat used in most other pronamide studies. The lowest LOAEL in the studies cited in the cancer mode of action analysis is 10 mg/kg/day from the male pubertal assay in CD(SD) rats submitted under the EDSP program. The NOAEL for the study is 2.5 mg/kg/day. Application of a 10x UF_L factor to the LOAEL of 40 mg/kg/day established in the ACN results in an extrapolated NOAEL of 4.0 mg/kg/day. The lower NOAEL of 2.5 mg/kg/day in the male pubertal assay is an artifact of dose selection; therefore, the higher extrapolated NOAEL is protective of the concern for the adverse effects observed at 10 mg/kg/day and higher doses in the toxicity database.

A chronic RfD of 0.04 mg/kg/day is derived using the POD of 4.0 mg/kg/day and an Uncertainty Factor of 100 which includes 10X for inter-species extrapolation, 10X for intra-species variation and a 1x FQPA SF.

Short and Intermediate Term Incidental Oral Exposure: The LOAEL of 40 mg/kg/day based on motor activity and food splay in the acute neurotoxicity study. The Level of Concern (LOC) is a target Margin of Exposure (MOE) of 1000 which includes 10X for inter-species extrapolation, 10X for intra-species variation and a 10X UF_L).

Dermal (Short and Intermediate-Term) Endpoints for Occupational and Non-Occupational Exposure Scenarios: The dermal endpoint was selected from a 28-day dermal toxicity study in rats. Although no target organ was identified, the significant ($p<0.05$) decreases in absolute body

weight (10%) and food consumption (7-8% during the final two week of the study) were seen in males at 500 mg/kg/day. These effects were slightly enhanced at the next highest dose (1000 mg/kg/day); 12% decrease in body weight and 8-13% decrease in food consumption. The NOAEL of 100 mg/kg/day was selected as the POD for dermal risk assessments.

The endpoint is appropriate for the route and duration of exposure as well as the population of concern. The occupational and residential LOC is a MOE of100 (includes UF_A=10x and UF_H=10x).

Inhalation (Short and Intermediate-term Endpoints for Occupational Exposure Scenarios:
In 2003 a request to waive the inhalation study for pronamide was granted based on use and exposure data available at the time. Since then, additional data on unit exposures and on pronamide usage have become available, however MOEs have not changed appreciably. Accordingly the waiver of the requirement to conduct an inhalation study remains in effect. The MOEs associated with occupational inhalation exposure all exceed 3,000.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Since the same endpoint/study is selected for incidental oral and inhalation exposure scenarios, these routes can be combined. The dermal POD for pronamide is based on a study that measures body weight decreases and decreased food consumption. No other effects were observed. Decreased body weight is also observed in most oral studies with pronamide, however the body weight effects in oral studies are associated with liver effects such as increased liver weights, hypertrophy and decreased T4 levels.

In the dermal study with pronamide there was no effect at all on the liver, and no other systemic effects to suggest that meaningful dermal absorption had occurred, and in addition there were local effects at the sight of application that could have had an effect on food consumption and body weight. For these reasons, HED recommends that dermal exposure not be combined with any other route of exposure.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment, pronamide is classified as "**Not Likely to be Carcinogenic to Humans"** at doses that do not result in induction of hepatic cell proliferation or metabolic enzymes leading to disruption of thyroid or gonadal endocrine axes (TXR 0057037). These decisions are based on the following considerations:

Pronamide induced liver tumors in male and female CD-1 mice and thyroid follicular tumors and testicular tumors in male Crl:CD rats. Mechanistic data to support the hypothesized MOAs were submitted for each tumor type and evaluated against the criteria established in the 2006 IPCS Human Relevance Framework. The MOAs were adequately supported by studies that clearly

identified the sequence of key events, dose-response concordance and temporal relationship to the particular tumor type.

Quantification of carcinogenic risk is not required. The chronic Reference Dose (RfD) would be protective of non-carcinogenic and carcinogenic effects observed in the mouse and rat carcinogenicity study or MOA studies conducted at higher doses.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Pronamide for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure (POD)	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	LOAEL = 40 mg/kg/day	UF_A=10X UF_H=10X UF_L= 10X FQPA SF =1X	aRfD=aPAD= 0.04 mg/kg/day	Acute neurotoxicity in rat: NOAEL was not established; **LOAEL = 40 mg/kg (the lowest dose tested)** based on the increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1.
Acute Dietary Females 13-49 years of age	An endpoint attributable to a single exposure was not available in the database including the developmental toxicity studies in rats and rabbits.			
Chronic Dietary (All Populations)	LOAEL = 40 mg/kg/day	UF_A=10X UF_H=10X UF_L= 10X FQPA SF =1X	cRfD=cPAD= 0.04 mg/kg/day	The POD of 40 mg/kg/day was selected based on a weight of evidence approach using the results from the 4 studies in rats listed below. **Subchronic neurotoxicity (SCN):** NOAEL of 2.38 mg/kg/day is based on the significant decreases in body weight, body weight gain, and food consumption seen at 11.28 mg/kg/day (LOAEL) in males. **Acute neurotoxicity (ACN):** NOAEL was not established. The LOAEL of 40 mg/kg/day with a 10X LOAEL to NOAEL uncertainty factor (UF_L) yields a derived **POD of 4 mg/kg/day (40÷10).** **Combined chronic toxicity/ carcinogenicity** NOAEL of 8.46/10.69 mg/kg/day is based on increased relative liver weight and histopathological lesions in the liver, thyroid, and ovaries at 42.59/55.09 mg/kg/day (LOAEL). **Male pubertal study.** NOAEL of 2.5 mg/kg/day. The LOAEL is 10 mg/kg/day based on decreased serum T4.
Incidental Oral Short-Term (1-30 days)	LOAEL = 40 mg/kg/day	UF_A=10X UF_H=10X UF_L= 10X FQPA SF =1X	Residential LOC for MOE = **1000**	See Chronic RfD

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Pronamide for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure (POD)**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 100 mg/kg/day	UF_A=10X UF_H=10X FQPA SF=1X	Residential LOC for MOE = **100**	**28-day dermal toxicity study in rat:** LOAEL = 500 mg/kg/day based on decreases in body weight and food consumption in males. No target organ (liver) toxicity was seen following repeated dermal dosing, and no effect in females.
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	LOAEL = 40 mg/kg/day	UF_A=10X UF_H=10X UF_L= 10X FQPA SF =1X	Residential LOC for MOE = **1000**	See chronic RfD.
Cancer (oral, dermal, inhalation)	Classification: "**Not Likely to be Carcinogenic to Humans"** *at doses that do not result in induction of hepatic cell proliferation or metabolic enzymes leading to disruption of thyroid or gonadal endocrine axes.*			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for Pronamide for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 100 mg/kg/day	UF_A=10X UF_H=10X	Occupational LOC for MOE = 100	**28-day dermal toxicity study in rat:** LOAEL = 500 mg/kg/day based on decreases in body weight and food consumption in males. No target organ (liver) toxicity was seen following repeated dermal dosing

Table 4.5.4.2 Summary of Toxicological Doses and Endpoints for Pronamide for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	LOAEL = 40 mg/kg/day	UF_A=10X UF_H=10X UF_L= 10X	Occupational LOC for MOE = 1000	See chronic RfD.
Cancer (oral, dermal, inhalation)	Classification: "**Not Likely to be Carcinogenic to Humans"** *at doses that do not result in induction of hepatic cell proliferation or metabolic enzymes leading to disruption of thyroid or gonadal endocrine axes*.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

4.6 Endocrine Disruption

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (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 that 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 for pronamide, 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), pronamide 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. A second list of chemicals identified for EDSP screening was published on June 14, 2013[2] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Pronamide is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2009-0326 for propyzamide (pronamide)).

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

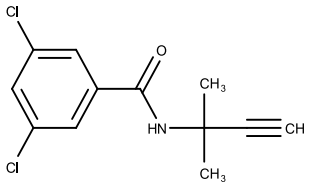
5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Primary Crops: The qualitative nature of the residue in plants is adequately understood on alfalfa, lettuce and similar crops (D275536, 02/28/2002). Soil applied pronamide is readily absorbed through the root system, translocated upward, and distributed into the entire plant. Conversely translocation from leaf absorption is not appreciable. Metabolism occurs primarily *via* oxidation of the aliphatic half of the pronamide molecule followed by conjugation to (malonyl) glucose. The terminal residues in alfalfa and lettuce consist mainly of pronamide *per se*, glucose conjugates, and glucose-malonyl conjugates, all containing the intact 3,5-dichlorobenzoyl moiety.

[2] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[3] http://www.epa.gov/endo/



Pronamide

No evidence of fragmentation of the benzene ring or loss of the chlorine substituents was observed. The terminal residues of concern are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety.

Rotational Crops: The qualitative nature of the residue in rotational crops is adequately understood based on an acceptable confined rotational crop study (MRID 41462001 and 41913506). In this study, uniformly ring labeled [^{14}C]pronamide was applied at a rate of 4.0 lb ai/A to bare ground plots, and crops were planted in the treated areas after 30 days, 6 months, and 1 year. The subplots representing each plantback interval (PBI) were allowed to remain fallow until such time that lettuce (a leafy vegetable), carrots (a root crop), and wheat (a small grain) were planted. The terminal residues of concern in rotated crops following treatment of primary crops with pronamide consist of the parent pronamide and its metabolites bearing the 3,5-dichlorobenzoyl moiety.

Livestock: The qualitative nature of the residue in livestock is adequately understood (D275536, 02/28/2002). Studies involving lactating goats and laying hens indicate that the primary route of elimination is by excretion (urine and feces). Minimal residues were distributed to goat and poultry muscle. The major metabolites in the eggs, liver, and fat of poultry are pronamide and 3,5-dichlorobenzoic acid. The major metabolites in the milk, fat, muscle, and liver of goats are pronamide, 3,5-dichlorobenzoic acid, and compounds containing the 3,5-dichlorobenzoyl moiety. The metabolic pathway involves modification of the aliphatic portion of pronamide. The terminal residues of concern in livestock commodities are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety.

The residues of concern for pronamide are summarized in Table 5.3.

Table 5.3. Summary of Pronamide Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

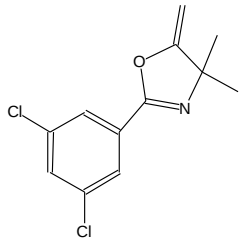
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety	pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety
	Rotational Crop		
Livestock	Ruminant		
	Poultry		
Drinking Water			Not Applicable

Conclusions. For purposes of Registration Review, no additional plant metabolism studies are required; however, because the available metabolism studies were conducted only on alfalfa and

lettuce, HED may request additional metabolism studies in the future should the petitioner seek for additional uses on other crop groups.

5.1.2 Summary of Environmental Degradation

The major routes of degradation of pronamide appear to be aerobic microbial degradation in soil and photolysis in water. Four major degradates of pronamide have been identified with a maximum applied radioactivity of 31.9%, 27.3%, 32.2%, and 15.0%, respectively.



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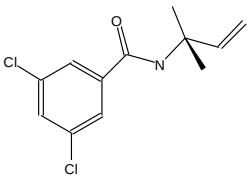

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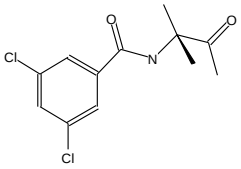

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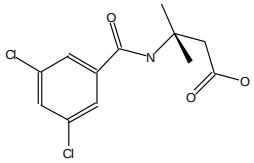

RH-26059

HED determined that all degradates of pronamide that contain the 3,5-dichlorobenzoyl moiety are of risk concern, assuming that their toxicity is similar to that of pronamide parent (USEPA, 2002). A total toxic residues (TTR) approach was therefore used to generate EDWCs that reflect residues, in drinking water, of the parent compound plus all such degradates of concern.

Pronamide has relatively low vapor pressure ($8.5x10^{-5}$ torr) and is soluble in water up to 15 mg/L. The compound is stable to hydrolysis, relatively resistant to soil photolysis and moderately susceptible to aquatic photolysis. Pronamide degrades relatively readily in aerobic soil environments, but is more persistent in anaerobic environments and aquatic environments. Sorption to soils is a function of organic carbon and also correlates with cation exchange capacity. Nonetheless the compound is mobile in soil, and thus presents a potential groundwater concern in some areas, *e.g.*, those with sandy soils and high water tables. Pronamide has been detected in both surface water and groundwater.

EDWCs based on total toxic residues for pronamide likely exceed actual concentrations in most drinking water supplies due to the conservative nature of the exposure models, use of national PCA (1.0), and limited acceptable environmental fate data.

5.1.3 Comparison of Metabolic Pathways

There is a common theme to pronamide metabolism whether in primary crops, rotational crops, livestock or rats. The 3,5-dichlorobenzoic acid moiety of pronamide is not altered whereas the aliphatic hydrocarbon moiety is extensively oxidized followed by conjugation of the oxidized fragments. In plants, glucose and malonyl conjugates are formed, whereas in livestock and rats, conjugates have not been identified.

The terminal residues of concern in plants and livestock commodities, and in drinking water, are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety.

5.1.4 Residues of Concern Summary and Rationale

The residues of concern in agricultural commodities, livestock and drinking water from use of pronamide consist of all residues convertible to 3,5-dichlorobenzoic acid. All such residues are assumed to be equipotent to parent pronamide based on the similarity of structure to the parent compound, pronamide.

5.2 Food Residue Profile

Tolerances are established in the 40 CFR § 180.317 for the use of pronamide on alfalfa, apple, artichoke, berries, endive, stone fruits, grape, head lettuce, pear, radicchio, field pea, and rhubarb. In addition, tolerances are established for livestock commodities, and several feed commodities. Generally, residues below 0.4 ppm are expected in most food commodities with the exception of head lettuce (1.0 ppm), endive (1.0 ppm) and radicchio (2.0 ppm). A tolerance of 1 ppm is recommended to support a proposed new use on leaf lettuce. This tolerance is supported by adequate residue data. Interim tolerances of 0.10 ppm, 1.5 ppm and 3.0 ppm are recommended for field pea seed, vines and hay, respectively. Additional crop field trial data is required to support the use on field pea. Adequate rotational crop field trials are available to support the use of pronamide. Label modifications recommended in Section 3.3 need to be addressed.

5.3 Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Propyzamide (Pronamide): Tier II Drinking Water Exposure Assessment in support of the Proposed Use of Propyzamide on Leaf Lettuce" (D414467, K. Milians, 04/21/2015) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Besides modeling the use of leaf lettuce, EFED modeled the use of artichoke because this use allows the maximum application rate (for any crop) of 8 lbs a.i./acre (i.e., 4 lbs a.i./acre x 2 assumed applications/yr). Table 5.3 shows the estimated drinking water concentrations in surface water and ground water (including values using Sci-Grow and PRZM-GW for ground water). Surface water EDWCs based on total toxic residues and maximum annual application rates were highest for leaf lettuce (102, 47.0 and 33.6 ppb, for peak concentration and chronic values, respectively). The EDWCs recommended by EFED are 102 ppb for the acute dietary assessment and 47.0 ppb for the chronic and cancer dietary assessments.

Table 5.3. Tier II Total Residue of Concern EDWCs in Surface Water and Ground Water from Propyzamide Uses on New Uses (Maximum EDWCs in Bold).

Drinking Water Source (Model, Use, Modeled rate)	Scenario	EDWCs		
		Acute (µg/L)	Chronic (µg/L)	Cancer (µg/L)
Surface Water (SWCC, Artichokes, 4 lb a.i./A x 2 applic.; total of 8 lb/A/yr)	CA row crop RLF (aerial application)	61.4	33.4	26.0
Surface Water (SWCC, Leaf Lettuce, 2 lb a.i./A x 2 applic.; total of 4 lb/A/yr)	CA lettuce (aerial application)	**102**	**47.0**	**33.6**
Ground Water (PRZM-GW, Artichokes, 4 lb a.i./A x 2 applic.; total of 4 lb/A/yr)	WI sands	21	18.6	18.6
Ground Water (SCI-GROW, Artichokes, 4 lb a.i./A x 2 applic.; total of 8 lb/A/yr)	N/A	0.802	0.802	0.802
Ground Water (SCI-GROW, Leaf Lettuce, 2 lb a.i./A x 2 applic.; total of 4 lb/A/yr)	N/A	0.401	0.401	0.401

N/A= Not Applicable

Values in bold show the EDWCs recommended for HED's acute (102 ppb) and chronic (47.0 ppb) and cancer (33.6 ppb) dietary risk assessment as they are considered protective of all the registered uses of pronamide.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Unrefined acute and chronic dietary assessments were performed. Tolerance level residues of pronamide (residues convertible to methyl 3,5-dichlorobenzoate) were used for the registered uses and proposed new use on leaf lettuce. Default processing factors and 100% of crop treated (CT) assumptions were incorporated. Drinking water was incorporated directly in the dietary assessment using the Tier II acute and chronic estimated drinking water concentration (EDWC) for surface water generated by the Surface Water Concentration Calculator (SWCC).

The EDWCs reported here are based on artichoke (CA) and leaf lettuce uses and represent the most conservative (highest) EDWCs for surface and groundwater, which are recommended for use in HED's dietary assessment. The leaf lettuce use generated the highest surface water and groundwater EDWCs. The total toxic residues of pronamide include pronamide parent and all degradates with the 3,5-dichlorobenzoyl moiety, which are assumed to have toxicity similar to that of pronamide parent. The recommended estimated drinking water concentrations (EDWCs) for the dietary assessment is 102 ppb for the acute dietary assessment and 47.0 ppb for chronic and cancer dietary assessments.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic assessments were performed by assuming that 100% of the crop was treated for all food commodities.

5.4.3 Acute Dietary Risk Assessment

The resulting acute dietary exposure estimates using the DEEM-FCID™ model were less than 100% of the acute population adjusted dose (aPAD) at the 95th percentile of exposure for the general U.S. population and all population subgroups. Pronamide acute dietary exposure (food + drinking water) was estimated at 0.007144 mg/kg/day for the general U.S. population (18% of the aPAD) and 0.018539 mg/kg/day (46% of the aPAD) for the most highly exposed population subgroup (All Infants < 1 year old). The results per user and per capita are similar.

5.4.4 Chronic Dietary Risk Assessment

The resulting chronic dietary exposure estimates using the DEEM-FCID™ model were less than 100% of the chronic population adjusted dose (cPAD) for the general U.S. population and all population subgroups. Pronamide chronic dietary exposure (food + drinking water) was estimated at 0.001706 mg/kg/day for the general U.S. population (4.3% of the cPAD) and 0.004410 mg/kg/day (11 % of the cPAD) for the most highly exposed population subgroup (Children 1-2 years old).

5.4.5 Cancer Dietary Risk Assessment

Pronamide was classified as "Not Likely to be Carcinogenic to Humans" at doses that do not result in induction of hepatic cell proliferation or metabolic enzymes leading to disruption of thyroid or gonadal endocrine axes; therefore, a cancer risk assessment is not needed.

5.4.6 Summary Table

As stated previously, for acute and chronic assessments, HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID analyses estimate the dietary exposure of the U.S. population and various population subgroups. The results reported in Table 4 are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years.

Table 4. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Pronamide.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.007144	18	0.001706	4.3
All Infants (<1 year old)	**0.018539**	**46**	0.003854	9.6
Children 1-2 years old	0.013317	33	**0.004410**	**11**
Children 3-5 years old	0.010013	25	0.003083	7.7
Children 6-12 years old	0.006963	17	0.001804	4.5
Youth 13-19 years old	0.005480	14	0.001241	3.1
Adults 20-49 years old	0.006570	16	0.001534	3.8
Adults 50-99 years old	0.005893	15	0.001526	3.8
Females 13-49 years old	0.006753	17	0.001558	3.9

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

The proposed use on leaf lettuce is not expected to result in residential exposure. In this assessment pronamide is assessed for the currently registered residential uses on turf grass and golf courses using the 2012 Residential SOPs. Residential post-application scenarios were assessed at a maximum application rate of 1.44 lb ai/A for liquid and 1.5 lb ai/A for wettable powder in Water Soluble Package (WSP) formulations. There were no residential risk estimates of concern identified.

6.1 Residential Handler Exposure

Residential handler exposures are not expected as pronamide is a Restricted Use Pesticide and as such can only be applied by Certified Applicator.

6.2 Post-Application Exposure

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with pronamide. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Physical activities on turf: adults (dermal) and children 1 to < 2 years old (dermal and incidental oral);
- Mowing: adults (dermal) and children 11 to < 16 years old (dermal); and
- Golfing: adults (dermal), children 11 to < 16 years old (dermal), and children 6 to< 11 years old (dermal).

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[4]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs4.

Application Rate: The application rates used in this assessment are provided in Table 4.1.

Exposure Duration: Residential post-application exposure is expected to be short-term in duration. While multiple applications may be possible, it is anticipated that these applications will be intermittent in nature and dissipation due to rainfall/irrigation, grass growth, and grass mowing is expected. There is the potential for intermediate-term exposure to pronamide,

[4] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

however, since the maximum yearly application rate is the same as the maximum single application rate, the short-term assessment is protective of intermediate-term soil ingestion exposure.

TTR Data: The parameters for estimation of post-application risk are based on a regression analysis of chemical specific TTR data in MRID 44952501 "Turf Transferrable Residues for Pronamide Applied to Turf" (D422661; September 20, 2015).

Combining Exposures/Risk Estimates

Dermal and incidental oral (hand-to-mouth) risk estimates were not combined in this assessment because the dermal and oral endpoints are not based on the same effect.

Combining Incidental Oral Exposure and Risk Estimates

The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. Combining these scenarios would be overly-conservative because of the conservative nature of each individual assessment. Therefore, these scenarios have not been combined.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

Table 6.2.1 provides a summary of the residential post-application exposures and risk estimates for pronamide. All dermal and incidental oral risk estimates for post-application exposure are not of concern (i.e., MOEs ≥ 100 for dermal estimates and ≥1000 for incidental oral estimates).

Table 6.2.1. Short-Term Residential Post-application Exposure and Risk Estimates for Pronamide

Lifestage	Post-application Exposure Scenario			Dose (mg/kg/day)[1]	MOEs[2]	Combined MOEs
Liquid formulation and wettable powder(WSP)**						
Adult	Turf Liquid formulation 1.5 lb ai/A	Dermal	Physical Activities on Turf	0.50	200	N/A
			Mowing	0.01	9,800	
			Golfing	0.039	2,500	
Child 11 to < 16 years old		Dermal	Mowing	0.012	8,600	
			Golfing	0.046	2,200	
Child 6 to < 11 years old		Dermal	Golfing	0.054	1,900	
Child 1 to < 2 year old		Dermal	Physical Activities on Turf	0.99	100	
		Hand to Mouth		0.020	2000	
		Object to Mouth		0.00062	65,000	
		Short- and Intermediate-term Incidental Soil Ingestion		0.000051	790,000	

1 Dose (mg/kg/day) equations provided in Appendix [A].

2 MOE = POD (Dermal = 100 mg/kg/day and Incidental oral = 40 mg/kg/day LOAEL from ACN) ÷ Dose (mg/kg/day). LOC = 100 for dermal and 1000 for incidental oral exposure.

6.3 Residential Bystander Post-Application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues

related to volatilization of pesticides from its FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010.[5] The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis.[6] During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies) or further analyses are required for pronamide.

6.4 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.4.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for pronamide

- The only residential scenario appropriate for aggregation is for children 1 to <2 years old short-term exposure associated with hand/object to mouth exposure from post-application exposure to turf .

Table 6.4.1. Recommendations for the Residential Exposures for the Pronamide Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)			MOE		
		Dermal	Inhalation	Oral	Dermal	Inhalation	Oral
Short-term							
Child to 1 < 2 year old	Post-application exposure from activities on turf (liquid formulation)	NA	NA	0.020	NA	NA	2000

6.5 Spray Drift

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

A quantitative spray drift assessment for pronamide is not required because the maximum application rate for a crop/target site (4 lb ai/A) multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (also 4 lb ai/A)[7] for any pronamide products. The turf post-application MOEs are protective for any potential exposures related to spray drift for pronamide and have previously been discussed in Section 6.2.

7.0 Aggregate Exposure/Risk Characterization

[5] http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html
[6] http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219
[7] 4.0 lb ai/A x 0.26 ≤ 4.0 lb ai/A

In accordance with FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For pronamide acute and chronic aggregate exposures are the same as dietary exposures that include food and drinking water. Oral and dermal exposure estimates were not combined in this assessment since the toxicological effects for these exposure routes were not the same.

7.2 Short-Term Aggregate Risk

The only scenario to be aggregated is children's short-term hand-to-mouth exposure following application of pronamide to turf. The short-term exposure is aggregated with the average chronic dietary exposure for children (1 to 2 years old from Table 4)

Table 7.2 Short-Term Aggregate Risk Calculations

Population	Short-Term Scenario						
	LOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Child	40	1000	0.04	0.004410	0.02	0.024	1700

[1] Based on a POD of 40 mg/kg from the LOAEL of an ACN study. The traditional inter- and intraspecies factors are applied as well as a UF_L of 10 for a total LOC of 1000.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = Oral exposure (hand-to-mouth) - Table 5.3.1.
[4] Total Exposure = Average Food & Water Exposure + Residential Exposure
[5] Aggregate MOE = NOAEL / (Average Food & Water Exposure + Residential Exposure)

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pronamide and any other substances and pronamide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pronamide has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

The most recent exposure assessment for pronamide was conducted in 2007 (M. Dow, D329436). At the maximum rate of 4 lb ai/A identified for most agricultural crops, including the proposed use on leaf lettuce, there were no occupational handler risks of concern.

Based on review of currently registered pronamide labels, uses on Christmas tree farms and landscape ornamentals were not covered by the previous assessment. These use patterns have been assessed in this document to complete the Registration Review for pronamide. Updated risk estimate tables have also been included for occupational handlers for all registered uses since the inhalation point of departure and LOC for pronamide have changed since the previous assessment.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for pronamide at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for pronamide

9.1 Occupational Handler Exposure/Risk Estimates

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios which covers all the registered and proposed uses of pronamide:

- Mixing/loading liquids to support aerial applications,
- Mixing/loading liquids to support chemigation applications,
- Mixing/loading liquids to support groundboom applications,
- Mixing/loading wettable powder in Water Soluble Package (WSP) to support aerial applications,
- Mixing/loading wettable powder in Water Soluble Package (WSP) to support chemigation applications,
- Mixing/loading wettable powder in Water Soluble Package (WSP) to support groundboom applications,
- Mixing/loading wettable powder in Water Soluble Package (WSP) for groundboom applications,
- Applying sprays with aircraft,
- Applying sprays with groundboom equipment,
- Mixing/loading/applying wettable powder in Water Soluble Package (WSP) or liquids via backpack,
- Mixing/loading/applying wettable powder in Water Soluble Package (WSP) or liquids via mechanically-pressurized handgun, and

- Mixing/loading/applying wettable powder in Water Soluble Package (WSP), or liquids via manually-pressurized hand wand
-

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: The application rates used in this assessment are provided in Appendix E. For similar crop/application method scenarios, the highest application rate was assessed assuming this would be protective of lower application rates.

Unit Exposures: The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[8]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[9].

Area Treated or Amount Handled: The inputs for area treated were primarily based on information in Expo SAC Policy 9.1.

Exposure Duration:

For the proposed use pattern, short- and intermediate-term exposures are anticipated for the following reasons: (1) up to two applications can be made 60 days apart; and (2) commercial applicators may apply this product at various locations within a region over a period of weeks. The same exposure durations are anticipated for all registered pronamide uses, and it should be noted that the short- and intermediate-term PODs are the same; therefore, short-term risk estimates are protective of longer-term exposures.

Mitigation/Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for "baseline," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). All of the pronamide registered labels require handlers to wear a double layer of clothing (long sleeved shirt and long pants) with either waterproof or chemical-resistant gloves.

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were not combined in this assessment, since the toxicological effects for these exposure routes were not the same.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

[8] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[9] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html

The occupational handler exposure and risk estimates indicate that the short- and intermediate-term dermal and inhalation MOEs are not of concern to HED (i.e., MOEs ≥ 100 for dermal and ≥1000 for inhalation) for the wettable powder formulation (WSP). For the liquid formulation, the short- and intermediate-term dermal and inhalation MOEs are not of concern to HED (i.e., MOEs ≥ 100 for dermal and ≥1000 inhalation, as long as double layer and gloves are worn for aerial application to high-acreage crops).

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Flaggers. HED has assessed the exposure potential to human flaggers. The Agency is mindful that the use of human flaggers has declined sharply in recent years and will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

(See Appendix E for detailed occupational handler exposures.)

9.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). The majority of pronamide usage occurs preemergence or when the plants are dormant. The only crop with post-application activities is lettuce.

9.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

Although a quantitative occupational post-application inhalation exposure assessment was not performed for pronamide, an inhalation exposure assessment was performed for occupational/commercial handlers. Exposure resulting from application of pesticides outdoors is likely to result in higher inhalation exposure than post-application exposure. Since no inhalation risks were identified for handlers of pronamide end use products, the handler inhalation exposure estimates are considered protective of most occupational post-application inhalation exposure scenarios.

9.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Most of the registered uses (with exception of lettuce), for pronamide are soil-directed preplant or pre-emergent uses where no crop foliage is present. In general, such exposures are considered to be negligible and therefore were not assessed.

The registered and proposed uses lettuce, turf (golf courses and sod farms) and nursery crops (ornamentals, and non-bearing plants)are not specifically soil-directed and, therefore, could result in potential post-application exposures. These exposures have been assessed in this risk assessment.

Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed below on an individual basis.

Exposure Duration: For the proposed pronamide use pattern, short- and intermediate-term exposures are anticipated for the following reasons: (1) up to two applications can be made 60 days apart; and (2) commercial applicators may apply this product at various locations within a region over a period of weeks. The same exposure durations are anticipated for all registered pronamide uses, and it should be noted that the short- and intermediate-term PODs are the same; therefore, short-term risk estimates are protective of longer-term exposures.

Transfer Coefficients: Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from Agricultural Reentry Task Force, L.L.C. (ARTF) exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[10]" which, along with additional information about the ARTF data, can be found at the Agency website[11].

Table 9.2.2.1. Summary of Post-Application Activities and Dermal Transfer Coefficients.

Crop	Policy Crop Group Category	Crop Height	Foliage Density	Transfer Coefficients (cm^2/hr)	Activities
Landscape ornamentals (Container, Field grown Ornamental plantings)	Nursery Crop (Ornamentals, Non-bearing Plants)	Low	Min	230	Grafting, Propagating, Transplanting
		Low	Full		Hand Harvesting, Hand Pruning, Scouting, Hand Weeding, Transplanting, Pinching, Tying/Training
		High	Min		Hand Harvesting, Hand Pruning, Transplanting
		High	Full		Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Pinching
		Low/High	Full	1,900	Handset Irrigation
Golf Courses	Turf/Sod	Low	Full	2,500	Maintenance, greens only
				3,700	Maintenance
Sod		Low	Full	6,700	Maintenance, Slab Harvesting, Transplanting/Planting
Lettuce	4	Low	Full	1,900	Handset Irrigation

[10] Available: http://www.epa.gov/pesticides/science/exposac_policy3.pdf
[11] Available: http://www.epa.gov/pesticides/science/post-app-exposure-data.html

Application Rate: The application rates used in this assessment are provided in Appendix E.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Dislodgeable Foliar Residue (DFR): In accordance with the updated Part 158 data requirements (2007), one or more DFR studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. As part of the recent revision to the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment*, HED analyzed a number of DFR studies and selected a new default value for the fraction of the application rate available to be dislodged after a foliar application (F_{AR}). This default value is 25% and is based on an analysis of 19 DFR studies where the F_{AR} value ranged from 2% to 89%. This value is recommended for use in both residential and occupational post-application assessments. Of the analyzed DFR studies, the maximum F_{AR} value seen was 89% or 3.6 times higher than the default residue transfer value. Therefore, HED has decided that a calculated MOE of approximately 2 times higher than the LOC (e.g., an MOE > 200 if the LOC =100) using the default dislodged residue values would provide an adequate margin of safety for any potentially higher residues seen in a chemical-specific DFR study (*Guidance for Requiring/Waiving Turf Transferrable Residue (TTR) and Dislodgeable Foliar Residue (DFR) Studies*. 12/12/2012, Exposure Science Advisory Council).

Since the highest estimated occupational post-application exposure using default DFR values for pronamide is not minimal in comparison to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 100 on day 1 compared to the LOC of 100; EPA is requiring the 40CFR DFR data. Therefore, EPA is requiring the 40CFR DFR data requirement to facilitate any necessary exposure assessments refinements and to further EPA's general understanding of the availability of dislodgeable foliar pesticide residues.

Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in Tadayon, DXXXXXX .

Occupational Post-application Non-Cancer Dermal Risk Estimates
The short- and intermediate-term post-application exposure scenarios associated with the registered uses of pronamide are summarized in Table 9.2.2.2. All scenarios resulted in adequate MOEs at or greater than the LOC of 100 (ranging from 100 to 2,600) on day 1 (24 hours after application); and, therefore, are not of concern to HED.

Table 9.2.2.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Pronamide						
Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	Application Rate (lb ai/A)	DFR or TTR [1]	Dermal Dose (mg/kg/day)[2]	MOE[3] (LOC = 100)
Short- and Intermediate-term						
Landscape ornamentals (Container, Field grown Ornamental plantings)	Hand Harvesting, Hand Pruning, Transplanting, Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Pinching	230	2	5.61	0.129	780
	Handset Irrigation	1,900			1.066	94 (day0)
				5.05	0.959	100 (day1)
Golf Courses	Maintenance, greens only	2,500	1.5	0.148	0.038	2600
	Maintenance	3,700			0.055	1800
Sod	Maintenance, Slab Harvesting, Transplanting/Planting	6,700			0.099	1,000
Lettuce	Handset Irrigation	1900	2	5.61	1.066	94 (day0)
				5.05	0.959	100 (day1)

1 DFR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day.
TTR= obtained from pronamide TTR study MRID # 449525-01

2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (80 kg).

3 MOE = POD (100 mg/kg/day) / Daily Dermal Dose.

Restricted Entry Interval. Based on the quantitative post-application assessment, the labeled REI of 24 hours is required to protect workers from exposures to pronamide

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses of pronamide are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
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)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes [a]
870.3200	28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	no
870.3700	Developmental Toxicity (rodent)	yes	yes [c]
870.3700	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (rodent)	yes	yes
870.4100	Chronic Toxicity (nonrodent)	no	yes
870.4200	Oncogenicity (rat)	yes	yes
870.4200	Oncogenicity (mouse)	yes	yes
870.5100	Mutagenicity—Bacterial reverse mutation assay	yes	yes
870.5300	Mutagenicity—*In vitro* mammalian cell gene mutation test	yes	yes
870.5375	Mutagenicity—*In vitro* mammalian chromosome aberration test	yes	yes
870.5395	Mutagenicity—Mammalian erythrocyte micronucleus test	yes	yes
870.6100	Acute Delayed Neurotoxicity (hen)	no	-
870.6100	90-Day Neurotoxicity (hen)	no	-
870.6200	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes [d]
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

[a] Test was not submitted; however, a chronic dog study was submitted instead.

[c] An acceptable, non-guideline study was submitted in rat which did not demonstrate an adverse effect at the highest dose tested, but did prove the rabbit to be the more sensitive species. Therefore this study requirement was considered to be satisfied.

[d] This study was waived by the HIARC 12/10/2001

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile – Pronamide

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [Rat]	00085505	LD_{50} > 5000 mg/kg	IV
870.1100	Acute oral [Rat]	43583901	LD_{50} > 5000 mg/kg	IV
870.1200	Acute dermal [Rabbit]	43583902	LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation [Rat]	44034201	LC_{50} > 2.1 mg/L	IV
870.2400	Acute eye irritation [Rabbit]	43583904	Non-Irritating	IV
870.2500	Acute dermal irritation [Rabbit]	43583903	Non-Irritating	IV
870.2600	Skin sensitization [Guinea Pig]	00062605	Negative	Non-Sensitizing

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3050	28-Day oral toxicity (rat)	42669402 (1987) Acceptable-non-guideline 0, 500, 1000 ppm ♂: 0, 37, 74 mg/kg/day ♀: 0, 44, 88 mg/kg/day	NOAEL = 74 mg/kg/day LOAEL was not observed All parameters required to be evaluated under the appropriate guideline (OCSPP 870.3050; OECD 407) for a 28-day oral toxicity study in the rat were not evaluated. Additionally, the animals could have tolerated a higher dose.
870.3050	28-Day oral toxicity (mouse)	45919801 (2002) Acceptable-guideline ♂: 0, 16, 81, 408, 892 mg/kg/day ♀: 0, 18, 84, 434, 1040 mg/kg/day	NOAEL = 81 mg/kg/day LOAEL = 408 mg/kg/day based on histopathology of the liver; and increased serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase Additionally at the high dose, the following findings were noted: decreased body weights in males, decreased food consumption in both sexes, increased serum total bilirubin, total protein, and creatinine in both sexes, decreased serum glucose in both sexes, gross and histological liver lesions, decreased thymus size with atrophy in males, and decrease fat in males.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	00085506 (1967) Acceptable-non-guideline ♂♀: 0, 50, 150, 450, 1350, 4050 ppm ♂♀: approximately equivalent to 2.5, 7.5, 22, 68, and 202 mg/kg/day, assuming 1 ppm = 0.05 mg/kg/day	NOAEL = 68 mg/kg/day LOAEL = 202 mg/kg/day based on decreased body weights in females All parameters currently required to be evaluated under the appropriate guideline (OCSPP 870.3050; OECD 407) for a 28-day oral toxicity study in the rat were not evaluated. Additionally, the animals could have tolerated a higher dose.
870.3100	90-Day oral toxicity (rat)	42669403 (1989) Acceptable-guideline ♂♀: 0, 40, 200, 1000, 4000 ppm ♂: 0, 2.5, 12, 60, 254 mg/kg/day ♀: 0, 3.1, 15, 75, 289 mg/kg/day	NOAEL = 60 mg/kg/day LOAEL = 254 mg/kg/day based on decreases in body weight and food consumption in both sexes and liver findings (increased weight, hypertrophy, and cholesterol in both sexes, and increased serum alkaline phosphatase (males) and triglycerides (females))
870.3100	90-Day oral toxicity (mouse)	Not submitted	
870.3150	90-Day oral toxicity (dog)	Not submitted; however, a chronic dog toxicity study was submitted.	This guideline is satisfied by the chronic dog
870.3200	28-Day dermal toxicity (F344 rat)	46885701 (2005) Acceptable-guideline ♂♀: 0, 100, 500, 1000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on decreases in body weight (10%) and food consumption (8%) in males – minimal toxicity, animals could have tolerated higher dosages. No additional findings were noted at the high dose, and body weight and food consumption were only marginally more affected (decrease of 12% in body weight and 13% in food consumption). Females were not affected at any dose.
870.3250	90-Day dermal toxicity (species)	Not submitted	28-Day dermal study submitted and dermal absorption value is available
870.3465	90-Day inhalation toxicity (species)	Not submitted	Waiver granted in 2003. (TXR# 0051730)

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700	Prenatal developmental (rat)	00125789 (1971) Unacceptable-guideline 0, 7.5, 15 mg/kg/day	An evaluation of the potential teratogenic effects could not be made due to the absence of data on external, visceral, and intracranial variations and malformations in fetuses. In addition, information on the test material's purity and stability of dosage mixtures, and individual animal data such as age, weight, or reproductive history were not available. The study was conducted with only two groups dosed with pronamide (instead of three) and one control.
870.3700	Prenatal developmental (rat)	40334501 (1987) Acceptable-non-guideline 0, 5, 20, 80, 160 mg/kg/day	**Maternal** NOAEL = 160 mg/kg/day LOAEL was not observed **Developmental** NOAEL = 160 mg/kg/day A LOAEL was not observed This was a scientifically sound study, which did not demonstrate an adverse effect at the highest dose tested. An adequate dose-selection rationale was not provided.
870.3700	Prenatal developmental (rabbit)	00148065 (1985) Acceptable-guideline 0, 5, 20, 80 mg/kg/day	**Materna**l NOAEL = 20 mg/kg/day; LOAEL = 80 mg/kg/day based on the following (#/18 treated vs #/18controls): abortions, mortality (1 vs 0), anorexia (10 vs 1), red urinary precipitate (7 vs 0), abortions (5 vs 0), hepatic necrosis (5 vs 0), eosinophilic hepatocytes (8 vs 1), swelling of hepatocytes (9 vs 0), pigmentation of Kupffer cells (6 vs 0), and punctate vacuolation of midzonal and centrilobular hepatocytes (13 vs 3). Mottled liver was commonly observed in the animals that aborted or died. It was also noted that a hunched appearance was more commonly observed in the treated animals. **Developmenta**l NOAEL = 20 mg/kg/day LOAEL = 80 mg/kg/day based on abortions

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	41540301 (1990) Acceptable-guideline ♂♀: 0, 40, 200 or 1500 ppm F0: ♂ = 0, 3.5, 17.5 and 123.2 ♀ = 0, 3.0, 15.4 and 114.0 mg/kg/day through 2 generations (one mating period per generation).	**Parental/Systemic Toxicity** NOAEL = 200 ppm (17.5 mg/kg/day-females and 15.4 mg/kg/day-males); LOAEL = 1500 ppm (123.2 mg/kg/day-females and 114.0 mg/kg/day-males), based upon decreases in body weight and feed consumption in both sexes, increased incidences of histopathology in the liver, adrenal glands, thyroid gland, and anterior pituitary gland in P1 and P2 generations, and increased incidences of uterine gross pathology in P2 females. **Reproductive Toxicity** NOAEL/LOAEL ≥ 1500 ppm **Developmental/Offspring Toxicity** NOAEL = 200 ppm (17.5 mg/kg/day-females and 15.4 mg/kg/day-males) LOAEL = 1500 ppm (123.2 mg/kg/day-females and 114.0 mg/kg/day-males) based upon decreases in combined male/female pup weight/litter.
870.4100	Chronic toxicity (CD rat) See under 870.4200	00133111 (1970) Acceptable-non-guideline 0, 30, 100, 300 ppm 0, 1.5, 5, 15 mg/kg/day (using standard conversion factor of 0.05)	Systemic Toxicity NOAEL = 15 mg/kg/day Systemic Toxicity LOAEL = not identified.
870.4100	Chronic toxicity (dog) Beagle	41807601/42130301 (1991) Acceptable-guideline 0, 300, 875, or 1750 ppm 0, 11.9, 33.1, or 67.7 mg/kg/day (males) 0, 11.9, 36.1, or 69.0 mg/kg/day (females)	NOAEL = 300 ppm [11.9 (males/females)] LOAEL = 875 ppm [33.1 (males); 36.1 (females)] based upon increased serum alkaline phosphatase activity (males), increases thyroid and liver weights and liver histopathology (hypertrophy, hyperplasia, and granular brown pigmentation and mononuclear infiltration of Kupffer cells).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200	Carcinogenicity (Crl:CD(BR) VAF/Plus rat)	41714001/41714002 (1990) 41799601 (1990) supplemental histopath Acceptable-guideline 0, 40, 200, 1000 ppm* ♂: 0, 1.73, 8.46, 42.59 mg/kg/day ♀: 0, 2.13, 10.69, 55.09 mg/kg/day *25, 100, 400 ppm for 2 weeks; then 35, 140, 560 ppm for 3 weeks; then 40, 200, 1000 ppm thereafter	Systemic Toxicity NOAEL = 8.46/10.69 mg/kg/day Systemic Toxicity LOAEL = 42.59/55.09 mg/kg/day, based on increased relative liver weight and increased non-neoplastic histologic changes in the liver (centrilobular hypertrophy, eosinophilic cell alteration; both sexes), thyroid (follicular cell hypertrophy; both sexes), and ovaries (sertoliform tubular hyperplasia). **evidence of carcinogenicity:** thyroid follicular cell adenomas (both sexes); benign testicular interstitial cell tumors in males.
870.4200	Carcinogenicity (CD-1 mouse)	46424801 (2004) Acceptable-guideline Pronamide (95.9% a.i.; Lot No. F0031-166) was administered in the diet to CD1 mice (50/sex/dose) for up to 78 weeks at doses of 0, 5, 50, or 250 mg/kg bw/day.	NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day, based on cardiotoxicity (increased incidences of thrombus in the heart and multifocal myocardial degeneration) in females and hepatotoxicity (bile stasis, focus of eosinophilic cellular alteration, bile duct hyperplasia, panlobular hepatocyte hypertrophy, and pigment-laden macrophages (bile) in both sexes; focus of basophilic cellular alteration, focus of vacuolated cellular alteration, multifocal necrosis, centrilobular-midzonal vacuolation, and individual hepatocyte vacuolation in males; and centrilobular hepatocyte hypertrophy in females) in both sexes. **evidence of carcinogenicity:** increased incidence of hepatocellular adenomas and carcinomas in both sexes at 250 mg/kg/day.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200	Carcinogenicity (male B6C3F1 mouse)	00114114 (1982) Acceptable-non-guideline, when used in conjunction with MRID 00107968 0, 0, 20, 100, 500, or 2500 ppm 0, 0, 3, 15, 75, or 375 mg/kg/day (standard conversion factor of 0.15 used)	NOAEL = 15 mg/kg/day LOAEL = 75 mg/kg/day, based on gross findings (increased incidences of hepatic nodules/masses and liver enlargement) observed in male mice after 24 months of treatment. At 375 mg/kg/day, decreased body weight, increased liver weights, and an increased incidence of parenchymal necrosis and cholestasis was observed in the liver. **evidence of carcinogenicity:** increased incidence of hepatocellular carcinomas and hepatocellular adenomas at 75 and 375 mg/kg/day.
870.4200	Carcinogenicity (C57BL/6 x C3H/anf F_1 mouse)	00107968 (1974) Acceptable-non-guideline, acceptable when used in conjunction with MRID 00114114 0, 1000 or 2000 ppm 0, 150 or 300 mg/kg/day (standard conversion factor of 0.15 used)	NOAEL = not identified LOAEL = not identified. This is a 2-dose non-GLP study. Females at 2000 ppm displayed decreased body weight (↓17% at week 78); increased liver weights reported in both sexes at week 30 (interim sacrifice); liver weight not reported at 18-month sacrifice. At terminal sacrifice, cholestasis in hepatocytes and/or Kupffer's cells in 28/99 males at 2000 ppm. Cholestasis was not accompanied by hepatocellular carcinoma. **evidence of carcinogenicity:** increased incidence of hepatocellular carcinomas at both dose levels (dose-related) in males.
870.5100	Reverse gene mutation assay in bacteria, *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvrA*	49167402 (2008) Acceptable, guideline 0, 1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 µg/plate, without and with activation,	There was no evidence of induced mutant colonies over background.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100	Genotoxicity Ames bacterial gene mutation assay *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *Escherichia coli* WP2 *hcr*	40090602 (1978) Acceptable, guideline *Salmonella typhimurium* ±S9: 10 to 5000 µg/plate *Bacillus subtilis* H17 *(rec$^+$)* and M45 *(rec$^-$)* ±S9: 20 to 2000 µg/disc	No evidence of mutagenic activity was seen at any dose level tested in the presence or absence of S-9 mix in either mutation test.
870.5300	Genotoxicity *In vitro* mammalian cell gene mutation (HGPRT locus in CHO) test	40211106 (1984) Acceptable, guideline 2.5 to 40 µg/mL with or without S9 activation.	no evidence of mutagenic activity. slightly cytotoxic at 40 µg/mL+/-S9
870.5375	Cytogenetics *in vitro* mammalian cell assay in Chinese hamster ovary (CHO) cells	40211108 (1987) Acceptable, guideline dose range 25-400µg/mL ±S9	no evidence of a clastogenic response either in the presence or the absence of S9 activation. doses ≥250 µg/mL insoluble; cytotoxicity was not seen.
870.6200	Acute neurotoxicity screening battery F344/DuCrl rats	48599202 (2011) Acceptable-guideline 0, 40, 200 or 600 mg/kg	NOAEL for acute neurotoxicity was not determined. LOAEL is 40 mg/kg (the LDT), based on the increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1.
870.6200	Subchronic neurotoxicity screening battery F344/DuCrl rats	48599204 (2011) Acceptable-guideline 0, 40, 200, or 1000 ppm (time-weighted average dosages of 0, 2.4, 11.8, or 59.5 mg/kg/day in males, and 0, 2.7, 13.3, or 65.2 mg/kg/day in females)	NOAEL is 40 ppm (equivalent to 2.38/2.67 mg/kg/day in M/F). LOAEL for this study is 200 ppm (equivalent to 11.8/13.3 mg/kg/day in M/F), based on decreased body weights, body weight gains, and food consumption in males.
870.6300	Developmental neurotoxicity	Not submitted	Waived by the HIARC 12/10/2001

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	41801801 (1991) 41929901 (1991) 42858001 (1993) ^{14}C-phenyl-Pronamide for 14 days	Pronamide is rapidly absorbed and completely and rapidly eliminated; radioactivity was recovered (93-103%) in the urine (40-61 %), feces (40-60%) and tissues and carcass (0.08-2.43%). No bioaccumulation was apparent. The elimination of radioactivity from the plasma of low dose rats was biphasic [rapid phase = 12.6 hrs (males) and 12.7 hrs (females); slow phase = 36.6 hrs (males) and 45.3 (females) and that of the high dose rats was monophasic *[t/z* = 24.1 hrs (males) and 24.8 hrs (females)]. Very little unchanged pronamide was recovered in the urine and no significant difference in urinary metabolite profile was observed between the doses or the sexes. The two major urinary metabolites were SS47-70 (3.0-5.9%) of the dose and metabolite 10 (12.7-18.9%). In the urine, 27 metabolites were found and none exceeded 3.3% of the dose, whereas, almost all of the unknowns in the feces were less than 1 % of the dose.
870.7600	Dermal penetration (rat)	41117201 (1989) 40256701 (1987) Acceptable, non-guideline Pronamide 99%a.i. ^{14}C-Pronamide [check – unintelligible]	The recoveries with the 50W formulation were 78% at the low dose and 122% at the high dose. Normalization of the low-dose data (worst-case scenario) for the 50W formulation to adjust for recover, and further adjustment for carcass residue, results in a dermal absorption factor (DAF) of 24%.
870.7800	Immunotoxicity (CD-1 mouse)	48599201 (2010) Acceptable, guideline 0, 15, 75, 250 mg/kg/day Achieved: 0, 14, 74, 244 mg/kg/day	Immunotoxicity NOAEL = 244 mg/kg/day Immunotoxicity LOAEL was not established. Systemic NOAEL = 15 mg/kg/day Systemic LOAEL = 75 mg/kg/day, based on increased liver weights.
890.1450	Female pubertal study (~3 weeks) (Crl:CD(SD) rats)	48673402 (2012). 0, 25,100,300 mg/kg/day (gavage)	LOAEL for decreased T4 (-25%) in serum is 25 mg/kg/day. There was no NOAEL
890.1500	Male pubertal study (~4 weeks) (Crl:CD(SD) rats)	48688001 (2012). 0, 2.5, 10, 25 mg/kg/day (gavage)	NOAEL = 2.5 mg/kg/day. The LOAEL is 10 mg/kg/day based on decreased serum T4 (-13%)
870.6200	Subchronic neurotox probe (4 weeks) F344/DuCrl rats	48599203 (2011) 0, 500, 1000, 2500 ppm	LOAEL = 500 ppm (40.5 mg/kg/day – males) based on increased relative liver weight (12% male & 9% female)

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Pronamide			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
MOA	13-week oral toxicity (CD rat – males only)	49167410 (2013) 0, 200, 1000, 2000 ppm	NOAEL = 200 ppm (15 mg/kg/day) based on 200-fold increase over background in CYP2B1

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

No single dose endpoint suitable for this exposure scenario could be identified in the database. In the developmental rabbit study, abortions were noted and could possibly be a result of fetal toxicity; however, as the abortions occurred very late (on or after GD 22), this finding was not considered to be a result of single dose of pronamide.

A.3.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Acute Neurotoxicity in Rats
MRID No.: 48599202
Executive Summary: In an acute neurotoxicity study (MRID 48599202), groups of fasted 7 week old F344/DuCrl rats (10/sex/dose) were given a single oral dose of pronamide (96.2% purity, Lot # XG1088R301, TSN003588-0004) in 0.5% METHOCEL™ (10 ml/kg) at doses of 0, 40, 200 or 600 mg/kg bw on Day 1 and observed for 15 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10 animals/sex/group at pre-dosing and Days 1, 8, and 15. Hand-held clinical observations were performed on Days 2, 3 and 4. Body weights were determined pre-dosing and on Days 1, 2, 8, and 15. Cholinesterase activity was not determined. At study termination, all surviving animals in the control and high dose groups were euthanized and perfused *in situ* for neuropathological examination, as well as five animals from the low dose group and seven males and nine females from the mid-dose group. Of the perfused animals, all of the control and high-dose group were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No treatment-related findings were observed in any dose group on Days 8 and 15. No adverse, treatment-related findings were noted on body weight, body weight gain, gross pathology, or neuropathology.

One 600 mg/kg female was sacrificed moribund on Day 2; all other animals were sacrificed on schedule. Although the cause of death was not provided, this death was considered treatment-related considering the profound effects observed in the 600 mg/kg females. Treatment-related clinical signs were present in the 600 mg/kg dose group on Day 2 and consisted primarily of decreased activity, decreased or absent feces, uncoordinated gait, and red periocular soiling. Other clinical signs on Day 2 were present only in females of the 600 mg/kg dose group and included slow or labored respiration and animals that were cold to touch. All of these clinical signs were resolved by Day 3 with the exception of 1 female with decreased activity and absent feces, which was resolved by Day 4, and 1 or 2 males and/or females with red periocular soiling on Days 3 or 4.

On Day 1 in the 200 and 600 mg/kg females, dose-related decreases were observed in resistance to removal, muscle tone, extensor thrust (NS at 200 mg/kg), reactivity to handling, level of activity (NS), response to noise, response to touch, and response to pinch; an increase in

incoordination was noted, and 5/10 females at 600 mg/kg were unable to walk. Additional effects noted in the 600 mg/kg females included decreases in palpebral closure, lacrimation, pupil size, and salivation; increased urination was also observed. Decreased rectal temperatures were noted in the 200 and 600 mg/kg females. Hindlimb and forelimb grip strengths were decreased in the 200 and 600 mg/kg females, with the effect being greater on forelimb grip. Landing foot splay increased at 200 and 600 mg/kg in males (increased 59%, 63%; 600 mg/kg not evaluated statistically) and the 40, 200, and 600 mg/kg females (increased 21%, 31% and 53%). FOB findings were most severe in the females.

In the 600 mg/kg males, decreases were observed in resistance to removal, muscle tone (NS), reactivity to handling, level of activity response to noise, response to touch, and response to pinch; increased incoordination was also noted. In the 200 mg/kg males, decreases in level of activity and response to noise were observed.

Repeated measure analysis on the square root of the motor activity indicated the following: (i) treatment effects were different between males and females at one or more intervals; (ii) treatment did not affect the within-session distribution of counts at any time interval; (iii) there were no differences between control and 40 mg/kg group at any time interval on the square root transformed data (p=0.0534); and (iv) there were differences between the 200 and 600 mg/kg groups and the control. However on day 1, there were large dose-dependent decreases in the untransformed total motor activity counts at 40, 200, and 600 mg/kg in males (-42%, -70%, and -79%) -and females (-41%, -83% and -91%) which are considered adverse and statistically significant at all doses.

The LOAEL (lowest-observed-adverse effect level) is 40 mg/kg (the LDT), based on the increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1. The NOAEL (the no-observed-effect level) for acute neurotoxicity was not determined.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).
Dose and Endpoint for Risk Assessment: POD = 40 mg/kg/day based on increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1 at the LOAEL = 40.
Comments about Study/Endpoint/Uncertainty Factors: *Acute Dietary Endpoint (General Population):* The acute neurotoxicity study in rats was selected for the acute dietary endpoint for the general population. The LOAEL is 40 mg/kg/day (lowest dose tested) which was based on the increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1. This endpoint is appropriate for both the exposure duration (acute/single dose) and the population of concern (general population).

The point of departure (POD) is the LOAEL of 40 mg/kg/day. The POD is divided by a combined 1000X uncertainty factor (UF), consisting of the usual 10x interspecies uncertainty factor for extrapolation from animal to human (UF_A); the usual 10x intraspecies factor for

variation in human response (UF_H); and a 10x factor for LOAEL to NOAEL extrapolation (UF_L). The acute reference dose (aRfD) is 0.04 mg/kg/day for the general population. Therefore, the aRfD is equivalent to the acute population adjusted dose (aPAD).

POD = LOAEL of 40 mg/kg/day
aRfd= aPaD= 40 mg/kg/day = **0.04 mg/kg/day**
1000 (UF)
Where 1000 (UF) = 10 (UF_A) x 10 (UF_H) x 10 (UF_L)

A.3.3 Chronic Reference Dose (cRfD), A.3.4 Incidental Oral Exposure (Short and Intermediate Term), Inhalation Exposure (short and intermediate term)

Study Selected: Acute Neurotoxicity in Rats
MRID No.: 48599202
Executive Summary: See Section A.3.2 above
Dose and Endpoint for Risk Assessment: POD = 4 mg/kg/day based on increase in landing foot splay in female rats and the decrease in motor activity seen in both genders on Day 1 at the LOAEL = 40. The POD = LOAEL ÷10 =4 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: The study selected is the ACN, the same study selected for acute risk assessment. Ordinarily an acute study is not used for longer term exposure scenarios, but in this risk assessment a POD based on the LOAEL of 40 mg/kg from the ACN study and dividing by an uncertainty factor of 10 for use of a LOAEL (UF_L) is considered appropriate to assess longer term assessments. The derived POD of 4 mg/kg/was selected for the chronic dietary, incidental oral (short-term), and inhalation (short- and intermediate-term) endpoints based on a weight of evidence approach using the results from 3 studies. The studies include the acute and subchronic neurotoxicity rat studies and the combined chronic toxicity/carcinogenicity rat study. The NOAELs/LOAELs from each study are listed below.

1) **Subchronic neurotoxicity (SCN) in F344 rats:** NOAEL of 2.38 mg/kg/day is based on the significant decreases in body weight, food consumption, and food efficiency seen at 11.28 mg/kg/day (LOAEL) in males.
2) **Acute neurotoxicity (ACN) in F344 rats:** NOAEL was not established. The LOAEL of 40 mg/kg/day with a 10X LOAEL to NOAEL uncertainty factor (UF_L) yields a derived **POD of 4 mg/kg/day (40÷10).**
3) **Combined chronic toxicity/carcinogenicity in CD rats:** NOAEL of 8.46 mg/kg/day is based on increased relative liver weight and histopathological lesions in the liver, thyroid, and ovaries at 43 mg/kg/day (LOAEL).

The lowest LOAEL of the three studies is 11.28 mg/kg/day from the SCN study. The highest NOAEL (8.6 mg/kg/day) in the combined rat study is not appropriate for a POD since that value is very close to the LOAEL of 11.28 mg/kg/day. The next highest value to consider is 4.0 mg/kg/day, the derived POD which is a factor of 3x lower than the LOAEL from the SCN. HED

considers 4.0 mg/kg/day to be the appropriate value for use as the POD as it will be protective of the suite of effects seen at the LOAELs of 11.28 mg/kg/day (SCN) and 42.6 mg/kg/day (chronic/carcinogenicity rat) and also 40 mg/kg/day (ACN). This POD is appropriate for use across all exposure durations.

Application of a 100-fold uncertainty factor has been determined to be appropriate (10X interspecies and 10X intraspecies).

For the chronic dietary risk assessment, the cRfD of 0.04 mg/kg/day is equivalent to the cPAD.

$$\text{Extrapolated POD} = \frac{\text{(LOAEL 40 mg/kg/day)}}{10\ (UF_L)} = 4 \text{ mg/kg/day}$$

$$\textbf{cRfd= cPaD=} \frac{4 \text{ mg/kg/day}}{100\ (UF)} = 0.04 \text{ mg/kg/day}$$

A.3.5 Dermal Exposure (Short-, Intermediate- and Long-Term)

Study Selected: 28-Day Dermal Toxicity Study in the Rat
MRID No.: 46885701
Executive Summary: In a 28-day dermal toxicity study (MRID 46885701), Pronamide (95.9% a.i., Lot No. F0031-166) in 0.5% aqueous methycellulose was applied as a paste suspension to the shaved skin of ten Fischer 344 rats/sex/dose at concentrations of 0, 100, 500, or 1000 mg/kg bw/day, six hours/day, seven days/week for at least 28 days.

No adverse, treatment-related effects were observed on mortality, clinical signs (including a limited functional observational battery), ophthalmoscopic findings, hematology, clinical chemistry, organ weights, or gross pathology.

Terminal body weight was decreased ($p \leq 0.05$) by 10% and 12% at 500 and 1000 mg/kg/day, respectively. Overall (Days 1-28) body weight gains of 500 and 1000 mg/kg/day male rats were decreased by 40% and 45%, respectively, while food consumption was decreased ($p \leq 0.05$) by 7-13% for 2 or 3 weeks in these groups. No treatment-related effects were found in female rats.

Treatment-related effects at the application site were limited to slight scaling in one 1000 mg/k/day male observed on Days 22-29 and increased incidences of very slight to slight epidermal hyperplasia and slight multifocal inflammation. These effects were considered to be adaptive responses to the irritant properties of the test material. No other treatment-related effects were found.

The LOAEL is 500 mg Pronamide/kg/day based on decreases in body weight, body weight gain, and food consumption in males. The NOAEL is 100 mg/kg/day. Dermal toxicity was not observed, and no effects were noted in females.

This 28-day dermal toxicity study in the Fischer 344 rat is **acceptable, guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in the rat.

Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg/day. The LOAEL = 500 mg/kg/day in males based on decreases in body weight (10%) and food consumption (8%) in males – minimal toxicity, animals could have tolerated higher dosages. Females were not affected.

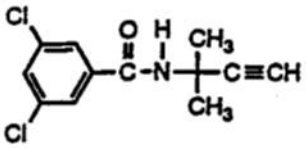
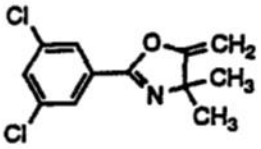
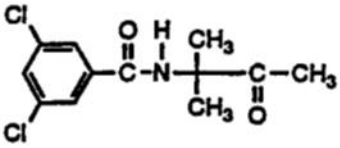
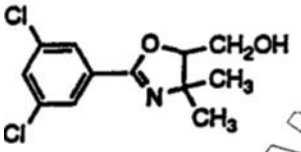
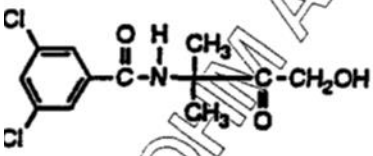
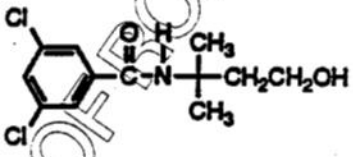
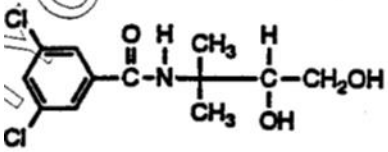
Comments about Study/Endpoint/Uncertainty Factors: The dermal endpoint was selected from a 28-day dermal toxicity study in rats. The POD was a NOAEL of 100 mg/kg/day. The LOAEL was 500 mg/kg/day based on decreases in body weight and food consumption in males. No target organ (liver) toxicity was seen following repeated dermal dosing. This is considered a conservative endpoint since the animals could have tolerated a higher dose. The endpoint is appropriate for the route and duration of exposure as well as the population of concern.

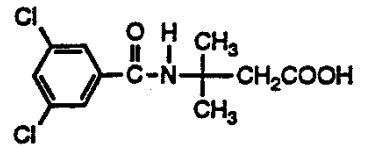
The occupational and residential levels of concern for the margin of exposure is 100 (includes UF_A=10x and UF_H=10x).

Appendix B. Metabolites and Metabolic Pathways for Pronamide

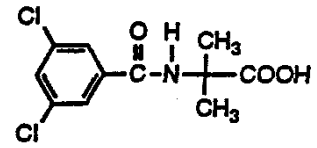
The following are rat metabolites found in the urine and feces.

Structures, Rohm and Haas Numbers, Roman Numeral Designations and Lot Numbers of Pronamide and Reference Standard Metabolites

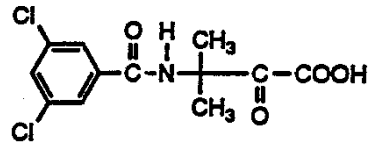
STRUCTURE	RH NUMBER	ROMAN NUMERAL DESIGNATION	LOT NUMBER
	RH - 315 (Parent)	K	RPO 78:77F
	RH - 24644	I	MW 6-71
	RH - 24580	II	HGW 54:28
	RH - 25891	III	TAM 33-85B
	RH - 26702	IV	MWS 7-7
	RH - 26377	V	MWS 8-27
	RH - 26521	VI	MJS 7-73



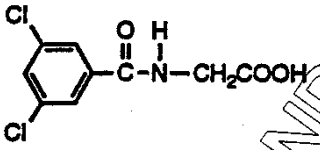
RH - 26059 VII TAM 33:61



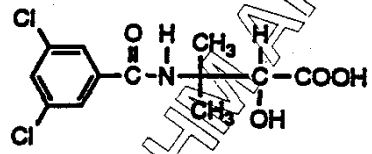
RH - 24650 VIII TAM 33:78E



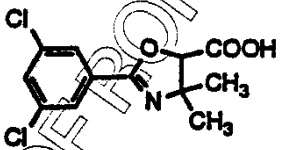
RH - 27619 IX MWS 8-76



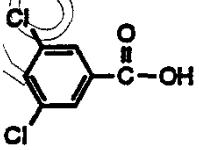
RH - 26691 X JMB11:10



RH - 27414 XII TAM 35:81

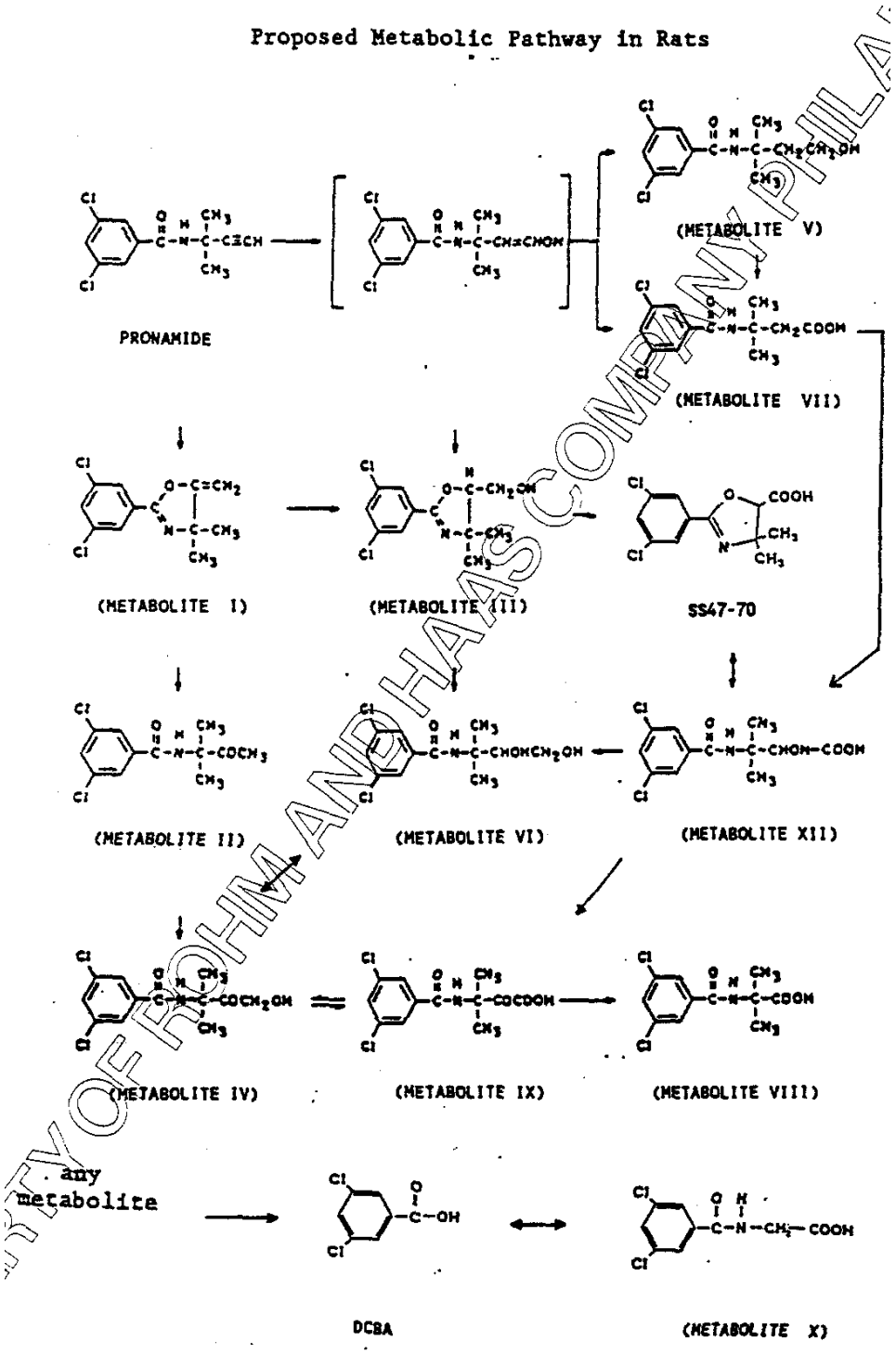


RH - 016911 SS 47-70



RH - 20839 D ALDRICH 3531CE

The following is the proposed metabolic pathway in the rat supplied by the registrant.



Appendix C. Physical/Chemical Properties

Table C1. Physico-Chemical Properties (Stillmeadow Technical)		
Parameter	**Value**	**Reference**
Molecular Weight	256.13	
pH	N/A	Tomlin, C.D.S. (ed.). The Pesticide Manual - World Compendium. 11th ed. Surrey, UK: The British Crop Protection Council, 1994, p. 862]
Water solubility (20°C)	15 mg/L	
Solvent solubility (g/L)(20°C to 25°C)	Methanol, isopropanol 150 Cyclohexanone, MEK 200 DMSO 330	
Vapor pressure (25°C)	0.058 mPa ($4.4x10^{-7}$ torr)	
Dissociation constant, pKa	Not applicable	
Octanol/water partition coefficient, log K_{OW} (25°C)	3.43	
Aerobic Soil Metabolism Half-life (days)	165	MRID 46413407 cited in Milians, D414467 (2015)

Appendix D. Summary of Registered and Proposed Uses for Pronamide

Crop/Use Site	Application Timing and Type of Application	Registered Formulations	Maximum Application Rate	Personal Protective Equipment (PPE) and Restricted Entry Interval (REI)
Agricultural Fallow/Idleland Agricultural Uncultivated Areas	September/December/Broadcast Aerial	L/WP(WSP)	0.5	24 hrs REI
Alfalfa	Spring/Fall/Winter/ Broadcast/ Aerial Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 50 days PHI
Apple	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Apricot	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Artichoke	Ratoon/ Broadcast/Aerial Chemigation/ Groundboom	L/WP(WSP)	4	24 hrs REI 60 days PHI
Blackberry	Fall/Winter/ Broadcast/ Chemigation/ Groundboom	L/WP(WSP)	3	24 hrs REI
Blueberry	Fall/Winter/ Broadcast/ Chemigation/ Groundboom,	L/WP(WSP)	3	24 hrs REI
Boysenberry	Fall/Winter/ Broadcast/ Chemigation/ Groundboom	L/WP(WSP)	3	24 hrs REI
Cherry	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Christmas Tree Plantations	Early winter/Fall/ direct spray/Aerial	L/WP(WSP)	4	24 hrs REI 365 days PHI
Clover	Fall/Winter/ Broadcast/Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 120 days PHI
Commercial/Industrial Lawns	Spring/Broadcast/Aerial/Chemigation/ Groundboom	L	1.44	24 hrs REI
Crown Vetch	Fall/Winter/ Broadcast/Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 120 days PHI
Endive	Postplant/Broadcast/Aerial /Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 55 days PHI
Golf Course Turf	Spring/Broadcast/Aerial/Chemigation/ Groundboom	L/WP(WSP)	1.44	24 hrs REI
Grapes	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Grasses Grown For Seed	Fall/Preemergence/Early Winter	WP(WSP)	0.375	24 hrs REI
Leafy Greens	Postemergence/ Chemigation/ Groundboom	L	2	24 hrs REI 55 days PHI
		WP(WSP)	1.5	
Lettuce	Postplant/Broadcast/Aerial / Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 55 days PHI
Leaf Lettuce **(Section 3)**	Postplant/Broadcast/Aerial / Chemigation/ Groundboom/ Hand held sprayer	L	1	24 hrs REI 45 days PHI
Nectarine	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Ornamental And/or Shade Trees	Fall/ direct spray/ Hand held sprayer	L/WP(WSP)	2	24 hrs REI
Ornamental Grasses	Broadcast/Aerial/ Chemigation/ Groundboom/Hand held sprayer	WP(WSP)	1.5	24 hrs REI
Ornamental Herbaceous Plants	Fall/ direct spray/ Hand held sprayer	L/WP(WSP)	2	24 hrs REI
Ornamental Lawns And Turf	Spring/Broadcast/Aerial/Chemigation/ Groundboom/ Hand held sprayer	L/WP(WSP)	1.44	24 hrs REI
Ornamental Nonflowering Plants	Fall/ direct spray/ Hand held sprayer	L/WP(WSP)	2	24 hrs REI
Ornamental Sod Farm (Turf)	Spring/Broadcast/Aerial/Chemigation/ Groundboom / Hand held sprayer	L	1.44	24 hrs REI
Ornamental Woody Shrubs And Vines	Fall/ direct spray/ Hand held sprayer	L/WP(WSP)	2	24 hrs REI
Peach	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Pear	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Peas	Broadcast/Early winter/ Chemigation/ Groundboom	L/WP(WSP)	1.5	24 hrs REI
Plum	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Prune	Fall/Postharvest direct spray	L/WP(WSP)	4	24 hrs REI
Raspberry (Black - Red)	Fall/Winter/ Broadcast/ Chemigation/ Groundboom	L/WP(WSP)	3	24 hrs REI
Rhubarb	Fall/Broadcast/ Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 38 days PHI
Sainfoin	Fall/Winter/ Broadcast/Chemigation/Groundboom	L/WP(WSP)	2	24 hrs REI 120 days PHI
Sugar Beet	Fall/Winter/ Broadcast/Chemigation/ Groundboom	L/WP(WSP)	1	24 hrs REI
Trefoil	Fall/Winter/ Broadcast/ Chemigation/ Groundboom	L/WP(WSP)	2	24 hrs REI 120 days PHI

Appendix E. Occupational Exposure/Risk Summary Tables

Occupational Handler Non-Cancer Exposure and Risk Estimates for Pronamide									
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate (lb ai/A)[2]**	**Area Treated (acres)[3]**	**Dermal (LOC = 100)**		**Inhalation (LOC = 1000)**	
		Mitigation Level = baseline unless indicated otherwise				**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**
Mixer/Loader									
Aerial application of Wettable powder in Water Soluble Package (WSP)	Nursery (ornamentals, vegetables, trees, container stock)	8.6 (Engineering Control)	0.083 (Engineering Control)	1.5	60	0.011	9,100	0.00027	150,000
	Sod			1.5	350	0.0644	1,600	0.00158	25,000
	Field crop, typical acreage[8] and Orchard[10]			4		0.171	580	0.0042	9,500
	Field crop, high-acreage[9]			2	1200	0.294	340	0.0072	5,600
Chemigation application of Wettable powder in Water Soluble Package (WSP)	Sod			1.5		0.0644	1,600	0.00158	25,000
	Field crop, typical acreage [8] and Orchard[10]			4	350	0.171	580	0.0042	9,500
	Field crop, high-acreage[9]			2		0.0585	1,200	0.0021	19,000
	Nursery (ornamentals, vegetables, trees, container stock)			1.5	60	0.011	9,100	0.00027	150,000
Groundboom application of Wettable powder in Water Soluble Package (WSP)	Golf course (fairways, tees, greens)			1.5	40	0.00735	14,000	0.00018	220,000
	Field-grown ornamental crops								
	Nursery (ornamentals, vegetables, trees, container stock)			1.5	60	0.011	9,100	0.00027	150,000
	Sod			1.5	80	0.0148	8,800	0.00036	110,000
	Field crop, typical acreage[8] and Orchard[10]			4		0.0393	2,500	0.00096	42,000
	Field crop, high-acreage[9]			2	200	0.049	2,000	0.0012	33,000
Aerial application of liquid formulation	Nursery (ornamentals, vegetables, trees, container stock)	37.6 (Single layer/Glove)	0.219	2	60	0.0564	1,800	0.000329	120,000
	Sod			1.44		0.238	420	0.00138	29,000
	Field crop, typical acreage[8] and Orchard[10]			4	350	0.658	150	0.00384	10,000
	Field crop, high-acreage[9]	29.1 (DL/G)	0.219	2	1200	0.873	110	0.00658	6,100
Chemigation application of a liquid formulation	Nursery (ornamentals, vegetables, trees, container stock)	37.6 (Single layer/Glove)	0.219	2	60	0.0564	1,800	0.000329	120,000
	Sod			1.44		0.238	420	0.00138	29,000
	Field crop, typical acreage[8] and Orchard[10]			4	350	0.658	150	0.00384	10,000
	Field crop, high-acreage[9]			2		0.329	300	0.00768	20,000
Groundboom application of liquid formulation	Nursery (ornamentals, vegetables, trees, container stock)			2	60	0.0564	1,800	0.000329	120,000
	Sod			1.44	80	0.0541	1,800	0.000315	130,000
	Golf course (fairways, tees, greens)				40	0.0271	3,700	0.000158	250,000
	Field crop, typical acreage[8]			4	80	0.15	670	0.000876	46,000
	Field crop, high-acreage[9]			2	200	0.188	530	0.0011	36,000

Occupational Handler Non-Cancer Exposure and Risk Estimates for Pronamide									
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate (lb ai/A)[2]**	**Area Treated (acres)[3]**	**Dermal (LOC = 100)**		**Inhalation (LOC = 1000)**	
		Mitigation Level = baseline unless indicated otherwise				**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**
Applicator									
Aerial spray application	Nursery (ornamentals, vegetables, trees, container stock)	2.08 (Engineering Control)	0.0049 (Engineering Control)	2	60	0.00313	32,000	0.00000735	5,400,000
	Sod			1.5	350	0.0136	7,400	0.0000321	1,200,000
	Field crop, typical acreage[8] and Orchard[10]			4		0.0364	2,700	0.0000858	470,000
	Field crop, high-acreage[9]			2	1200	0.0624	1,600	0.000148	270,000
Groundboom spray application	Golf course (fairways, tees, greens)	78.6	0.34	1.5	40	0.059	1,700	0.000255	160,000
	Field-grown ornamental crops								
	Nursery (ornamentals, vegetables, trees, container stock)			2	60	0.118	850	0.00051	78,000
	Sod			1.5	80	0.118	850	0.00051	78,000
	Field crop, typical acreage[8] and Orchard[10]			4		0.315	320	0.00136	29,000
	Field crop, high-acreage[9]			2	200	0.393	250	0.0017	24,000
Flagger									
Flagger for aerial spray application	Nursery (ornamentals, vegetables, trees, container stock)	11	0.35	2	60	0.0165	6,100	0.00525	76,000
	Sod			1.5	350	0.0723	1,400	0.0023	17,000
	Field crop, typical acreage[8] and Orchard[10]			4		0.193	520	0.00613	6,500
	Field crop, typical and high-acreage[9]			2		0.0963	1,000	0.00306	13,000

Occupational Handler Non-Cancer Exposure and Risk Estimates for Pronamide									
Exposure Scenario	**Crop or Target**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate (lb ai/A)[2]**	**Area Treated (acres)[3]**	**Dermal (LOC = 100)**		**Inhalation (LOC = 1000)**	
		Mitigation Level = baseline unless indicated otherwise				**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**
Mixer/Loader/Applicator									
Wettable powder in Water Soluble Package (WSP) via Backpack	Orchard[10] crops (ground soil directed)	8260	2.58	0.1 lb ai/gal	40 gallons	0.413	240	0.000129	310,000
Wettable powder in Water Soluble Package (WSP) via Backpack	Landscaping, turf (lawns, athletic fields, parks, etc.)	8,260	2.58	0.075		0.31	320	0.0000968	410,000
Wettable powder in Water Soluble Package (WSP)via Manually-Pressurized Handwand	Landscaping, turf (lawns, athletic fields, parks, etc.)	430 (Single layer/Glove)	30			0.0161	6,200	0.00113	35,000
Wettable powder in Water Soluble Package (WSP) via Mechanically-pressurized Handgun	Golf course (fairways, tees, greens)	1350	18	1.5	5	0.126	790	0.00169	24,000
	Landscaping, turf (lawns, athletic fields, parks, etc.)								
Liquids via Backpack	Orchard[10] crops (ground soil directed)	8,260	2.58	0.2	40 gallons	0.826	120	0.000258	160,000
	Nursery (ornamentals, vegetables, trees, container stock)			0.072		0.298	340	0.0000929	430,000
Liquids via Manually-pressurized Handwand	Landscaping, turf (lawns, athletic fields, parks, etc.)	430 (Single layer/Glove)	30			0.0155	6,500	0.00108	37,000
Liquids via Mechanically-pressurized Handgun	Golf course (fairways, tees, greens)	1,140	1.9	1.44	5	0.103	970	0.000171	230,000
	Landscaping, turf (lawns, athletic fields, parks, etc.)								
	Orchard[10] crops (ground soil directed)	390 (Single layer/Glove)	3.9	0.2	1000 gallons	0.971	100	0.00975	4,100
	Nursery (ornamentals, vegetables, trees, container stock)			0.072		0.351	280	0.00351	11,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2013);
2 Based on registered and proposed labels.
3 Exposure Science Advisory Council Policy #9.1 and Registrant information.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (100 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
7 Inhalation MOE = ACN LOAEL (40 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Field crops, typical acreage category covers the following crops: asparagus, Brassica, head and stem, Brassica, leafy greens, cabbage, berries, edamame, fallow cropping systems, flax, fruiting vegetables, okra, horseradish, lima beans, melons, rhubarb, strawberry, succulent peas, tobacco, turnips, Christmas tree farms, mint, peanuts, peppermint, spearmint, potato sugarcane, dry shelled peas and beans and sunflower @ a maximum of 2lb ai/A and for berries @ 3 lb ai/A
9 Field crops, high acreage crops category covers the following crops: corn, soybeans and wheat @2 lb ai/A.
10 Orchard crops, apples, apricot, artichoke, cherry, peach, pear, peach, pear, plum, nectarine, citrus fruits, tree nuts, grapes, Christmas tree plantations @4 lb ai/A

Appendix F. International Residue Limits Table

Pronamide (aka Propyzamide; PC Code 101701)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR 180.317: (a) General. (1) propyzamide residues convertible to methyl 3,5-dichlorobenzoate, expressed as the stoichiometric equivalent of propyzamide, 3,5-dichloro-N-(1,1-dimethyl-2-propynyl)benzamide		3,5-dichloro-*N*-(1,1-dimethyl-2-propyn-1-yl)benzamide, including metabolites containing the 3,5-dichlorobenzoate moiety		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Alfalfa, seed	10.0			
Animal feed, nongrass, group 18	10.0			
Apple	0.1	0.1		
Artichoke, globe	0.01			
Blackberry	0.05			
Blueberry	0.05	0.05 lowbush blueberries		
Boysenberry	0.05			
Cattle, fat	0.2			
Cattle, kidney	0.4			
Cattle, liver	0.4			
Cattle, meat	0.02			
Cattle, meat byproducts, except kidney and liver	0.02			
Egg	0.02			
Endive	1.0			
Fruit, stone, group 12	0.1			
Goat, fat	0.2			
Goat, kidney	0.4			
Goat, liver	0.4			
Goat, meat	0.02			
Goat, meat byproducts, except kidney and liver	0.02			
Grape	0.1			
Hog, fat	0.2			
Hog, kidney	0.4			
Hog, liver	0.4			
Hog, meat	0.02			
Hog, meat byproducts, except kidney and liver	0.02			
Horse, fat	0.2			
Horse, kidney	0.4			
Horse, liver	0.4			
Horse, meat	0.02			
Horse, meat byproducts, except kidney and liver	0.02			
Lettuce, head	1.0	1 lettuce		
Milk	0.02			

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
Pear	0.1	0.1		
Poultry, fat	0.02			
Poultry, liver	0.2			
Poultry, meat	0.02			
Poultry, meat byproducts, except liver	0.02			
Radicchio	2.0			
Raspberry	0.05			
Sheep, fat	0.2			
Sheep, kidney	0.4			
Sheep, liver	0.4			
Sheep, meat	0.02			
Sheep, meat byproducts, except kidney and liver	0.02			
Completed: M. Negussie; 05/07/15				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

(c) *Tolerances with regional registrations.* Tolerances with regional registration, as defined in §180.1(l), are established for residues of the herbicide propyzamide, including its metabolites and degradates, in or on the commodities in the table in this paragraph. Compliance with the tolerance levels specified in this paragraph is to be determined by measuring only those propyzamide residues convertible to methyl 3,5-dichlorobenzoate, expressed as the stoichiometric equivalent of propyzamide, 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide, in or on the commodity.

Commodity	Parts per million
Pea, field, seed	0.05
Rhubarb	0.1

(d) *Indirect or inadvertent residues.* Tolerances are established for indirect or inadvertent residues of the herbicide propyzamide, including its metabolites and degradates, in or on the commodities in the table in this paragraph. Compliance with the tolerance levels specified in this paragraph is to be determined by measuring only those propyzamide residues convertible to methyl 3,5-dichlorobenzoate, expressed as the stoichiometric equivalent of propyzamide, 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide, in or on the commodity.

Commodity	Parts per million
Grain, cereal, forage, group 16	0.6
Grain, cereal, hay, group 16	0.2
Grain, cereal, straw, group 16	0.3