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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 5, 2002

CERTIFIED MAIL

Dear Registrant:

This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of FQPA Tolerance Reassessment Progress and Interim Risk Management Decision" (TRED) for pronamide that was completed on July 5, 2002. A Notice of Availability, soliciting public comment for a 30 day period, will be published in the *Federal Register* (FR) shortly.

The Federal Food Drug and Cosmetic Act (FFDCA), as amended, requires EPA to reassess all the tolerances for registered chemicals in effect on or before the date of the enactment of the Food Quality Protection Act (FQPA) in August of 1996 against the new safety standard adopted in the FQPA. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. The tolerances are considered reassessed once the safety finding has been made or a modification or revocation occurs. A reregistration eligibility decision (RED) for pronamide, was completed May 1994, prior to FQPA enactment. Therefore, it needed to be updated to reassess the tolerances under the FQPA standard.

The Agency has evaluated the dietary risk associated with pronamide and has determined that, provided the risk mitigation measures outlined in this document are implemented, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to pronamide when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, the tolerances established for residues of pronamide in/on raw agricultural commodities are now considered reassessed as safe under section 408(q) of the FFDCA.

FQPA requires that EPA consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the other substances individually.

EPA did not perform a cumulative risk assessment as part of this tolerance reassessment review of pronamide, because the Agency has not determined if there are any other chemical substances that have a mechanism of toxicity common with that of pronamide. If EPA identifies other substances that share a common mechanism of toxicity with pronamide, then a cumulative risk assessment will be conducted that includes pronamide once the final framework EPA will use for conducting cumulative risk assessments is available. Further, EPA is in the process of developing criteria for characterizing and testing endocrine disrupting chemicals and plans to implement an Endocrine Disruptor Screening Program. Pronamide will be reevaluated at that time and additional studies may be required.

The Agency's human health findings for the pesticide pronamide, were discussed in a closure conference call held on June 28, 2002, and are summarized in the attached chemical overview of the risk assessments. These risk assessments and other documents pertaining to the pronamide tolerance reassessment decision are listed at the end of this document and are available on the Internet at http://www.epa.gov/pesticides/reregistration/status.htm and in the public docket for viewing.

Pronamide tolerances are established under 40 CFR §180.317 (a), (b) and (c). The tolerance expression, listed in (a) and (c), is in terms of the combined residues of the herbicide propyzamide and its metabolites (containing the 3, 5-dichlorobenzoyl moiety and calculated as 3, 5 dichloro-*N*- (1,1-dimethyl-2-propynyl)benzamide). The tolerance expression, listed in (b), is in terms of the parent only. The Agency recommends that the tolerance expression under (b) be modified to include the metabolites. The Agency also recommends the following:

- Decreasing the established tolerance for artichokes;
- Increasing the tolerances for cattle fat, goat fat, hog fat, horses fat, and sheep fat;
- Revoking the tolerance for poultry kidney and grass, forage; and,
- Proposing a tolerance for alfalfa seed and pea vines and hay.

The Table below summarizes EPA's tolerance reassessment decision which accounts for 47 tolerance reassessments.

The Codex Commission has established several maximum residue limits (MRLs) for residues of pronamide in/on various raw agricultural and processed commodities. The Codex MRLs are expressed in terms of pronamide per se. The Codex MRLs and the U.S. tolerances will be incompatible when the U.S. tolerance expression for plant commodities is revised to include residues of pronamide and the metabolites.

Tolerance Reassessment Summary for Pronamide

Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity definition*
Tolerances Listed Under 40 CFR §180.317(a)			
Apples	0.1	0.1	
Artichokes	0.1	0.01	Residues of pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety were nondetectable (less than the level of concern (LOC) of 0.01ppm) in/on each sample of artichokes harvested 61 days following a single application of a representative pronamide formulation at 4.0 or 8.0 lb ai/A.
Blackberries	0.05	0.05	
Blueberries	0.05	0.05	
Boysenberries	0.05	0.05	
Cattle, fat	0.02	0.20	Fat tolerance raised due to linear extrapolation of maximum residues observed in fat at 40 ppm feeding level relative to the Maximum theoretical dietary burdens (MTDB)
Cattle, kidney	0.4	0.4	
Cattle, liver	0.4	0.4	
Cattle, mbyp (except kidney, liver)	0.02	0.02	
Cattle, meat	0.02	0.02	
Eggs	0.02	0.02	
Endive (escarole)	1.0	1.0	
Goats, fat	0.02	0.20	Fat tolerance raised due to linear extrapolation of maximum residues observed in fat at 40 ppm feeding level relative to the MTDB
Goats, kidney	0.4	0.4	
Goats, liver	0.4	0.4	
Goats, mbyp (except kidney, liver)	0.02	0.02	
Goats, meat	0.02	0.02	
Grapes	0.1	0.1	
Hogs, fat	0.02	0.20	Fat tolerance raised due to linear extrapolation of maximum residues observed in fat at 40 ppm feeding level relative to the MTDB
Hogs, kidney	0.4	0.4	
Hogs, liver	0.4	0.4	
Hogs, mbyp (except kidney)	0.02	0.02	
Hogs, meat	0.02	0.02	
Horses, fat	0.02	0.20	Fat tolerance raised due to linear extrapolation of maximum residues observed in fat at 40 ppm feeding level relative to the MTDB

Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity definition*
Horses, kidney	0.4	0.4	
Horses, liver	0.4	0.4	
Horses, mbyp (except kidney)	0.02	0.02	
Horses, meat	0.02	0.02	
Lettuce	1.0	1.0	*Lettuce Head* Only head lettuce is supported by acceptable data; leaf lettuce uses must be removed from the label. Alternatively, the label may be revised to specify a practical PHI (35-day) for leaf lettuce and supporting data be submitted.
Milk	0.02	0.02	
Non-grass animal feeds	10.0	10.0	*Non-grass animal feeds (forage, fodder, straw, and hay) group*
Pears	0.1	0.1	
Poultry, fat	0.02	0.02	
Poultry, kidney	0.2	Revoke	Tolerances are typically not established for poultry kidneys.
Poultry, liver	0.2	0.2	
Poultry, mbyp (except kidney, liver)	0.02	0.02	
Poultry, meat	0.02	0.02	
Radicchio, greens (tops)	2.0	2.0	
Raspberries	0.05	0.05	
Sheep, fat	0.02	0.20	Fat tolerance raised due to linear extrapolation of maximum residues observed in fat at 40 ppm feeding level relative to the MTDB
Sheep, kidney	0.4	0.4	
Sheep, liver	0.4	0.4	
Sheep, mbyp (except kidney, liver)	0.02	0.02	
Sheep, meat	0.02	0.02	
Stone fruit	0.1	0.1	

Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity definition*
Tolerances To Be Proposed Under 40 CFR §180.317(a)			
Alfalfa Seed	--	10.0	Tolerance recommendation is contingent upon required label revision to specify a 50-day PHI and a maximum seasonal rate of 2.0 lb ai/A
Tolerances Listed Under 40 CFR §180.317(b)			
Cranberries	0.05	--	Temporary tolerance associated with a FIFRA section 18 that will expire 12/31/03.
Grass, forage	1.0	--	Tolerance expired 12//31/01.
Tolerances Listed Under 40 CFR §180.317(c)			
Peas, dried	0.05	TBD	Pea, field, seed. European data currently used to support tolerance. Registrant needs to submit field trial data as confirmatory data.
Rhubarb	0.1	0.1	
Tolerances To Be Proposed Under 40 CFR §180.317(c)			
Pea, field, hay	–	TBD	
Pea, field vines	–	TBD	

*TBD=To Be Determined

Risk Mitigation:

As a result of risk concerns for children identified in the March 8, 2002 risk assessment, Dow AgroSciences agreed to voluntarily cancel all product labeled for residential use (EPA Reg. No. 8660-85; see 67 FR 13627). Additionally, in order to further address this risk concern and minimize the likelihood of non-dietary exposure to children, the following label statement must appear on Pronamide end-use products:

> "This product may only be used on turf grown for seed or sod or on non-residential sites including golf course, industrial and office building sites, stadium fields or professional athletic fields."

To minimize adult non-occupational exposure, the following label statement must appear on Pronamide end-use products:

> "For all uses except those specified below, do not enter or allow others to enter until sprays have dried. When applied to stadium or professional athletic fields, water-in immediately after application or, do not enter or allow others to enter treated area for 24-hours after application. If product is watered-in after treatment, do not enter or allow other persons to enter until area had dried"

The risk assessment also identified a slight cancer risk due to pronamide exposure in drinking water from surface water sources (EECs are 4.3 ppb compared to the cancer DWLOC of 1.1 ppb). However, the Agency is not concerned because of the conservative inputs used in the surface water modeling. The PRZM-EXAMS assessment was based on the maximum label rates for pronamide, whereas typical rates for many crops are 25%-50% less. The model also assumed a Percent Crop Area (PCA) of 87%, which is likely to be an overestimate for the crops being considered. In addition, pronamide data exists for only one soil in the aerobic soil metabolism study. When aerobic soil metabolism data is only available in one soil, a conservative extrapolation factor is used which is likely to contribute to over-estimating potential persistence and exposure. As a result, Dow AgroSciences has agreed to conduct an aerobic soil metabolism study (two additional soils) and an aerobic aquatic metabolism study as confirmatory data.

The Agency will be issuing a generic Data Call-In (DCI) that outlines further data requirements for this chemical. The following additional data are required for pronamide. The registrants of pronamide must respond within 90 days of receipt of this letter from the Agency.

Most pertinent product chemistry data requirements are satisfied for technical grade active ingredients. The following is required:

- Product Chemistry

GDLN	Description
860.1200	Direction for use
860.1380	Storage Stability Data

Additional data are also required for the 51% Formulation Intermediate (FI) concerning the following:

GDLN	Description
830.6314	oxidation/reduction
830.6316	explodability
830.6317	storage stability
830.6320	corrosion characteristics

The registrant must either certify that the supplier of beginning materials and the manufacturing processes have not changed since the last comprehensive product chemistry reviews or submit complete updated product chemistry data packages.

Although there is confidence in the overall scientific quality of the available toxicity data, several data gaps were identified which are required to fulfill the OPPTS harmonized test guidelines:

- Toxicity

GDLN	Description
870.3700	developmental study in rats
Non GDLN	comparative thyroid rat assay in adult animals and offspring
870.3200	21-day dermal toxicity study
Non GDLN	28-day inhalation study
870.7600	dermal penetration study

A review of registered uses and the supporting residue chemistry data indicates the following residue data are required:

- Residue (GDLN 860.1500 Crop Field Trials)

dried winter peas
vines and hay of winter peas

Confirmatory storage stability data (GDLN 860.1380) are required for regulated pronamide metabolites on the following:

alfalfa
apples
grapes
lettuce
peaches
plums

A confirmatory aerobic soil metabolism study (835.4100) and an aerobic aquatic metabolism study (835.4300) are required.

The registrant is required to further optimize/improve the revised animal enforcement method (TR 34-91-68) to yield acceptable recoveries at a fortification level equal to established animal tolerances. Following method improvement, the registrant is required to submit bridging independent laboratory validation (ILV) data; the required ILV data should include two control samples fortified at 0.4 ppm, the reassessed tolerance level for the kidney and liver of ruminants.

The following label amendments are required for lettuce, peas, and alfalfa grown for seed:

GDLN	Description
860.1850	Confined Accumulation in Rotational Crops
860.1900	Field Accumulation in Rotational Crops • 30-day plant-back interval for leafy vegetables (except *Bra*ssica vegetables) • 90-day plant-back interval for root and tuber vegetables • 360-day plant-back interval for cereal grains, forage and fodder, and straw of cereal grain

If you have questions on this document, please contact the Chemical Review Manager, Cecelia Watson, at (703)305-4329. For questions regarding label changes and registration action, please contact Jim Tompkins of the Registration Division at (703) 305-5697.

Sincerely,

Lois A. Rossi, Director
Special Review and
Reregistration Division

Enclosures:

- Overview and Summary of Pronamide (Propyzamide) Risk Assessment
- Hazard Identification Assessment Review Committee (HIARC) report (M. Centra, December 10, 2001)
- Report of the FQPA Safety Factor Committee (C. Christensen, December 19, 2001)
- Toxicology Chapter of the Tolerance Reassessment Eligibility Decision (TRED) (M. Centra, March 7, 2002)
- Report of the Mechanism of Toxicity Assessment Review Committee (MTARC) (M. Centra, January 21, 2001)
- Review of Pronamide Incident Reports (J. Blondell & M.. Spann, August 12, 2001)
- Chronic and Cancer Dietary Exposure Assessments (D. Soderberg, et al., February 7, 2002)
- Pronamide Residue Chemistry chapter (J. Morales, February 28, 2002)
- Residential Risk Assessment, (B. O'Keefe, March 7, 2002)
- Drinking Water Assessment to Support TRED for Propyzamide (Pronamide) (L. Shanaman, May 16, 2001)
- Addendum to EPA March 8, 2002: Pronamide. Tolerance Reassessment Eligibility Decision (TRED). (G. Bangs May 21, 2002)
- Tier II Water Assessment to Support TRED for Pronamide (Propyzamide) (L. Shanaman, May 31, 2002).

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

OFFICE OF
PREVENTION, PESTICIDES,
ANDTOXIC SUBSTANCES

March 8, 2002

MEMORANDUM

SUBJECT: Pronamide. Tolerance Reassessment Eligibility Decision (TRED). Chemical ID No. 101701. DP Barcode No. D275194.

FROM: Gary Bangs, Risk Assessor
Michelle Centra, Pharmacologist
Jose Morales, Chemist
Barry O'Keefe, Biologist
David Soderberg, Chemist

Reregistration Branch 3
Health Effects Division (7509C)

THRU: Catherine Eiden, Branch Senior Scientist
Reregistration Branch 3
Health Effects Division (7509C)

TO: Cecelia Watson, Chemical Review Manager
Michael McDavit, Acting Branch Chief
Reregistration Branch II
Special Review and Reregistration Division (7508W)

This memorandum and attachments constitute the Tolerance Reassessment Eligibility Decision (TRED) for pronamide and updates the Health Effects Division (HED) Chapter of the Reregistration Eligibility Decision Document (RED) for pronamide (August 24, 1993) taking into consideration requirements of the 1996 Food Quality Protection Act (FQPA). The Agency RED for pronamide was issued in May 1994. A Tolerance Reassessment Eligibility Decision (TRED) document is required because EPA completed the RED for pronamide before passage of the FQPA. This document only discusses the human health risk assessment required for reassessment of pesticide residue tolerances and does not revise the occupational risk assessment conducted in the 1993 HED human health risk assessment document. Therefore, data submitted for assessment of occupational exposure have been used only for non-dietary (i.e., residential) risk assessment under FQPA. Cumulative risk assessment considering risks from other pesticides which have a common mechanism of toxicity is also not addressed in this

document.

NOTE: Only the Rohm and Haas 94.6% technical and 51% wettable powder formulation are subject to the tolerance reassessment. Rohm and Haas sold this product to Dow Agro Sciences (Letter sent to J. Tompkins in RD, 9/21/01). In addition, Earth Care, Division of United Industries Corp., (previously Pursell Industries) has requested voluntary cancellation of the product GREEN UP KERB 50W, EPA Reg. No. 8660-85, which is the only label which contains a residential turf use. However, as of the time of this TRED, the product is registered and a postapplication residential exposure and risk assessment have been included in this document. Cancellation of the GREEN UP label (8660-85) would eliminate all uses that result in potential public or residential exposure.

Attachments:

- Hazard Identification Assessment Review Committee (HIARC) report (M. Centra, December 10, 2001)
- Report of the FQPA Safety Factor Committee (C. Christensen, December 19, 2001)
- Toxicology Chapter of the Tolerance Reassessment Eligibility Decision (TRED) (M. Centra, March 7, 2002)
- Report of the Mechanism of Toxicity Assessment Review Committee (MTARC) (M. Centra, January 21, 2001)
- Review of Pronamide Incident Reports (J. Blondell & M.. Spann, August 12, 2001)
- Chronic and Cancer Dietary Exposure Assessments (D. Soderberg, et al., February 7, 2002)
- Pronamide Residue Chemistry chapter (J. Morales, February 28, 2002)
- Residential Risk Assessment, (B. O'Keefe, March 7, 2002)
- Drinking Water Assessment to Support TRED for Propyzamide (Pronamide) (L. Shanaman, May 16, 2001)

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1.0 EXECUTIVE SUMMARY

Purpose

A Tolerance Reassessment Eligibility Decision (TRED) document is required for pronamide (propyzamide). EPA completed the 1994 RED for pronamide before passage of the 1996 Food Quality Protection Act (FQPA). Consequently, pronamide is herein reassessed in accordance with the FQPA. This document only discusses the human health risk assessment required for reassessment of pesticide residue tolerances. Potential drinking water and residential exposure is also considered in order to estimate the potential aggregate risk. Cumulative risk assessment considering risks from other pesticides which have a common mechanism of toxicity is not addressed in this document.

Uses: Pronamide [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, nursery stocks, turf, and fallow land. Pronamide is a restricted use herbicide applied as a liquid spray, which is packaged in water soluble pouches and then mixed in water before application. It is a soil active systemic herbicide with uptake by susceptible weeds occurring through the roots. Application rates range from 0.5 to 6 lbs active ingredient (ai) per acre per application, with one to four applications per year, but no more than 8 lbs ai per acre per year.

Only the Rohm and Haas 94.6% technical and 51% wettable powder formulation are subject to the tolerance reassessment. Rohm and Haas sold this product to Dow Agro Sciences (Letter sent to J.Tompkins in RD, 9/21/01). In addition, Earth Care, Division of United Industries Corp., (previously Pursell Industries) has requested voluntary cancellation of the product GREEN UP KERB 50W, EPA Reg. No. 8660-85 (letter to C. Watkins, B. Metzger, 1/14/02), which is the only label containing a residential/recreational turf use. Cancellation of the GREEN UP label (8660-85) would eliminate all uses that result in potential public or residential exposure.

Hazard Assessment

Pronamide technical 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.

The active ingredient pronamide appears to be a liver toxicant. Adverse liver-related effects (increases in liver weight and/or liver-related serum enzymes and/or histopathology) were consistently observed in every animal species studied, including the rat (subchronic, chronic, and multi-generation reproduction studies), mouse (carcinogenicity studies), rabbit (developmental toxicity study), and dog (subchronic and chronic studies). Other target organs included the thyroid in rats (increase in weight and/or histopathology observed in the chronic toxicity/carcinogenicity and the multi-generation reproduction studies as well as a subchronic, special 13-week thyroid function study), the testes in rats (histopathology in the chronic toxicity/carcinogenicity study) and the kidneys, adrenal glands, thymus, heart, testes, and brain in dogs (increase in organ weights in the chronic toxicity study), and the pituitary in rats (histopathology observed in the subchronic and multi-generation reproduction studies).

There was no quantitative or qualitative evidence of 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 multigeneration reproduction study in rats, any observed toxicity to the fetuses or offspring occurred at equivalent or higher doses than did toxicity to parental animals. In the rat developmental toxicity study, the highest dose of pronamide tested exceeded the doses tested in both the rabbit developmental toxicity study and the rat multigeneration reproduction study without demonstrating toxicities in either maternal animals or fetuses. Since this study failed to provide evidence concerning the potential increased susceptibility to infants and children (a LOAEL was not be established) as required by the Food Quality Protection Act (FQPA) of 1996, a repeat developmental toxicity study in the rat is required to fulfill the OPPTS harmonized test guideline 870.3700.

Results of the battery of mutagenicity studies (forward and reverse gene mutation, *in vivo* and *in vitro* cytogenetic/structural chromosome aberration and unscheduled DNA synthesis assays) indicate that pronamide is not a mutagenic agent. However, the Carcinogenicity Peer Review Committee (CPRC) classified Pronamide as a group B2 - probable human carcinogen (with inadequate evidence in humans) based on the finding of two tumor types in the rat (benign testicular interstitial cell tumors and uncommon thyroid follicular cell adenomas) and one tumor type in the mouse (hepatocellular carcinomas). A linear, low dose approach (Q_1*) is used for human risk characterization. The most potent unit risk Q_1*, based on male mouse liver adenoma and/or carcinoma combined tumor rates, is 2.59×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents [converted from animals to humans by use of the $(mg/kg\ body\ weight)^{3/4}$ interspecies scaling factor].

Pronamide has been identified by the Agency's Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) as a potential endocrine disruptor. Evidence of endocrine effects from several guideline toxicity studies as well as two special studies submitted to the Agency by the Registrant include, in part,: (i) histopathology of the thyroid gland, pituitary gland, adrenal glands, testes and ovaries, (ii) changes in hormone levels; decreased T4 and increased TSH, LH and FSH, and (iii) the induction of enzymes such as cytochrome-P_{450} and -B_5, and NADPH-cytochrome-c-reductase in addition to those enzymes involved in the oxidation of testosterone.

Mammalian neurotoxicity studies for pronamide have not been conducted. However, since pronamide does not belong to a class of chemicals known to exhibit neurotoxicity, and there is no evidence of neurotoxicity seen in any of the existing studies, neurotoxicity studies (e.g., an acute delayed neurotoxicity study in the hen, a neurotoxicity screening battery or a developmental neurotoxicity study) are not required.

Pronamide is rapidly absorbed and completely and rapidly eliminated equally in the urine (40-61%) and feces (40-60%) within 7 days post-dosing. No bioaccumulation was apparent and very little unchanged pronamide was recovered in the urine. All of the fecal metabolites were unidentified and comprised less than 1% of the dose whereas two major urinary metabolites have been identified and quantified; 2-(3,5-dichlorophenyl)-4,4-dimethyl-5-carboxyoxazoline (metabolite SS47-70, 3.0-5.9% of the administered dose) and N-carboxymethyl-3,5-dichlorobenzamide (metabolite 10, 12.7-18.9% of the administered dose).

There is no acceptable dermal absorption study in the pronamide data base. In addition, there were no dermal toxicity studies submitted which could be used for comparison to oral toxicity studies. Therefore, a 100% (default value) dermal absorption factor was determined for risk assessment

purposes.

A FQPA safety factor is required for all population subgroups when assessing dietary and residential exposure scenarios because of the evidence of endocrine effects in the pronamide data base. However, the FQPA safety factor was reduced to 3x because: (i) the toxicological database is adequate for FQPA assessment (ii) there is no indication of quantitative or qualitative increased susceptibility of rabbits to *in utero* exposure or to rats following pre/post-natal exposure. Also, in the available, unacceptable rat study, no increased susceptibility was seen even though the animals could have tolerated higher doses (iii) a developmental neurotoxicity study is not required and (iv) the dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposures for infants and children.

Toxicological endpoints were established for all relevant exposure scenarios. Acute dietary exposure for females 13-50 years of age or for the general population is not assessed since there was no appropriate endpoint attributable to a single dose available in the pronamide data base. Two toxicological studies determined all toxicological endpoint doses used in the risk assessment: a prenatal developmental toxicity study in the rabbit and a chronic toxicity/carcinogenicity in the rat. A discussion of the dose-response relationships for chronic dietary endpoints as well as residential exposure endpoints follows the presentation of the summary of toxicological endpoint selection (See Table 3, Section 3.3 of the text).

A chronic reference dose (cRfD) of 0.08 mg/kg/day was determined on the basis of the two-year chronic toxicity/carcinogenicity study in rats and the application of an uncertainty factor of 100 (10x for inter-species extrapolation and 10x for intra-species variation). The NOAEL in this study was 8.46 mg/kg/day and the LOAEL was 42.59 mg/kg/day based upon increased relative liver weight and the non-neoplastic histologic changes in the liver (centrilobular hypertrophy and hepatocellular eosinophilic alteration in males and females), thyroid (follicular cell hypertrophy in males and females) and ovaries (sertoliform tubular hyperplasia in females). The 3x FQPA safety factor was applied to the chronic dietary risk assessment because there is evidence of endocrine effects (thyroid, testes, ovaries, adrenal glands, pituitary gland, thymus) identified in the majority of subchronic/chronic studies conducted across species. The cPAD is the cRfD adjusted for the FQPA safety factor. Therefore, the cPAD is 0.027 mg/kg/day. Dietary risk estimates which are less than 100% of the cPAD do not exceed HED's level of concern.

For risk assessments based on short-term (1-30 days) incidental oral, dermal and inhalation exposures, an adjusted dose of 8.46 mg/kg/day was established for use in this risk assessment. The dose selection is based on a maternal toxicity NOAEL of 5 mg/kg/day and the clinical signs (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes) observed at the LOAEL of 20 mg/kg/day in the developmental toxicity study conducted in rabbits. Although selection of this study for short-term exposure scenarios is appropriate for the route (oral) and duration (13 days), the NOAEL of 5 mg/kg/day is lower than the NOAEL (8.46 mg/kg/day) established in the chronic toxicity/carcinogenicity study in the rat. The apparent disparity between these NOAELs is driven by the doses of pronamide selected for testing in these studies. The Hazard Identification Assessment Review Committee (HIARC) concluded that using a more realistic NOAEL of 8.46 mg/kg/day rather than 5 mg/kg/day would provide a sufficiently protective dose for risk assessment. The 3x FQPA safety factor was also applied to these risk assessments because of the evidence of endocrine effects in the pronamide toxicity data base. Due to the lack of appropriate dermal or inhalation endpoints, absorption factors of

100% (default value) were used with the oral endpoints.

Intermediate- and long-term toxicity endpoints were also selected, however only short-term oral, dermal or inhalation exposures to pronamide are anticipated, based on its' use pattern.

Exposure and Risk Assessment

There is a potential for dietary (food and drinking water) exposure from commercial applications of pronamide in agriculture and for postapplication dermal and incidental oral exposures from residential/recreational uses (lawns and turf). If the label allowing residential/recreational turf uses is canceled, the nondietary exposures will be eliminated. The occupational exposure was assessed in the 1993 HED RED chapter. However, because this is a tolerance reassessment document, only non-occupational dietary and residential postapplication exposures to pronamide are considered in this document. Short-term, chronic and cancer exposures were assessed for pronamide residues in food and water.

A review of incident data sources found that relatively few incidents of pronamide poisonings were reported. There are only two Poison Center reports, no incident reports in OPP's Incident Data System and only two reports from the California Pesticide Illness Surveillance Program.

Dietary

The dietary risk assessment for chronic exposures to pronamide shows that chronic dietary exposure to pronamide is not a significant exposure pathway. As stated previously, an acute toxicity endpoint was not selected, therefore an acute exposure assessment was not conducted. Refined tier 3 chronic and cancer dietary exposure assessments were conducted for all supported food uses (i.e., all currently registered and proposed uses). Pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety are the residues of concern and are included in the assessment. Although tolerance level residues were used for four registered crops (dried peas, endives, radicchio, and cranberries), the assessment was based primarily upon residue monitoring data for fruits and vegetables and upon calculation of anticipated residues for meat, milk, poultry and eggs, and is the most refined assessment to date for pronamide. These data are based mostly upon non-detectable residues. Estimates of percent crop treated (%CT) generated by the Biological and Economic Analysis Division (BEAD) were used to further refine the dietary exposure assessment.

Estimates were generated for chronic (long-term) and cancer dietary exposure using the most recent version of the Dietary Exposure Evaluation Model (DEEM™, Version 7.75). This assessment showed that the chronic dietary risk estimates are below the Agency's level of concern (<100% of the cPAD) for the U.S. population and for all population subgroups. The chronic dietary exposure estimates for the two most highly exposed population subgroups, children (1-6) and seniors (55+), are both estimated at 0.000005 mg/kg/day (<1% cPAD). The cancer dietary risk estimate is 1.06×10^{-7} for the U.S. population, and is below the level that the Agency generally considers to be of concern (1.0×10^{-6} or one in one million).

Residential Postapplication Exposure

Based on the application frequency and rate of residue dissipation, only short-term residential

postapplication exposures to pronamide are anticipated after lawn and turf treatments. A margin of exposure (MOE) of 300 (10x for interspecies extrapolation, 10x for interspecies variation and a 3x FQPA safety factor) is required for short-term incidental oral, dermal and inhalation risk assessments. Therefore, short-term residential risk estimates with a MOE > 300 do not exceed the level of concern.

The risk assessment for short-term residential postapplication exposure indicates that dermal exposures to pronamide are a significant pathway of exposure. All pronamide end use products are labeled as restricted use pesticides. Therefore, consumers are restricted from handling or applying pronamide products. Consequently, only residential/recreational postapplication exposures to the general population are anticipated and are evaluated in this assessment. Adults and children are potentially exposed to pronamide residues via the dermal route after application of pronamide products by professional lawn care operators (LCOs) in residential/recreational settings. Inhalation exposure to pronamide is not anticipated after application due to the low vapor pressure of the active ingredient and outdoor air dilution. Incidental oral exposure is expected to occur for small children and is combined with their dermal exposures, where applicable (i.e., playing on turf). Residential exposures were estimated based on label application frequency and the persistence of pronamide. Most assumptions for risk estimation were based on the Agency's Residential SOPs. Residents are assumed to play or work on treated lawns or recreational turf within the first 24 hours of spraying. Only short-term risks from residential postapplication dermal and incidental oral exposures are anticipated since turf residues dissipate below the limit of quantitation by day 14 following application (based on the submitted pronamide turf transferable residue (TTR) study).

Risk estimates based on residue data from the TTR study for short-term dermal exposures to treated turf during high contact lawn activities on day zero following application (DAT 0) exceed HED's level of concern, i.e. result in MOEs < 300 for adults (MOE = 71) and children (MOE = 42). After the turf was watered, residues declined sufficiently that all risk estimates were below the level of concern for adults (MOE = 890) and children (MOE = 530). However, label language regarding immediate watering-in after application to turf is neither required nor enforceable for consumers. Risk estimates for short-term dermal contact with residues on treated turf during the low contact activities of grass mowing or golfing on the day of treatment do not exceed the level of concern for adults (MOEs 2100 and 1000, respectively). Postapplication cancer risk was estimated using 14-day average residues and only a single day's activity, based on a single dormant season application. The estimated cancer risk from one day per year of high-contact (e.g., playing on lawn) postapplication dermal exposure to pronamide treated turf was 8.4×10^{-7} and did not exceed the Agency's level of concern of 1×10^{-6}. Other, lower contact activities (e.g., golfing) could be conducted for several days without exceeding the level of concern.

The risk estimates for small children's incidental ingestion of pronamide from treated turf indicate that risks do not exceed the level of concern (i.e. MOEs > 300) for hand-to-mouth (MOE = 380), ingestion of soil (MOE = 113,000), and object to mouth (MOE = 1500) scenarios. The small children's combined oral hand-to-mouth incidental ingestion scenarios (MOE = 300) also do not exceed the level of concern. When risks from dermal exposures to pronamide by small children are combined with risks from incidental oral exposures, the combined short-term risk estimates exceed the level of concern (MOEs < 300), with a MOE of 37. There is significant uncertainty involved in predicting co-occurrence of exposures by different routes and in adding these scenarios, as well as the degree of conservatism generated in the combined risk estimate.

Drinking Water

Risk assessment for short-term and chronic exposure to pronamide indicates that drinking water is not a significant exposure pathway, but may be of some potential concern for cancer. Risk estimates for exposure to pronamide in drinking water are assessed by comparing drinking water levels of comparison (DWLOCs) to the estimated environmental concentrations (EECs) of pronamide in surface water and groundwater. In the case of pronamide, there are monitoring data available for surface and ground water. The monitoring database used in the risk assessment is considered to be of good quality (US Geological Survey), but the data are not specific to pronamide use areas. Therefore they are cited for comparison, rather than verification of modeling estimates.

A Tier I Drinking Water Assessment for pronamide was calculated (L. Shanaman, May 16, 2001) using the SCIGROW model to provide groundwater EECs. The Tier I groundwater concentration estimates were predicted from application of pronamide at maximum label rate, and represent upper-bound estimates of the concentrations that might be found in shallow groundwater at vulnerable sites due to the use of pronamide/propyzamine. The resulting modeled groundwater screening concentration is 3.0 ppb, which does not exceed the DWLOC for short-term exposure for the most sensitive populations (females >55 years) of 560 ppb.

The Tier II PRZM-EXAMS model (L. Shanaman, *in progress*, 2002) was used to predict EECs for pronamide in surface water, i.e., 90^{th} percentile average annual concentration values for use in chronic exposure assessments, and 36-year mean concentration values for use in "cancer" exposure assessments. Maximum label application rates were used for major use crops. Chronic exposure values ranged from 1.5 to 6.4 ppb, which are lower than the chronic DWLOC of 300 ppb for the most sensitive populations, infants and children. Conservative inputs were used for the environmental (soil and water metabolism) assumptions, i.e., 2-3x uncertainty factors were applied to soil and water half-lives used in the PRZM-EXAMS assessment.

The Tier II cancer risk assessment for exposure to pronamide in water indicates that drinking water may be a significant exposure pathway. The the refined Tier II modeling result is greater than the aggregate cancer DWLOC estimate of <0.1 ppb and therefore exceeds the cancer level of concern of 1×10^{-6}. The estimated DWLOC for cancer based on dietary exposures only (food + water) is 1.2 ppb, which is below some of the drinking water concentrations estimated by EFED and above others (0.535 - 4.3 ppb for surface water and 3 ppb for groundwater) and therefore is of concern for some scenarios. Surface and ground water monitoring data are available for pronamide from routine USGS sampling, and are being analyzed to determine if they provide support for the modeling estimates.

Aggregate Exposure

Aggregate risk assessments were conducted for short-term and chronic exposures, and for cancer. All of the aggregate risk estimates are considered high-end, or conservative, due to the compounding of conservative assumptions in individual exposure route estimates. Aggregate risk estimates for acute exposures were not conducted as no acute endpoint was selected from the toxicity database. Because there are no intermediate-term or chronic non-dietary exposures to pronamide, the chronic aggregate risk assessment only considers exposures from dietary (via food and drinking water) consumption. HED has no concerns for aggregate chronic exposures to pronamide residues in food and drinking water.

Estimated drinking water exposures using Tier 2 modeling and actual sampling data for surface water and groundwater result in equivocal cancer risk estimates of approximately 1 to 3 x 10^{-6}, independent of dietary and residential exposures to pronamide. Therefore, HED has some concerns for the potential exposures from surface and groundwater sources under the cancer asessment, particulary for the scenario assessed surface water for alfalfa in California. Aggregated exposures from food, water, and residential uses result in cancer risk estimates that further exceed HED's level of concern for cancer.

The short-term aggregate risk assessment conducted for pronamide considered ingestion of food and drinking water, combined with postapplication dermal and incidental oral exposures. Because the risk estimates for high-contact dermal exposures for both children and adults alone are of concern, a short-term aggregate exposure assessment was not conducted for those populations and scenarios, as they would only further exceed the HED's level of concern. Risk estimates are in excess of the level of concern (MOE < 300) for short-term dermal exposures to pronamide residues on turf for adults (MOE = 71) and children (MOE = 42) engaged in high-contact activities, such as playing on treated turf immediately after pronamide application.

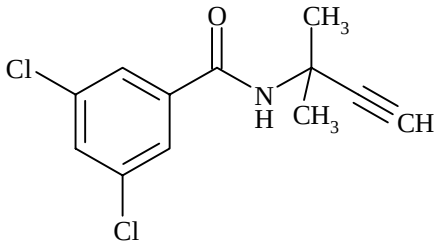
However, as the risk estimate for short-term exposures of adults golfing does not exceed HED's level of concern, HED included this short-term residential exposure with food and drinking water exposure in a short-term aggregate risk assessment. The aggregate risk estimate for food and golfing exposure was a MOE of 1050, and there was still enough room to add the estimated drinking water exposure without exceeding the HED DWLOC. This short-term aggregate risk estimate including adults engaged in low-contact activities on turf may be useful in risk management decisions. HED notes that all of the residential scenarios with risk estimates of concern, including the aggregate cancer risk estimate are considered high-end estimates based on standard HED assumptions and a 100% dermal absorption factor.

Data Gaps

Most pertinent product chemistry data requirements are satisfied for the Rohm and Haas 94.6% T/TGAI, and 51% FI. Some additional physical chemistry and processing information are required. There is confidence in the overall scientific quality of the available toxicity data, but several data gaps were identified: a developmental toxicity study in rats, a 21-day dermal toxicity study, 28-day inhalation toxicity study, a dermal penetration study and a comparative thyroid rat assay in adult animals and offspring. Some label amendments and data submissions are required, including additional residue data for use on grasses, dried winter peas (outstanding), the vines and hay of winter peas, grass forage, and hay. The registrant is required to improve the analytical method for animal residue data; and to submit bridging independent laboratory validation data. Additional confirmatory storage stability data for the regulated pronamide metabolites on alfalfa, apples, grapes, lettuce, and peaches or plums are required.

2.0 PHYSICAL CHEMICAL PROPERTIES CHARACTERIZATION

The chemical name for pronamide is [3,5-dichloro-N-(1,1-dimethyl-2-propynyl)benzamide]. The chemical structure is



Empirical Formula:	$C_{12}H_{11}NOCl_2$
Molecular Weight:	256.13
CAS Registry No.:	23950-58-5
PC Code:	101701

Technical pronamide is a white crystalline solid with a melting point of 155-156 °C, specific gravity of 0.48 g/cc, octanol/water partition coefficient (log P_{OW}) of 3.05-3.27, and vapor pressure of 8.50×10^{-5} torr at 25 °C. Because of its' low vapor pressure, pronamide is not expected to present an inhalation exposure risk when used outdoors. There are no toxicologically significant impurities in the manufacturing process.

3.0 HAZARD CHARACTERIZATION

The active ingredient pronamide appears to be a liver toxicant. Adverse liver-related effects (increases in liver weight and/or liver-related serum enzymes and/or histopathology) were consistently observed in every animal species studied. Other target organs included the thyroid, testes and pituitary in rats, and the kidneys, adrenal glands, thymus, heart, testes, and brain in dogs.

3.1 Hazard Profile

Acute Toxicity

The acute toxicity data base for pronamide technical is considered complete. No additional studies are required at this time. Pronamide technical 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. The acute toxicity data for pronamide is summarized below in Table 1.

Table 1. Acute Toxicity of Pronamide (Propyzamide)				
Guideline Number	**Study Type**	**MRID Number**	**Results**	**Toxicity Category**
870.1100 (§81-1)	Acute Oral - Rat, > 92.0% a.i.	00085505	LD_{50} (males and females) is greater than 5000 mg/kg	IV
870.1100 (§81-1)	Acute Oral (Limit test) - Rat, 95.7% a.i.	43583901	LD_{50} (males and females) is greater than 5000 mg/kg	IV
870.1200 (§81-2)	Acute Dermal (Limit Test) - Rabbit, 95.7% a.i.	43583902	LD_{50} (males and females) is greater than 2000 mg/kg	III
870.1300 (§ 81-3)	Acute Inhalation - Rat, 95.7% a.i.	44034201	LC_{50} is greater than 2.1 mg/L following a 4 hour exposure	III
870.2400 (§81-4)	Primary Eye Irritation - Rabbit, 95.7% a.i.	43583904	Mild occular irritant	IV
870.2500(§ 81-5)	Primary Dermal Irritation - Rabbit, 95.7% a.i.	43583903	Slight dermal irritant	IV
870.2600 (§81-6)	Dermal Sensitization - Guinea pig, > 92.0% a.i.	00062605	Not a sensitizer	N/A

Subchronic Toxicity

The data base for subchronic toxicity is considered incomplete. The HIARC identified two subchronic toxicity study data gaps and recommended the following studies be conducted in order fulfill the requirements cited for a food/feed use chemical (40 CFR 158.340):

1) a 21-day dermal toxicity study (guideline 870.3200; old 82-2); and
2) a 28-day inhalation toxicity study (non-guideline)

However, the pronamide subchronic data base does contain two acceptable studies conducted in the rat that can be used for regulatory purposes; a 4-week oral toxicity study (non-guideline) and a 13-week oral toxicity study (guideline). In the non-guideline, 4-week study, systemic toxicities were noted in males treated with 37.24 or 74.05 mg/kg/day pronamide and in females treated with 43.65 or 87.65 mg/kg/day pronamide. These toxicities were limited to the liver and included increases in absolute and relative (to body) liver weights (males: both doses; females: high-dose) and a positive trend in the increased incidence of centrilobular hypertrophy (males). When pronamide was administered in the diet for 13 consecutive weeks, male rats treated with 60.0 mg/kg/day and females rats treated with 74.6 mg/kg/day presented with the following systemic toxicities in one or both sexes: decreased body weight, body weight gain and food consumption, increased blood cholesterol levels, increased relative (to body) liver weights and incidence of hepatic centrilobular hypertrophy. At the highest dose tested (254.0 mg/kg/day for males and 289.2 mg/kg/day in females), many of these toxicities were observed in both

sexes and showed an increase in incidence and/or severity. The following additional changes were also observed in high-dose animals: clinical signs (brown and/or yellow staining of the anogenital area (males), increased enzyme activity (SGOT and alkaline phosphatase) in males, triglyceride blood levels (females), increased absolute liver weights (males and females), and increased incidences of thyroid follicular cell hypertrophy (males and females) sexes and anterior pituitary cellular hypertrophy (males). After 4 weeks of recovery, most of the adverse effects observed at the high-dose were partially or completely reversed with the exception of the increase in incidence of pituitary cellular hypertrophy (males only).

Reproductive & Developmental Toxicity

There was no quantitative or qualitative evidence of increased susceptibility in the fetuses or the offspring of rats or rabbits following pre- and/or postnatal exposure to pronamide. Fetal/offspring effects in both of these species were observed at either the same or higher dose levels which produced maternal/parental toxicity. In the developmental toxicity study in rabbits, abortions were observed at a higher dose level (80 mg/kg/day) compared to the dose (20 mg/kg/day) at which maternal toxicity (soiled anal area, anorexia and punctate vacuolation of hepatocytes) was observed. Also, no evidence of increased susceptibility was demonstrated in the two-generation reproduction study in rats. Offspring toxicity (decreased combined male/female pup weight/litter) was observed at the same dose that caused parental toxicity (decreased body weight and food consumption in both sexes, increased incidences of histopathology of the liver, adrenal gland, thyroid gland, and anterior pituitary gland in both P1 and P2 generations, and increased incidences of uterine gross pathology in P2 females). Parental and offspring toxicities were observed at the same LOAEL of 1500 ppm (130.1 mg/kg/day for males and 120.7 mg/kg/day for females).

Evidence for susceptibility could not be ascertained in the developmental toxicity study conducted in rats. No toxicities were observed in either maternal animals or fetuses at any dose tested (5-160 mg/kg/day); a LOAEL could not be established in the rat developmental toxicity study. Since this study failed to provide evidence concerning the potential increased susceptibility to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, a repeat developmental toxicity study in the rat is required to fulfill the OPPTS harmonized test guideline 870.3700.

Chronic Toxicity: Following chronic exposure (mid-dose and/or high-dose groups; 33.1 mg/kg/day and/or 67.7 mg/kg/day) in dogs, systemic toxicities presented as decreased body weights, body weight gains, food consumption, serum albumin, platelet counts, increased enzyme activity (alkaline phosphatase, alanine aminotransferase, and gamma glutamyltransferase), increased absolute and/or relative weights of the thyroid, liver, heart, testes, adrenal glands, kidneys and thymus, and histopathology of the liver (hepatocytic hypertrophy, hyperplasia and granular brown pigmentation/mononuclear infiltration of Kupffer cells) and kidneys (granular brown pigment in the epithelial cells of the proximal convoluted tubules). In rats, the toxicities observed included decreased body weight/body weight gain, increased liver weight and histopathology of the liver (hypertrophy accompanied by eosinophilic cell alteration), thyroid (follicular cell hypertrophy and hyperplasia), and ovaries (sertoliform tubular hyperplasia) at 42.59 mg/kg/day (LOAEL). In the carcinogenicity study conducted in mice, systemic toxicities observed at the LOAEL of 75 mg/kg/day were limited to decreased body weight/body weight gain, increased liver weight and histopathology of the liver (hypertrophy, nodules/masses, parenchymal necrosis, and cholestasis). Under the conditions of this study, there was evidence of a treatment-related increase in tumor incidence in the liver of male mice when compared to controls. Dosing is considered adequate to assess the carcinogenic potential of

pronamide based on liver effects (non-neoplastic lesions and increased weight).

Mutagenicity: With the exception of one gene mutation assay, the remaining five mutagenicity studies were determined to be acceptable for regulatory purposes (The acceptable studies satisfy the 1991 mutagenicity guideline requirements). The results from these studies indicate that pronamide was not mutagenic in *Salmonella typhimurium, Escherichia coli* or in cultured Chinese hamster lung cells and did not produce a genotoxic response in *Bacillus subtiltis* or in cultured primary rat hepatocytes. There was also no evidence of clastogenicity in cultured Chinese hamster ovary cells and pronamide administration did not result in the induction of micronucleated polychromatic erythrocytes in bone marrow of mice. Overall, the data suggest that pronamide is negative for mutagenicity *in vitro* and *in vivo*.

Carcinogenicity: The Carcinogenicity Peer Review Committee (CPRC) classified Pronamide as a group B2 - probable human carcinogen with inadequate evidence in humans (Memorandum: E. Rinde, May 26, 1993). This decision was based on the finding of two types of tumors in the rat (benign testicular interstitial cell tumors and uncommon thyroid follicular cell adenomas), and one type of tumor in the mouse (hepatocellular carcinomas). A linear, low dose approach (Q_1*) is used for human risk characterization and the tumor incidence data used in this calculation is derived from the 1982 mouse carcinogenicity study (MRID 00114114, 00151822). The most potent unit risk Q_1*, based on male mouse liver adenoma and/or carcinoma combined tumor rates, is 2.59×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents [converted from animal to humans by use of the $(mg/kg\ body\ weight)^{3/4}$ interspecies scaling factor] (Memorandum: L. Brunsman, October 26, 2001).

Neurotoxicity: Mammalian neurotoxicity studies for pronamide have not been conducted. However, since pronamide does not belong to a class of chemicals known to exhibit neurotoxicity, and there is no evidence of neurotoxicity seen in any of the existing studies, neurotoxicity studies (e.g., an acute delayed neurotoxicity study in the hen, a neurotoxicity screening battery or a developmental neurotoxicity study) were not required.

Metabolism: Pronamide is rapidly absorbed from the gastrointestinal tract and extensively and rapidly metabolized; 93-103% the radioactivity administered was recovered . It is excreted (7 days post-dosing) equally in both the urine (40-61%) and the feces (40-60%). No bioaccumulation was apparent; radioactivity recovered in all tissues were consistently highest at the first sampling time (8 hours post-dose) then gradually declined to insignificant levels 7 days after dosing. 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 hrs (females)] and that of the high dose rats was monophasic [t½ = 24.1 hrs (males) and 24.8 hrs (females)]. Tissues with the highest radioactivity contents were, in decreasing order, the fat, adrenals, bone marrow, thyroids, liver, kidney, and plasma. Very little unchanged pronamide was recovered in the urine and no significant difference in the urinary metabolite profile was observed between the doses or the sexes. Approximately 27 unidentified metabolites were found in the urine and none exceeded 3.3% of the dose whereas all of the fecal metabolites were unidentified and comprised less than 1% of the dose. Two major urinary metabolites have been identified and quantified; 2-(3,5-dichlorophenyl)-4,4-dimethyl-5-carboxyoxazoline (metabolite SS47-70, 3.0-5.9% of the administered dose) and N-carboxymethyl-3,5-dichlorobenzamide (metabolite 10, 12.7-18.9% of the administered dose).

Dermal Absorption/Toxicity: No dermal penetration study conducted with pronamide technical is available in the toxicity data base. A dermal penetration study conducted with the Kerb 50W and 3.3F

pronamide formulations was submitted, however, this study was classified as unacceptable-guideline (the actual doses applied to the skin were not determined and there were discrepancies in the percent radioactive recovery). In addition, there were no dermal toxicity studies submitted which could be used for comparison to oral toxicity studies. Therefore, a 100% (default value) dermal absorption factor was determined for risk assessment purposes. A repeat dermal penetration study in the rat is required to fulfill the OPPTS harmonized test guideline 870.7600.

Endocrine Effects:

Pronamide is an organochlorine herbicide which has been identified by the Agency's Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) as a potential endocrine disruptor. Evidence of endocrine effects from several guideline toxicity studies as well as two special studies submitted to the Agency by the Registrant include, in part: (i) histopathology of the thyroid gland, pituitary gland, adrenal glands, testes and ovaries, (ii) changes in hormone levels; decreased T4 and increased TSH, LH and FSH, and (iii) the induction of enzymes such as cytochrome-P_{450} and -B_5, and NADPH-cytochrome-c-reductase in addition to those enzymes involved in the oxidation of testosterone.

Two special studies were conducted by the Registrant to evaluate pronamide's effect on hormonal balance in support of a threshold mechanism for the induction of thyroid and testicular neoplasms. Although the results of these special endocrine studies are suggestive of a pronamide-induced thyroid and testicular neoplastic effect via disruption of the pituitary-thyroid and pituitary-testis hormonal balance, these data are far from conclusive. Based on the absence of any additional information as well as the Mechanism of Toxicity Assessment Review Committee's (MTARC) evaluation of the existing pronamide toxicology data base (Memorandum: M. Centra, January 21, 2001) and the Agency's previous hazard characterization of this active ingredient (Memorandum: N. Thoa, May 26, 1993), it was determined that the postulated threshold mechanism for the induction of thyroid and testicular neoplasms is not supported by the available data. Therefore, HED has recommended that additional studies be conducted with pronamide to determine its mechanism of endocrine toxicity. One such study, a comparative assay in the rat that is designed to assess thyroid function in adult animals and their offspring as well as potential central nervous system effects in the young, is required because of the endocrine toxicities observed in various organ systems (thyroid gland, testes, ovaries, adrenal glands, pituitary gland) of rats and/or dogs.

The toxicity study profile is summarized in Table 2.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.3100 (§82-1a) 4-Week Oral Toxicity - Rat	MRID 42669402 (6/18/87)/Acceptable-Nonguideline ppm = 0, 500, or 1000 mg/kg/day (males) = 0, 37.24, or 74.05 mg/kg/day (females) = 0, 43.65, or 87.65	NOAEL = less than 500 ppm (37.24 mg/kg/day for males; 43.65 mg/kg/day for females) LOAEL = less than or equal to 1000 ppm (74.05 mg/kg/day for males; 87.65 mg/kg/day for females) based upon increased absolute and relative (to body) liver weights in males and females and a positive trend in increased incidence of liver centrilobular hypertrophy in males.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100 (§82-1a) 90-Day Oral Toxicity - Rat	MRID 42669403 (11/2/67)/Acceptable-Guideline ppm = 0, 40, 200, 1000, or 4000 mg/kg/day (males) = 0, 2.5, 12.3, 60.0, or 254.0 mg/kg/day (females) = 0, 3.1, 15.0, 74.6, or 289.2	NOAEL (males and females) = 200 ppm (12.3 mg/kg/day in males; 15.0 mg/kg/day in females) LOAEL = 1000 ppm (60.0 mg/kg/day in males; 74.6 mg/kg/day in females) based upon increased relative liver weights and increased incidence of centrilobular hypertrophy of the liver in both sexes, decreased body weight, body weight gain and food consumption in females and increased blood cholesterol levels in males.
870.3700 (§83-3a) Developmental Toxicity - Rat	MRID 40334501 (7/10/87)/Unacceptable-Guideline (not upgradeable) mg/kg/day = 0, 5, 20, 80, or 160	Maternal Toxicity NOAEL = greater than or equal to 160 mg/kg/day LOAEL = greater than 160 mg/kg/day (highest dose tested; LOAEL not established) Developmental Toxicity NOAEL = greater than or equal to 160 mg/kg/day LOAEL = greater than 160 mg/kg/day (highest dose tested; LOAEL not established)
870.3700 (§83-3b) Developmental Toxicity - Rabbit	MRID 00148065, 00148064 (6/4/85)/Acceptable-Guideline mg/kg/day = 0, 5, 20, or 80	Maternal Toxicity NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based upon clinical signs of toxicity (soiled anal area, anorexia and punctate vacuolation of hepatocytes) and liver effects (hepatocellular necrosis, eosinophilia, swelling of hepatocytes, pigmentation of Kupffer cells). Developmental Toxicity NOAEL = 20 mg/kg/day LOAEL = 80 mg/kg/day based upon abortions.
870.3800 (§83-4) Multigeneration Reproductive Toxicity - Rat	MRID 41540301 (1968)/Acceptable-guideline ppm = 0, 40, 200, or 1500 mg/kg/day (males) = 0, 3.1, 16.0, or 120.7 mg/kg/day (females) = 0, 3.6, 18.0, or 130.1	Parental/Systemic Toxicity NOAEL = 200 ppm (16.0 mg/kg/day for females and 18.0 mg/kg/day for males) LOAEL = 1500 ppm (120.7 mg/kg/day for females and 130.1 mg/kg/day for males) based upon decreases in body weight and feed consumption in both sexes and increased incidences of histology of the liver (centrilobular hepatocyte hypertrophy; both sexes), adrenal glands (zona glomerulosa cellular hypertrophy; both sexes), thyroid gland (follicular cell hypertrophy; females), and anterior pituitary gland (cellular hypertrophy; males) in both P1 and P2 generations, and increased incidences of uterine gross pathology (black foci/serosal surface) in P2 females. Reproductive Toxicity NOAEL = greater than or equal to 1500 ppm LOAEL = greater than 1500 ppm; not established

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.4100 (§83-1b) Chronic Toxicity - Dog	MRID 41807601,41807602, 4213030 (8/5/68)/Acceptable-Guideline ppm = 0, 300, 875, or 1750 mg/kg/day (males) = 0, 11.9, 33.1, or 67.7 mg/kg/day (females) = 0, 11.9, 36.1, or 69.0	NOAEL (males, females) = 300 ppm (11.9 mg/kg/day) LOAEL = 875 ppm (33.1 mg/kg/day in males; 36.1 mg/kg/day in females) based upon increased serum alkaline phosphatase (males), increased thyroid and liver weights (females), and increased incidence in liver histopathology (males and females; increased incidence of hepatocyte hypertrophy, granular pigmentation, mononuclear infiltration, and granular brown pigmentation in Kupffer cells).
870.4300 (§83-1/2a/5) Combined Chronic Toxicity/ Carcinogenicity -Rat	MRID 41714001, 41714002 (10/1/90)/Acceptable-Guideline ppm = 0, 40, 200, or 1000 mg/kg/day (males) = 0, 1.73, 8.46, or 42.59 mg/kg/day (females) = 0, 2.13, 10.69, or 55.09	NOAEL (males and females) = 200 ppm (8.46 mg/kg/day in males; 1069 mg/kg/day in females) LOAEL = 1000 ppm (42.59 mg/kg/day in males; 55.09 mg/kg/day in females) based upon increased relative liver weight and the non-neoplastic histologic changes in the liver (centrilobular hypertrophy and hepatocellular eosinophilic alteration in males and females), thyroid (follicular cell hypertrophy in males and females) and ovaries (sertoliform tubular hyperplasia in females). Rats fed diets containing 1000 ppm pronamide showed an increased incidence of thyroid follicular cell adenomas in male and female rats and benign testicular interstitial cell tumors in male rats. There was no progression of tumors to carcinomas. Under the conditions of this study, the dosing was considered to be adequate based upon decreased body weight gain and the non-neoplastic histologic changes in the liver.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.4200 (§83-2b) Carcinogenicity -Mouse	MRID 00107968 (1974)/Although this study would not normally meet the guideline requirement for a carcinogenicity study (870.4300) in this species (i.e., study deficiencies included lack of dietary analyses and food consumption to ensure homogeneity, stability, and concentration of test material in the diet, and to assess potential palatability problems with the diet), confidence in the reported tumor data is enhanced by the findings of a subsequent 1982 special carcinogenicity study in male mice (MRID 00114114) that confirm the tumor findings. If reviewed in conjunction with the 1982 study, the present study is adequate to assess the carcinogenic potential of pronamide in mice and it can be used for regulatory and risk assessment purposes. ppm = 0, 1000, or 2000 mg/kg/day = 0, 150, or 300	NOAEL (males, females) = not established LOAEL = 1000 ppm (150 mg/kg/day) based upon decreases in body weight gain in high-dose females and increases in relative (to body) weight of the liver in both sexes. Male and female B6C3F1 mice fed diets containing pronamide for 18 months showed a dose related increase in the incidence of hepatocellular carcinomas in male mice. Pronamide did not induce hepatocellular carcinomas in female mice. Under the conditions of this study, the dosing was considered to be adequate based upon decreases in body weight gain in high-dose females and increases in relative (to body) weight of the liver in both sexes at doses greater than or equal to 1000 ppm.
870.4300 (§83-1/2a/5) Carcinogenicity -Mouse (Males)	MRID 00114114, 00151822 (1982)/This special carcinogenicity study in the male mouse is classified as **Acceptable-Nonguideline**. The data confirmed the results of a previously conducted carcinogenicity study in mice (1974, MRID 00107968). When reviewed in conjunction with the 1974 carcinogenicity study, these two studies fulfill the guideline requirement for a carcinogenicity study [870.4200 (§83-2b)] in mice and can be used for regulatory and risk assessment purposes. ppm = 0, 20, 100, 500, or 2500 mg/kg/day = 0, 3, 15, 75, or 375	NOAEL (males) = 100 ppm (15 mg/kg/day) LOAEL = 500 ppm (75 mg/kg/day) based upon gross findings (increased incidences of hepatic nodules/masses and hepatic enlargement) observed after 24 months of treatment.
870.5100 (§84-2) Gene Mutation/ *In vitro* mammalian cell assay in Chinese hamster ovary [CHO] cells	MRID 40090601 (2/10/87)/Unacceptable-Guideline Fg/plate = 1, 10, 100 and 500	**Negative.** Pronamide did not induce a mutagenic or genotoxic effect in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 1, 10, 100 and 500 Fg/plate ± S9 activation.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.5100 (§84-2) Gene Mutation in *Salmonella typhimurium*, *Bacillus subtilis* and *Escherichia coli*	MRID 40090602 (8/10/78)/Acceptable-Guideline *Escherichia. coli* Fg/plate = 10 - 5000 *Bacillus subtilis* Fg/disk = 20 - 2000	**Negative.** Pronamide did not induce a mutagenic or genotoxic effect in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 or WP2 hcr of *Escherichia coli* at concentrations of 10-5000 Fg/plate ± S9 activation. Pronamide did not induce DNA damage in *Bacillus subtilis* at concentrations of 20-2000 Fg/disk.
870.5300 (§84-2) Gene Mutation/ *In vitro* mammalian cell assay in Chinese hamster V79 cells	MRID 40211106 (10/29/84)/Acceptable-Guideline Fg/ml = 2.5, 5, 10, 20 and 40	**Negative.** Pronamide did not induce a mutagenic effect in Chinese hamster V79 cells at [noncytotoxic] concentrations of 2.5, 5, 10, 20 and 40 Fg/ml ± S9 activation following a 48, 96 or 168 hour incubation period.
870.5300 (§84-2) Gene Mutation/ *In vitro* mammalian cell assay in Chinese hamster ovary [CHO] cells	MRID 40211108 (2/10/87)/Acceptable-Guideline Fg/ml = 25, 50, 75, 100 and 150	**Negative.** Pronamide did not induce a mutagenic effect in Chinese hamster ovary cells at [noncytotoxic] concentrations of 25, 50, 75, 100 and 150 Fg/ml ± S9 activation.
870.5385 (§84-2) Cytogenetics/ *In vivo* cytogenetics bone marrow assay in mice	MRID 40211105 (10/31/84)/Acceptable-Guideline g/kg = 0, 0.48, 1.94 or 4.94	**Negative.** Pronamide did not induce any structural chromosomal aberrations in bone marrow cells of male mice given doses of 0, 0.48, 1.94 or 4.94 g/kg in either acute or subacute dosing regimens.
870.5900 (§84-2) Other Mutagenic Mechanisms/ *In vitro* Unscheduled DNA Synthesis in primary rat hepatocytes	MRID 40211107 (2/11/87)/Acceptable-Guideline g/ml = 1, 5, 10, 25 or 50	**Negative.** There was no evidence that Pronamide caused unscheduled DNA synthesis in primary rat hepatocytes at concentrations of 1, 5, 10, 25 or 50 g/ml.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.7485 (§85-1) Metabolism and Phamacokinetics- Rat	MRID 41801801, 41929901 (2/21/91, 6/25/91)/ Acceptable-Guideline single oral dose (2 or 100 mg/kg) or multiple low doses (20 ppm a.i. in the diet for 14 days) followed by a low dose (2 mg/kg) ^{14}C-pronamide	Pronamide is rapidly absorbed and completely and rapidly eliminated. Over a 7 day period, most of the radioactivity administered was recovered (93-103%) in the urine (40-61%) and feces (40-60%). Only 0.08-0.21 and 0.83-2.43 percent of the administered dose were recovered in tissues and carcasses, respectively. No bioaccumulation was apparent; radioactivity recovered in all tissues were consistently highest at the first sampling time (8 hours post-dose) then gradually declined to insignificant levels 7 days after dosing. Tissues with the highest radioactivity contents were, in decreasing order, the fat, adrenals, bone marrow, thyroids, liver, kidney, and plasma. Very little unchanged pronamide was recovered in urine. Of the twenty metabolites found, only thirteen (constituting $\preceq$ 51.1% of the total radioactivity in urine) were clearly identified. The feces was not examined for metabolites. However, when these data (MRID 41801801, 41929901) are reviewed in conjunction with the characterization of the urinary and fecal metabolites of pronamide (MRID 42858001), the guideline requirement for a metabolism and pharmacokinetics study [OPPTS 870.7485 (§85-1)] is satisfied.
870.7485 (§85-1) Metabolism and Pharmacokinetics - Rat	MRID 42858001 (7/15/93)/Acceptable-Guideline single oral dose (2 or 100 mg/kg) or multiple low doses (20 ppm a.i. in the diet for 14 days) followed by a low dose (2 mg/kg) ^{14}C-pronamide	Urinary and fecal metabolites of pronamide were identified in male and female rats. No significant difference in urinary metabolite profile was observed between sex or dose. The major urinary metabolites were: 2-(3,5-dichlorophenyl)-4,4-dimethyl-5-carboxyoxazoline (metabolite SS47-70, 3.0-5.9% of the administered dose) and N-carboxymethyl-3,5-dichlorobenzamide (metabolite 10, 12.7-18.9% of the administered dose). In the urine, approximately 27 unidentified metabolites were found and none exceeded 3.3% of the dose. In contrast, significant differences in the fecal metabolite profile was observed between doses. Fecal excretion of parent ranged from 9.2-10.9% of the dose for the low dose and low repeated dose groups and 37.4-40.9% for the high dose group. In the feces, almost all of the unidentified metabolites are under 1% of the dose. The metabolic pathway(s) of the test compound have been postulated in rats. This study adequately describes the characterization of urinary and fecal metabolites of pronamide in rats following low- and high-dose oral and repeated oral exposure. When these data (MRID 42858001) are reviewed in conjunction with previous metabolism studies (MRID 41801801, 41929901), the guideline requirement for a metabolism and pharmacokinetics study [OPPTS 870.7485 (§85-1)] is satisfied.

TABLE 2. Subchronic, Chronic and Other Toxicity Profiles for Pronamide (Propyzamide		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.7600 (§85-3) Dermal Penetration - Rats, Kerb 50W and 3.3F - **formulations only**	MRID 40256701, 41117201 (4/14/87, 1/27/89)Unacceptable-Guideline (not upgradeable) 0.08 and 4.4 mg/cm^2	The dermal absorption rates per 6 hours were 19% and 17% for 50W and 15.1% and 5.4% for 3.3F. However, these data are based on a normalization of numerical values rather than the actual results obtained from the study. The actual doses applied to the skin were not determined and there were discrepancies in recovery for the 50W doses (78% and 122% of nominal doses). A default dermal absorption factor of 100% is used in this risk assessment.
Non -Guideline Thyroid Function and Hepatic Clearance of Thyroxine in Male Rats. This non-guideline study was submitted to the Agency as an addendum to the chronic toxicity/ carcinogenicity study in rats (MRID 41714001, 41714002)	MRID 42093401 (10/9/91)/Acceptable-Nonguideline ppm = 0, 40, 1000, or 4000 mg/kg/day = 0, 3, 67 or 279	Systemic and Thyroid Toxicity NOAEL = 40 ppm (3 mg/kg/day) LOAEL = 1000 ppm (67 mg/kg/day) based upon decreases in body weight and food consumption, increases in absolute and/or relative weight of the liver and thyroid, an increase in serum TSH (at 4 weeks but not at 13 weeks), a decrease in serum T4, and an increase in incidences of thyroid and pituitary hypertrophy/hyperplasia.
Non- Guideline Effects of Endocrine Regulation of the Testis in Rats - Pilot Study	MRID 42139601 (12/6/91)/Acceptable-Nonguideline ppm = 0, 40, 1000, or 4000	In the 13 week study, Pronamide treatment (4000 ppm) resulted in decreased body weight (weeks 1-13) and food consumption (weeks 1-8), increased serum LH and FSH (respective increases at 4 and 13 weeks were 60% and 58% for FSH, and 100% and 77% for LH), increased absolute and relative (to body) liver weight, increased microsomal protein content, increased oxidation of testosterone, increased activity of cytochrome-P450 and -B5, and NADPH-cyochrome-c-reductase, increased gross pathology of the liver (enlarged/dark), increased relative (to body) testicular weight, and increased testicular interstitial cell hyperplasia. In the 4-week study, alterations in clinical chemistry parameters were noted only at 4000 ppm as increases in sreum LH and FSH. These effects were comparable with increases observed after 13 weeks.

3.2 FQPA Considerations

On December 3, 2001, the FQPA Safety Factor Committee evaluated the hazard (See Section 5.0, Hazard Characterization and Dose Response Assessment Summary), endocrine (See Section 9.0, Endocrine Disruption) and exposure data for pronamide and made the recommendation for the FQPA safety factor to be used in human health risk assessments as required by Food Quality Protection Act of August 3, 1996. (Memorandum: C. Christensen, December 19, 2001).

Based on these available data, the FQPA SF Committee determined that the safety factor is necessary when assessing the risk posed by pronamide because:

1. There is evidence of endocrine effects (thyroid, testes, ovaries, adrenal glands, pituitary gland, thymus) identified in the majority of studies conducted across species. A special study designed to assess thyroid function in adult animals and their offspring will be required.

However, the Committee concluded that the FQPA safety factor could be **reduced to 3x** in assessing the risk posed by exposure to pronamide because:

1. The toxicological database is adequate for FQPA assessment; and,
2. There is no indication of quantitative or qualitative increased susceptibility of rabbits to *in utero* exposure or to rats following pre/post-natal exposure. Also, in the available, unacceptable rat study, no increased susceptibility was seen even though the animals could have tolerated higher doses.
3. A developmental neurotoxicity study is not required; and,
4. The dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposures for infants and children.

The 3x FQPA safety factor for pronamide is applicable to all population subgroups when assessing dietary and residential exposure scenarios because of evidence of endocrine effects. The FQPA safety factor was not applied to the acute dietary endpoint because no appropriate endpoint was available to quantitate risk to either the general population or to females13-50 years of age from a single-dose administration of pronamide.

A MOE of 300 (10x for interspecies extrapolation, 10x for interspecies variation and a 3x FQPA safety factor) is required for short-term, intermediate- and long-term incidental oral, dermal, and inhalation risk assessments. Therefore, short-term, intermediate to long-term risk estimates with a MOE $\geq$300 do not exceed the HED level of concern.

3.3 Hazard Endpoint Selection

The strengths and weaknesses of the pronamide toxicology database were considered during the process of toxicity endpoint and dose selection.

Table 3. Summary of Toxicological Dose and Endpoints for Pronamide for Use in Human Risk Assessment[1]			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary females 13-50 years of age and the general population including infants and children	No appropriate acute dietary endpoints were available to quantify risk to females 13-50 years of age or to the general population from a single-dose administration of pronamide. The adverse effect observed in the rabbit developmental toxicity study, abortions, were not considered to occur after a single dose because they were observed in rabbits during the postdosing phase of the study (days 22-24). Therefore, no acute dietary endpoints were selected which represented toxicities from a single-dose exposure.		
Chronic Dietary all populations	NOAEL = 8.46 mg/kg/day UF = 100 **Chronic RfD** = 0.08 mg/kg/day	FQPA SF = 3 **cPAD** = chronic RfD / FQPA SF = 0.027 mg/kg/day	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.
Short-Term Oral (1-30 days) (Residential)	oral study NOAEL = 8.46 mg/kg/day	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Developmental Toxicity Study - Rabbit LOAEL = 20 mg/kg/day based on Clinical signs of toxicity (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes).
Intermediate-Term Oral (1 - 6 months) (Residential)	oral study NOAEL = 8.46 mg/kg/day	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.
Short-Term Dermal (1-30 days) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day dermal absorption rate $^{\beta}$ = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Developmental Toxicity Study - Rabbit LOAEL = 20 mg/kg/day based on Clinical signs of toxicity (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes).
Intermediate-Term Dermal (1-6 months) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day dermal absorption rate $^{\beta}$ = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.
Long-Term Dermal (6 months - lifetime) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day dermal absorption rate $^{\beta}$ = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.

Table 3. Summary of Toxicological Dose and Endpoints for Pronamide for Use in Human Risk Assessment[1]			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Short-Term Inhalation (1-30 days) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day inhalation absorption rate [β] = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Developmental Toxicity Study - Rabbit LOAEL = 20 mg/kg/day based on Clinical signs of toxicity (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes).
Intermediate-Term Inhalation (1-6 months) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day inhalation absorption rate [β] = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.
Long-Term Inhalation (6 months - lifetime) (Occupational/Residential)	oral study NOAEL = 8.46 mg/kg/day inhalation absorption rate [β] = 100%	**LOC for MOE** = 300 (Residential, includes the FQPA SF)	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 42.59 mg/kg/day based on increased relative (to body) liver weight and non-neoplastic histological changes in the liver, thyroid, and ovaries.
Cancer (oral, dermal, inhalation)	Group B2 - "Probable human carcinogen"	**$Q1^* = 2.59 \times 10^{-2}$ $(mg/kg/day)^{-1}$**	Cancer classification based on thyroid follicular cell adenomas (males and females) and benign interstitial cell tumors (males) in rats and hepatocellular carcinomas in mice (males).

[1]UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, LOC = level of concern, MOE = margin of exposure, Q1* = the low-dose linear extrapolation value used to express the risk to the human population for development of cancer following exposure to pesticide residues.

[α] An adjusted dose of 8.46 mg/kg/day was established for use in this risk assessment based on a maternal toxicity NOAEL of 5 mg/kg/day and clinical signs of toxicity (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes) observed at the LOAEL of 20 mg/kg/day in the developmental toxicity study conducted in rabbits.

[β]Since an oral endpoint was selected, a dermal absorption factor of 100% (default value) and an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Acute Dietary Risk Assessment: No appropriate acute dietary endpoints were available to quantify risk to females 13-50 years of age or to the general population from a single-dose administration of pronamide. The adverse effect observed in the rabbit developmental toxicity study, abortions, were not considered to occur after a single dose because they were observed in rabbits during the postdosing phase of the study (days 22-24). Therefore, no acute dietary endpoints were selected which represented toxicities from a single-dose exposure.

Chronic Dietary Risk Assessment: A chronic reference dose (cRfD) of 0.08 mg/kg/day was determined on the basis of the two-year chronic toxicity/carcinogenicity study in rats and the application of an uncertainty factor of 100 (10x for inter-species extrapolation and 10x for intra-species variation). The

NOAEL in this study was 8.46 mg/kg/day and the LOAEL was 42.59 mg/kg/day based upon increased relative liver weight and the non-neoplastic histologic changes in the liver (centrilobular hypertrophy and hepatocellular eosinophilic alteration in males and females), thyroid (follicular cell hypertrophy in males and females) and ovaries (sertoliform tubular hyperplasia in females). The 3x FQPA safety factor was applied for chronic dietary risk assessment because there is evidence of endocrine effects (thyroid, testes, ovaries, adrenal glands, pituitary gland, thymus) identified in the majority of subchronic/chronic studies conducted across species. The chronic population adjusted dose is the cRfD adjusted for the FQPA safety factor. Therefore, the chronic population adjusted dose (cPAD) is 0.027 mg/kg/day.

Short-Term Incidental Oral, Dermal and Inhalation Exposure Risk Assessments: An adjusted dose of 8.46 mg/kg/day was established for use in this risk assessment. This dose selection is based on a maternal toxicity NOAEL of 5 mg/kg/day and the clinical signs (soiled anal area and anorexia) and liver effects (punctate vacuolation of hepatocytes) observed at the LOAEL of 20 mg/kg/day in the developmental toxicity study conducted in rabbits. Although selection of this study for short-term exposure scenarios is appropriate for the route (oral) and duration (13 days), the NOAEL of 5 mg/kg/day is lower than the NOAEL (8.46 mg/kg/day) established in the chronic toxicity/carcinogenicity study in the rat. The apparent disparity between these NOAELs is driven by the doses of pronamide selected for testing in these studies. The HIARC concluded that using a more realistic NOAEL of 8.46 mg/kg/day rather than 5 mg/kg/day would provide a sufficiently protective dose for risk assessment. The 3x FQPA safety factor was also applied to these risk assessments because of the evidence of endocrine effects in the pronamide toxicity data base.

Intermediate-Term Incidental Oral, Dermal and Inhalation Exposure Risk Assessments: A NOAEL of 8.46 mg/kg/day was selected from the combined chronic toxicity/carcinogenicity study conducted in the rat. This NOAEL is based on increased relative liver weight and the non-neoplastic histological changes in the liver, thyroid, and ovaries which were observed at the LOAEL of 42.59 mg/kg/day. The HIARC determined that this study is appropriate for the (1-6 months) intermediate-term exposure duration because (i) the organ toxicities (liver, thyroid, and ovaries) observed in the 24 month study occurred as early as 6 months and continued to study termination and (2) this NOAEL (8.46 mg/kg/day) is numerically close to the NOAEL of 12.3 mg/kg/day established in the 90-day subchronic toxicity study conducted in the rat. Although the 90-day subchronic study in rats demonstrated liver toxicities (increased absolute and relative liver weights and hepatocellular hypertrophy) at a LOAEL of 60 mg/kg/day, these effects were considered minimal. Therefore the developmental NOAEL 12.3 mg/kg/day is not recommended for this exposure scenario. The 3x FQPA safety factor is applicable because of the evidence of endocrine effects in the pronamide toxicity data base.

Long-Term Dermal and Inhalation Exposure Risk Assessments: The NOAEL of 8.46 mg/kg/day was also selected from the combined chronic toxicity/carcinogenicity study in rats and is considered appropriate for these exposure scenarios. This NOAEL is based on increased relative liver weight and the non-neoplastic histological changes in the liver, thyroid, and ovaries which were observed at the LOAEL of 42.59 mg/kg/day. The 3x FQPA safety factor is applicable because of the evidence of endocrine effects in the pronamide toxicity data base.

Dermal and Inhalation Absorption: Since no dermal or inhalation toxicity studies were submitted, the selected endpoint is from an oral study of the appropriate duration of exposure and a 100% (default) absorption factor was applied to dermal and inhalation exposure routes.

Aggregating doses: For short-term exposure, incidental oral, dermal, and inhalation routes can be aggregated because of the use of oral equivalents and a common endpoint (clinical signs of toxicity and liver effects). For intermediate-term and long-term exposure, incidental oral, dermal and inhalation routes can be aggregated because of oral equivalents and a common endpoint (increased relative liver weight and non-neoplastic histologic changes in the liver, thyroid, and ovaries).

3.4 Endocrine Disruption

Many chemicals belonging to the class of organochlorine chemicals are known to produce disruption of the endocrine system. Pronamide is an organochlorine herbicide which has been identified by the Agency's Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) as a potential endocrine disruptor. Evidence of endocrine effects from several guideline toxicity studies as well as two special studies submitted to the Agency by the Registrant include, in part: (i) histopathology of the thyroid gland, pituitary gland, adrenal glands, testes and ovaries, (ii) changes in hormone levels; decreased T4 and increased TSH, LH and FSH, and (iii) the induction of enzymes such as cytochrome-P_{450} and -B_5, and NADPH-cytochrome-c-reductase in addition to those enzymes involved in the oxidation of testosterone.

On October 23, 2001, the Mechanism of Toxicity Assessment Review Committee (MTARC) reviewed the available toxicology data submitted in support of a proposed threshold mechanism for the induction of thyroid and testicular neoplasms resulting from exposure to pronamide. Although the results of these special endocrine studies conducted by the Registrant are suggestive of a pronamide-induced thyroid and testicular neoplastic effect via disruption of the pituitary-thyroid and pituitary-testis hormonal balance, these data are far from conclusive. Based on the Committee's (MTARC) evaluation of the existing pronamide toxicology data base (Memorandum: M. Centra, January 21, 2001) and in the absence of any additional information, it was determined that the postulated threshold mechanism for the induction of thyroid and testicular neoplasms is not supported by the available data. Therefore, HED has recommended that additional studies be conducted with pronamide to determine its mechanism of endocrine toxicity. One such study, a comparative assay in the rat that is designed to assess thyroid function in adult animals and their offspring as well as potential central nervous system effects in the young, is required by the Agency because of the endocrine toxicities observed in various organ systems (thyroid gland, testes, ovaries, adrenal glands, pituitary gland) of rats and/or dogs.

The Agency is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, pronamide may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Pronamide [3,5-dichloro-N-(1,1-dimethyl-2-propynyl)benzamide], or propyzamide, is a selective, systemic, pre-and post-emergence herbicide registered for use in agricultural, ornamental, and residential settings. There are two manufacturers of pronamide end-use products with only two active section 3 registrations. There are also nine active Section 24C registrations. Approximately 225,000 lb of active ingredient are used domestically each year.

Major food/feed crops include: stone fruits (apricot, cherry, nectarine, peach, plum, prune), pome fruits (apple, pear), grapes, artichokes, berries (blackberry, blueberry, boysenberry, red raspberry, black raspberry), leafy greens (lettuce, endive, radicchio), winter peas, chicory, rhubarb, sugarbeets, and forages (alfalfa, clover, birdsfoot trefoil, crown vetch, sainfoin). Non-agricultural uses include woody ornamentals, ornamental warm season grasses grown for turf (i.e. bermudagrass, zoysiagrass, St. Augustine, and centipedegrass) or seed (bermudagrass), residential/recreational turf (bermudagrass lawns, playing fields, and golf courses), Christmas trees, grasses grown for seed, rangeland, and fallow land.

In terms of pounds a.i., total usage is allocated mainly to head lettuce (29%), other lettuce (19%), seed crops (13%), fallowland (11%), hay other than alfalfa (8%), horticulture (3%) and alfalfa (3%). Rates per application and rates per year are each generally less than 2 pounds a.i. per acre for agricultural sites (based on the economic analysis by A. Holverson, September 26, 2001). Pronamide label rates range from 2 to 8 lbs ai per acre per year at 0.5 to 6 lbs ai per acre per application, with from one to four applications per year. Pronamide is formulated as a wettable powder and may be applied by ground or aerial spray, depending on the crop. States with significant usage in terms of pounds a.i. include Arizona, California, Oregon and Washington. Pre-harvest intervals, where specified, are generally long, ranging from 25 to 180 days.

There are several active Section 24C state labels. For risk assessment purposes the use sites and use patterns on these 24C labels are covered by EPA Reg. No. 707-159.

4.2 Dietary Exposure and Risk Assessment

4.2.1 Residues in Food

Background

Pronamide/propyzamide [3, 5 dichloro- n-(1,1-dimethyl-2-propynyl) benzamide] tolerances are established under 40 CFR §180.317(a), (b), and (c). The tolerance expression, listed in (a) and (c), is in terms of "the combined residues of the herbicide propyzamide and its metabolites (containing the 3,5-dichlorobenzoyl moiety and calculated as 3,5-dichloro-N-(1,1-dimethyl-2-propynyl)benzamide)." The

tolerance expression, listed in (b), is in terms of the parent only. Pronamide tolerances listed in 40 CFR §180.317(a) range from 0.02 ppm (for certain animal commodities) to 10.0 ppm (for a non-grass animal feeds group). The time-limited tolerances listed in 40 CFR §180.317(b), with an expiration date of 12/31/01, are for Section 18 emergency exemptions for pronamide uses on cranberries (0.05 ppm) and grasses (forage 1.0 ppm and hay 0.5 ppm). The tolerances listed in 40 CFR §180.317(c) are for regional registrations of pronamide on dried (winter) peas (0.05 ppm) and rhubarb (0.1 ppm).

Residue Profile

The qualitative nature of the residue in plants is adequately understood. The 4/16/93 Residue Chapter reported that studies with alfalfa and lettuce indicate that pronamide is readily absorbed by plants through the root system, translocated upward, and distributed into the entire plant. The degree of translocation from leaf absorption is not appreciable. Metabolism primarily occurs via conjugation to (malonyl) glucose. No evidence of fragmentation or loss of the chloro substituent of the aromatic ring was observed. The terminal residues of concern are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety. For purposes of reregistration, no additional plant metabolism studies are required; however, because the available metabolism studies were only conducted on alfalfa and lettuce, the Agency may require additional metabolism studies in the future should the registrants seek for additional uses on other crop groups.

The qualitative nature of the residue in animals is adequately understood. The 4/16/93 Residue Chapter reported 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 are pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety.

An adequate residue analytical method is available for plant and animal tolerance enforcement, a GLC/ECD method listed in the Pesticide Analytical Manual (PAM) Volume II. Designated as Method I, it converts residues of pronamide and its metabolites to methyl 3,5-dichlorobenzoate.
The data-collection method used in the analysis of samples, collected from a recently reviewed field rotational crop study, was a GLC/ECD method entitled “An Improved Analytical Method for the Determination of Kerb Residues in Crops and Soil.” The method was adequately validated by the registrant and is deemed adequate for data-gathering purposes. This method should be validated by EPA in order to support the established and proposed tolerances for pronamide.

Since the 1993 dietary chapter was published, the registrant has submitted independent laboratory validation for a revised animal method (TR 34-91-68). However, prior to Agency validation of Method TR 34-91-68, the registrant is required to further optimize/improve the method to yield acceptable recoveries at higher fortification levels. Then, following method improvement, the registrant is required to submit bridging ILV data.

Multiresidue method testing data for pronamide and a metabolite containing the 3,5-dichlorobenzoyl moiety are also available (MRID434932-03); these data have been forwarded to FDA.

Plant product residue storage stability data were submitted but provided only indirect evidence that the precursors to the 3,5 dichlorobenzoyl moiety, are most likely stable. Additional confirmatory storage stability data for the regulated pronamide metabolites on alfalfa, apples, grapes, lettuce, and peaches or plums are required. Likewise, animal product storage stability data were submitted, but an analysis of metabolites containing the 3,5-dichlorobenzoyl moiety was not included in the study. Additional confirmatory storage stability data for the regulated pronamide metabolites on milk are required.

4.2.2 Acute Dietary Risk from Food Sources

As there was no toxicological endpoint selected for acute exposure, an acute dietary risk assessment was not performed.

4.2.3 Chronic and Cancer Dietary Risk from Food Sources

A refined tier 3, chronic and cancer dietary exposure assessment has been performed for pronamide. The analysis is based primarily upon residue monitoring data for fruits and vegetables from the U. S. Department of Agriculture (USDA), Agricultural Marketing Service's Pesticide Data Program (PDP) and FDA data. Tolerance level residues were used for four registered crops (dried peas, endives, radicchio, and cranberries), and anticipated residues were calculated for meat, milk, poultry and eggs. The percent crop treated (%CT) data from OPP's Biological and Economic Assessment Division (BEAD) (September 26, 2001) were used to further refine the dietary exposure assessment.

Pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety are the residues of concern and should be included in the assessment. The residues measured in field trials include the other metabolites by incorporation of a hydrolysis step. However, the PDP analyses measured only the parent compound; therefore, the method limit of detection (LOD) was used instead of 1/2 the LOD to account for metabolites of concern for the treated portion of those crops.

No processing information was used in this assessment. DEEM™ default processing factors were used wherever they existed for processed food derived from the relevant crops. However, because residue data were available in the PDP database for grape juice, pear juice and apple juice, these PDP data were used directly, i.e. without DEEM default processing factors, for grape juice and grape wine, and for pear juice and apple juice. Factors for the juice concentrates were estimated from the ratio of the DEEM default factors for juice/juice concentrate.

The dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.75, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software.

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups from the general U.S. population which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups are not reported explicitly but are included within larger

representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

For chronic and cancer exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

A summary of the pronamide chronic dietary risk estimates are shown in Table 4.
The dietary cancer risk estimates are shown in Table 5.

Table 4. Results of Chronic Dietary Exposure Analysis

Population Subgroup	cPAD[1] (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.03 mg/kg/day	0.000004	<1%
All Infants (< 1 year)	0.03 mg/kg/day	0.000002	<1%
Children 1-6 years	0.03 mg/kg/day	0.000005	<1%
Children 7-12 years	0.03 mg/kg/day	0.000004	<1%
Females 13-50	0.03 mg/kg/day	0.000004	<1%
Males 13-19	0.03 mg/kg/day	0.000003	<1%
Males 20+ years	0.03 mg/kg/day	0.000004	<1%
Seniors 55+	0.03 mg/kg/day	0.000005	<1%

cPAD[1] = Chronic PAD = Chronic Population Adjusted Dose = 0.03 mg/kg/day

Table 5. Results of Dietary Cancer[1] Exposure Analysis

Population Subgroup	Exposure (mg/kg/day)	Cancer Risk Estimate
U.S. Population (total)	0.000004	1.06×10^{-7}

[1] $Q_1^* = 0.0259$ mg/kg/day $^{-1}$

Because the estimated exposure is well below the chronic and cancer levels of concern, and conservative assumptions were used, any uncertainties are unlikely to cause the exposure to exceed a level of concern. However, there are some conservative assumptions that may have introduced some uncertainties into this assessment. Tolerance level residues and 100 % CT was used for endives, dried peas, cranberries and radicchio. The LOD was used instead of ½LOD for the non-detects in the PDP data. For the animals ARs the maximum percent crop treated was assumed instead of the average percent crop treated. Default DEEM processing factors were used for many processed foods.

4.3 Dietary Exposure from Water Sources

4.3.1. Environmental Fate

According to the May 1994 Reregistration Eligibility Decision for pronamide, results from environmental fate studies indicate that pronamide is very persistent in soil and water with half-lifes of many months. Pronamide is very stable in water and photolytically persistent in water and on soil. It is very persistent in soil under aerobic conditions, with an estimated half-life of 13 months, and even more persistent under anaerobic conditions. Pronamide is persistent but relatively mobile in soil. Additionally, rotational crop studies show accumulation in several crop types at one, six and twelve months after application. For these reasons, residues of pronamide, *per se*, are the residues of concern in assessing drinking water exposures.

4.3.2 Drinking Water Exposure Estimates

Although there is no legal requirement under the Safe Drinking Water Act to monitor for pronamide, it has been detected in surface and groundwater in various locations in the U.S. The maximum level detected was 0.365 ppb (surface water) at Zollner Creek near Mt. Abgel, OR on Nov. 16, 1998 and the range was 0.0037 to 0.365 (surface water) ppb or ug/liter (USGS - NAWQA Data Retrieval). The maximum ground water detection at Benton Ozark, AK was 0.82 ppb on April 13, 1994, and ranging from 0.005 - 0.82 ppb (ground water).

A Tier I Drinking Water Assessment for pronamide was calculated (L. Shanaman, 2001) using the SCIGROW model for groundwater concentration estimates. The Tier I groundwater estimates were predicted from application of pronamide at maximum label rate (2 lbs active ingredient per acre four times per year) for ornamental herbaceous plants, and represent upper-bound estimates of the concentrations that might be found in groundwater due to the use of pronamide/propyzamine. The resulting modeled groundwater screening concentration is 3.0 ppb.
The Tier II PRZM-EXAMS model (L. Shanaman, 2002) was used to predict EECs for pronamide in surface water, i.e., 90th percentile average annual concentration values for use in chronic exposure assessments, and 36-year mean concentration values for use in "cancer" exposure assessments. Maximum label application rates were used for major use crops. Chronic exposure values ranged from 1.5 to 6.4 ppb, and cancer average exposure values ranged from 0.535 to 4.3 ppb. Conservative inputs were used for the environmental (soil and water metabolism) assumptions, i.e., 2-3x uncertainty factors were applied to soil and water half-lives used in the PRZM-EXAMS assessment.

4.4 Residential Exposure

4.4.1 Residential/Recreational Postapplication Exposure and Risk

Pronamide is a restricted-use herbicide, so the public/consumers are prohibited from handling this chemical. Therefore only postapplication exposures were assessed.

Earth Care, Division of United Industries Corp., (previously Pursell Industries) has requested voluntary cancellation of the product GREEN UP KERB 50W, EPA Reg. No. 8660-85, which is the only end use product label that allows professional application in a residential/recreational setting. Pending

cancellation of this use, a residential/recreational exposure assessment was conducted. The agricultural label (EPA Reg. No. 707-159) allows one application per year to grasses grown for turf for sod or seed. Based on the application rate, timing, and residue dissipation data, there are no concerns for residential/recreational exposure to the treated turf from a sod farm.

This label No. 8660-85 indicates a maximum application rate of 1.5 lb ai/acre for pre-emergence applications by lawn care operators (LCOs) to lawns, playing fields, and golf courses as a single application. The maximum application rate for post-emergence applications is 1.0 lb ai/acre. This residential label does not specify or restrict the number of applications allowed per year to turf. Applications to turf are only made in the late Fall or late Winter. For residential turf, HED assumed one application per year to estimate short-term exposures.

The scenarios assessed for the purpose of determining screening-level risk estimates included adults and children (toddlers) performing high-contact play or work activities on treated lawns, and adults mowing lawns or golfing (see Tables 6a, 6b, and 6c) . Small children (toddlers) were also assessed for incidental oral exposure from ingestion of soil, object-to-mouth activity (turfgrass mouthing), and hand-to-mouth activity while playing on treated lawns. Some of these exposures were combined, where it was deemed reasonably likely that activities would co-occur. Residential risk estimates utilized data from a submitted turf transferable residue (TTR) study, as well as the EPA's original and revised Draft SOPs for Residential Exposure Assessment.[3, 5] For pronamide short-term non-occupational risks, HED has established a level of concern for MOEs < 300.

Results from a recent turf transferable residue study on turf using pronamide (i.e. MRID 44952501) indicate that the half-life of turf transferrable (TTR) residues was slightly less than two days. The residential label (EPA Reg. No. 8660-85) instructs applicators to lightly irrigate within a day of application if no rain occurs. Such irrigation occurred at 24 hours after application in the TTR study. Since the compound is soluble in water, and therefore mobile, it is likely the irrigation dissolves the compound and transports it from the turf into the soil. Study data showed that residues dissipate to below the level of quantification by day 14 following application. Therefore, only short-term (i.e., one day to one month) exposures would be anticipated, since most of the pesticide should move into the soil, and any remaining foliar residues should dissipate within a month. While residues in soil could persist for greater than 30 days, it is unlikely that children will play on or contact soil for greater than 30 consecutive days during the winter months.

Risk estimates based on residue data from the TTR study for short-term dermal contact with treated turf during high contact lawn activities on day zero following application (DAT 0) exceed HED's level of concern, i.e. result in MOEs < 300 for adults (MOE = 71) and children (MOE = 42). However, using DAT 2 residue data from the TTR study yielded MOEs that do not exceed the level of concern (MOEs ≥ 300) for adults (MOE = 890) and children (MOE = 530) during high contact lawn activities. Note that the test plots were irrigated immediately after the DAT 1 samples were taken, i.e. 24 hours after application of pronamide, as specified on the label. Using DAT 2 residue data from the TTR study yielded MOEs that do not exceed the level of concern (MOEs ≥ 300) for adults (MOE = 890) and children (MOE = 530) during high contact lawn activities. The data show that thorough watering-in the pronamide product clearly alleviates the risk concerns for dermal exposure. Risk estimates for short-term dermal contact with residues on treated turf during the low contact activities of grass mowing or golfing on the day of treatment do not exceed the level of concern (MOEs ≥ 300) for adults (MOEs 2050 and 1025, respectively).

Based on the pesticide label, a typical residential/recreational lawn application rate of 1.0 lb/acre, with an application frequency of once per year, was assumed for the residential cancer risk assessment. Pronamide is applied in the dormant season, which reduces the number of contact days expected. A single exposure is deemed more likely, but up to 14 days exposure could occur based on the residue dissipation pattern. The 14-day average turf residues from the TTR study (MRID 44952501) were used (i.e. 0.07913 µg/cm^2, when adjusted to a typical application rate of 1.0 lb ai/acre); since residues in the TTR study dissipated to the level of quantitation by 14 days after application. The average residue, and an exposure frequency of one day per year, or 50 days in a lifetime, was assumed for high contact activities (e.g. playing and working on lawns and turf) and low contact activities (e.g. mowing or golfing). An adult mowing a treated lawn one day each year has a cancer risk of 5.7×10^{-8}. The average golfer plays 18 times per year, so one day's exposure is possible if pronamide is applied once per year on average. The adult golfer cancer risk is estimated at 1.2×10^{-7}. An adult performing dermal high contact activities on turf during the 2 week period of residue dissipation has a cancer risk of 8.4×10^{-7}. The HED endeavors to reduce estimated cancer risks for the general population to less than one in one million (10^{-6}). In order to exceed the cancer risk (1.0×10^{-6}), exposure frequencies of 17.5, 8.7 and 1.2 days per year would be needed for the activities of mowing, golfing and high contact work, respectively.

Both the short-term exposure estimates and the cancer risk estimate relied on a 100% dermal absorption factor, which results in a high-end dose estimate. The short-term dose selection from a developmental study is based on a weight-of-evidence evaluation of the entire pronamide database, but is considered protective of all populations.

Table 6a: Pronamide Residential Postapplication Activities on Treated Turf: Dermal Exposure and Non-Cancer Risk Estimates

		Short-term Risk Estimates at DAT 0 using TTR Data from Turf Study			Short-term Risk Estimates at DAT 2 using TTR Data from Turf Study		
Activity	Transfer Coefficient (cm^2/hr) (a)	TTR µg/cm^2 DAT 0 (b)	Dermal Dose (mg/kg/ day) (c)	MOE (d)	TTR µg/cm^2 DAT 2 (b)	Dermal Dose (mg/kg/ day) (c)	MOE (d)
high contact lawn activities: adults	14,500	0.2886	0.1196	**71**	0.023	0.00953	890
high contact lawn activities: toddler	5,200	0.2886	0.2001	**42**	0.023	0.0159	530
mowing turf: adults	500	0.2886	0.00413	2100	0.023	0.000329	26,000
golf course reentry: adult	500	0.2886	0.00825	1000	0.023	0.000657	13,000

a Transfer coefficients from the Residential SOP's (02/01).

b TTR Source: MRID # 44952501 turf transferable residue study - see study review for raw data and regression statistics. Mean observed residue values from DAT 0 through DAT 0.5 were used for the DAT 0 short-term assessments. Mean observed residue values from DAT 2 were used for the DAT 2 short-term assessments.

c Dermal Dose = TTR (µg/cm^2) x TC (cm^2/hr) x conversion factor (1 mg/1,000 µg) x exposure time (2 hrs/day playing & mowing; 4 hrs golfing) x Dermal Absorption Factor (100%/100)/ body weight (70 kg adult or 15 kg child 1-6 yrs). Short-term MOEs were calculated using DAT 0 or DAT 2 values.

d MOE = NOAEL (8.46 mg/kg/day; based on an oral study) / dermal dose; Note: Target MOE is 300 or greater; numbers are rounded to two significant figures.

Note: TTR = turf transferable residue

DAT = days after treatment

MOEs in bold exceed HEDs level of concern (i.e. MOEs < 300).

Table 6b: Pronamide Postapplication Dermal Cancer Risk Estimates for Activities on Treated Turf

Activity	Typical Application Rate (lb ai/acre) (a)	Days of Exposure per Year (b)	14-day avg TTR, adjusted for "typical" rate (µg/cm^2) (c)	Transfer Coefficient (cm2/hr) (d)	Absorbed Dermal Daily Dose (mg/kg/day) (e)	LADD (mg/kg/day) (f)	Cancer Risk (g)	Days of Exposure per Year to Exceed 1.0E-06
High-contact activities	1.0	1	0.07913	7300	1.65E-02	3.23E-05	8.36E-07	1.2
Mowing	1.0	1	0.07913	500	1.13E-03	2.21E-06	5.73E-08	17.5
Golfing	1.0	1	0.07913	500	2.26E-03	4.42E-06	1.15E-07	8.7

a Typical (not maximum) application rates were used to adjust TTR study residue data; rate confirmed per label and registrants' comments.

b Average or typical days per year for cancer risk estimates, based upon a single annual application and a fairly rapid foliar dissipation rate (half life of 1.8 days, from TTR study, i.e. MRID # 44952501).

c TTR source: MRID # 44952501 turf transferable residue study - see residential exposure assessment for raw data and regression statistics. Mean observed residue values for DAT 0 through DAT 14 were used for the assessment. The study was conducted in NC using a maximum application rate of 1.5 lb ai/acre. When assessing activities involving a different application rate than what was used in the study, the TTR values are adjusted proportionately to reflect the different application rate. For example, for the "typical" application rate of 1.0 lb ai/acre : normalized (adjusted) TTR = Turf study TTR x 1.0 lb ai/A assessed rate / 1.5 lb ai/A study rate; 0.1187 µg/cm^2 x 1.0 lb ai/A assessed rate / 1.5 lb ai/A study rate = 0.07913 µg/cm^2.

d Transfer coefficient from the updated Residential SOP's (02/01).

e Absorbed daily dose = Average day 0-14 TTR (µg/cm^2) x intermediate-term transfer coefficient (cm^2/hr) x mg/1,000 µg x exposure duration (2 hrs/day for playing/gardening/mowing; 4 hrs/day to play golf) x dermal absorption factor (100%) / body weight (70 kg adult).

f LADD = absorbed daily dose (mg/kg/day) x days of exposure/year x 50 years of expected exposure/ (365 days/year x 70 year lifetime);

g Cancer Risk = LADD x Q_1^*, where $Q_1^* = 2.59 \times 10^{-2}$ (mg/kg/day)$^{-1}$

TTR used for cancer risk estimate = 0-14 DAT average residue normalized for typical application rate.

TTR = turf transferable residue

DAT = days after treatment

HED also assessed short-term risks to small children from incidental oral ingestion of pronamide residues following application to residential lawns. The risk calculations for small children's non-dietary ingestion of pronamide on treated turf indicate that risks do not exceed the level of concern (i.e. MOEs ≥ 300) for hand-to-mouth (MOE = 380), incidental ingestion of soil (MOE = 11,000), and incidental object to mouth (MOE = 1500). The small children's combined oral hand-to-mouth scenarios (MOE = 300) also do not exceed the level of concern. When risks from dermal exposures from pronamide to small children are combined with risks from incidental oral exposures, the combined short-term risk estimates exceed the level of concern (MOEs < 300), with an MOE at 37. Note that the high-contact dermal exposure is driving the overall risk. Also, the likelihood of all of the assessed incidental oral exposures co-occuring with dermal exposures is low.

Table 6c. Residential Oral Nondietary Short-term Postapplication Risks to Children from "Hand-to-Mouth" and Ingestion Exposure When Reentering Lawns Treated with Pronamide

Type of Exposure	Short-term Oral Dose[a] (mg/kg/day)	Short-term MOE[b]
(1) Hand to Mouth Activity	0.0224	380
(2) Incidental Object to Mouth (Turfgrass Mouthing)	0.0056	1500
(3) Incidental Ingestion of Soil	7.51E-5	113,000
Combined Oral Nondietary [c]	0.028	300
Combined Oral and Dermal[d]	---	**37**

a Application rate for the short-term estimates represents maximum label rate from current EPA registered label: EPA Reg. No. 8660-85 wettable powder product formulation, max rate is 1.5 lb ai/acre. Incidental oral doses were calculated using formulas presented in the Residential SOPs (updated 1999-2000). Short--term doses were calculated using the following formulas:
(1) Hand-to-mouth oral dose to children on the day of treatment (mg/kg/day) = [application rate (lb ai/acre) x fraction of residue dislodgeable from potentially wet hands (5%) x 11.2 (conversion factor to convert lb ai/acre to µg/cm^2)] x median surface area for 1-3 fingers (20 cm^2/event) x hand-to-mouth rate (20 events/hour) x exposure time (2 hr/day) x 0.001 mg/µg] x 50% extraction by saliva / bw (15 kg child 1-6 yrs). This formula is based on proposed changes to the December 1999 Residential SOPs.
(2) Turf mouthing oral dose to child on the day of treatment (mg/kg/day) = [application rate (lb ai/acre) x fraction of residue dislodgeable for transfer to mouth (20%) x 11.2 (conversion factor to convert lb ai/acre to µg/cm^2) x ingestion rate of grass (25 cm^2/day) x 0.001 mg/µg] / bw (15 kg child 1-6 yrs).
(3) Soil ingestion oral dose to child on the day of treatment (mg/kg/day) = [(application rate (lb ai/acre) x fraction of residue retained on uppermost 1 cm of soil (100% or 1.0/cm) x 4.54e+08 µg/lb conversion factor x 2.47e-08 acre/cm^2 conversion factor x 0.67 cm^3/g soil conversion factor) x 100 mg/day ingestion rate x 1.0e-06 g/µg conversion factor] / bw (15 kg; child 1-6 yrs). Short term dose based residue on the soil on day of application.

b Short-term MOE = NOAEL (8.46 mg/kg/day) / Oral Dose (mg/kg/day). NOAEL from a non-developmental toxicity study in rabbits; target MOE of 100. Numbers are rounded to two significant figures.

c Combined MOEs = NOAEL / [sum of incidental oral doses], with a target MOE of 100.

d Combined Dermal + Incidental Oral MOEs = 1/ [1/MOE$_{dermal}$ + 1/MOE$_{oral}$]; see Table 6a for dermal MOE for high-contact short-term activity for toddlers on turf (MOE = 42).

MOEs in bold exceed HEDs level of concern (i.e. MOEs < 300).

The exposure estimates generated for the residential/recreational turf uses used the HED SOPs that are based on some upper-percentile assumptions (i.e., duration of exposure and maximum application rate for short-term assessments) and are considered to be representative of high end exposures. The

uncertainties associated with this assessment stem from the use of assumptions regarding the transfer of pronamide residues. The exposure estimates are believed to be reasonably high-end estimates, since the maximum application rate is used, a 100% dermal absorption factor is assumed, and exposures are assumed to occur on the day of treatment.

4.4.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

FQPA requires an aggregate risk assessment to be conducted considering all non-occupational sources, including exposure from water, food, and residential use. Because there are potential exposures to treated turf, the aggregate exposure assessment for pronamide includes exposure estimates from residential sources as well as food and drinking water.

HED has calculated drinking water levels of comparison (DWLOCs) for chronic exposure to pronamide in surface and groundwater which are presented in Tables 7a, 7b and 7c. DWLOCs were calculated using default body weights and drinking water consumption figures. Assumptions used in calculating the DWLOCs include 70 kg body weight for the U.S. population, 60 kg body weight for adult females, 10 kg body weight for children, two liters of water consumption per day for adults, and one liter consumption for children.

Generally, risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and groundwater. In the case of pronamide, there are monitoring data available for surface and ground water. The monitoring database used in the risk assessment is considered to be of good quality (USGS), but the data are not from sampling specifically targeted for pronamide use areas. These data have been compared to the model results to characterize the Tier I and Tier II estimates for the groundwater and surface water, respectively. As can be seen from that comparison, the monitoring data are typically at least 10-fold lower than the model estimates. The USGS monitoring data are also lower than the short-term and chronic DWLOC.

However, the model estimates for Northwest pears and apples, and alfalfa grown in CA indicate that an extreme case using highest label rates might present a concern for cancer. Typical rates for the fruit are one-half , and alfalfa is one-quarter the rates used in the model, according to the latest QUA report. The model estimates would therefore be decreased proportionately for those crops if pronamide were applied

at the lower or more typical use rate. See Tables 7a, 7b, 7c.

5.1 Acute Risk

Acute aggregate risk was not estimated as no acute toxicological endpoints were identified for pronamide.

5.2 Short-Term Risk

5.2.1 Aggregate Short-Term Risk Assessment

Because the short-term dermal postapplication exposure estimates for children exceeded the level of concern, an aggregate exposure estimate combining dermal exposure with food and drinking water intake was not conducted for that population. Adults engaged in high-contact activities on newly treated turf also had dermal exposures which exceeded the level of concern. However, an aggregate short-term exposure assessment was conducted for the low-contact adult golfing exposure scenario. This short-term risk estimate may be useful in risk management decisions. The short-term aggregate exposure estimate which included the golfer dermal exposure did not exceed the level of concern (golfer MOE = 1000) .

5.2.2 Short-Term DWLOC Calculations

Since the drinking water calculations were based on modeling estimates, Drinking Water Levels of Comparison (DWLOCs) were calculated for short-term exposure. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit in light of *total* aggregate exposure to that chemical from food, water, and (for short-term estimate) non-occupational (residential) sources. Comparisons are made between DWLOCs and the estimated concentrations of pronamide in surface water and ground water generated via PRZM/EXAMS and SCI-GROW, respectively. If the model estimate is less than the DWLOC, there is generally no drinking water concern.

Monitoring data for pronamide in surface water had a maximum value from all samples and all years of 0.365 ppb, and 0.82 ppb for groundwater. Monitoring data ranged from 0.0037 to 0.365 ppb in surface water, and from 0.82 - 0.005 ppb in ground water. Results showed that for low-contact adult activities, such as, mowing and golfing, modeled and measured concentrations of pronamide are considerably less than the DWLOCs (range 560 -700 ppb) for all populations. Consequently, for these adult, low-contact activities, there is no short-term concern for drinking water from surface or groundwater sources. However, as noted above, short-term postapplication dermal/incidental oral exposures of children to pronamide on lawns after application result in risk estimates that exceed HED's levels of concern. Aggregating children's exposures through food, water, and residential uses results in risk estimates that further exceed levels of concern.

Table 7a. Short-Term Aggregate Risk and DWLOC Calculations for Adult Low-Contact Activities only

Population	Short-Term Scenario									
	NOAEL mg/kg/day	Target MOE[1]	Max Exposure[2] mg/kg/ day	Average Food Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] mg/kg/day	Ground Water EEC[6] (µg/L)	Surface Water EEC[6] (µg/L)	Short-Term DWLOC[7] (µg/L)
Adult Male[8]	8.46	300	0.0282	4 e-06	0.00825	1000	0.020	3	1.6-6.5	700
Adult Female				4 e-06	0.0096	880	0.0186			560
Child				5 e-06	0.20[9]	NA[9]	0			0
Highest Exposed Adult Subpop[10]				5 e-06	0.0096	880	0.0186			560

[1] Based on 10x uncertainty for interspecies and 10x for intraspecies variation and 3x for FQPA for endocrine effects; body weights used are 70kg male, 60 kg female, 10 kg child)

[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE

[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]

[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]

[5] Maximum Water Exposure (mg/kg/day) = Target Maxium Exposure - (Food Exposure + Residential Exposure)

[6] The crop producing the highest level was used.

[7] $\text{DWLOC}(\mu g/L) = \frac{[\text{maximum water exposure (mg/kg/day)} \times \text{body weight (kg)}]}{[\text{water consumption (L)} \times 10^{-3}\ \text{mg}/\mu g]}$; where male bw = 70 kg; female bw= 60 kg; child 1-7 bw = 10 kg; water consumption 2 L/day (adults); 1 L/day (infants and children)

[8] While the high-contact dermal exposure estimate *alone* exceeds the level of concern, the lower-contact exposure from golfing does not and was aggregated to illustrate the total risk for this non-residential, recreational use scenario

[9] NA = doses not aggregated, as the small child estimated hand-mouth incidental oral exposure *alone* exceeds the level of concern

[10] Exposure refers to the highest **dietary** exposure, in this case for female seniors.

5.3 Intermediate-Term Risk

Based on the label use pattern, including seasonal applications, and residue dissipation on turf in 14 days, no intermediate or long-term residential non-dietary exposures to pronamide are anticipated. An intermediate-term risk assessment was not conducted as there were no exposures of applicable (30 days to six months) duration.

5.4 Chronic Risk

5.4.1 Chronic Aggregate Risk Assessment

Due to the short-term, intermittent nature of residential or recreational exposure to pronamide, only dietary and water intake were included in the chronic aggregate exposure estimate. The $DWLOC_{chronic}$ is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD when considered together with other sources of exposure. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the chronic PAD to obtain the acceptable chronic exposure to pronamide in drinking water. The DWLOC was calculated and compared to the EECs. The EECs for average concentrations of pronamide were based on PRZM-EXAMS for surface water and SCI-GROW for groundwater. The chronic DWLOCs (300 - 1050 ug/L) were greater than the EECs for modeled surface water (1.6-6.5 ug/L), and modeled groundwater (3 ug/L). In addition, non-targeted USGS monitoring data ranged from 0.0037 to 0.365 ppb in surface water, and from 0.005 - 0.82 ppb in ground water. HED concludes the chronic aggregate risk estimates do not exceed the level of concern.

5.4.2 Chronic DWLOC Calculations

Table 7b. Pronamide - Summary of Chronic DWLOC Calculations

Population Subgroup	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	Chronic DWLOC (µg/L)	EFED Generated EECs[1]		USGS SW / GW Monitoring[6] (µg/L)
					Ground Water (SCI-GROW) (µg/L)	PRZM-EXAMS Chronic (µg/L)	
U.S. Population[a]	0.03	4 e-06	0.03	1050	3	1.6 - 6.5	SW: 0.0037 - 0.365 GW: 0.005 - 0.82
Females 13-50 yrs [b]		4 e-06		900			
Children 1-6 yrs		25 e-06		300			
All Infants		2 e-06		300			

Chronic aggregate exposures represent only dietary and water consumption; no chronic non-dietary exposures anticipated
[1]EEC = Estimated Environmental Concentrations
[2]Pronamide surface water EECs are from FIRST modeling .

$$DWLOC = \frac{\text{water exposure X body weight}}{\text{Liters of water X } 10^{-3}}$$ (where water exposure = cPAD - food exposure)

Body weight = 70 kg for U.S. Population, 60 kg for females, 10 kg for infants and children
Consumption = 2L/day for Adults and 1L/day for infants and children
[5]USGS - NAWQA Data Retrieval; Maximum ground water detection at Benton Ozark, AK at 0.82 ppb on April 13, 1994, data ranging form 0.82 - 0.005 ppb (ground

water).

5.5 Cancer Risk Estimates

5.5.1 Cancer Aggregate Risk Assessment

The estimated cancer risk from one day per year of postapplication (high or low contact) exposure to average pronamide residues on treated turf did not exceed the Agency's level of concern of 1.0×10^{-6} (one in a million). High contact activities for more than one day would exceed the level of concern. Based on the seasonal use pattern, only one to several days postapplication exposure are considered likely, and it is unlikely that a single person would have have daily high contact exposure during the 14-day dissipation period. The use of a 100 % dermal absorption factor adds to the conservatism of the cancer risk estimate. For average dietary consumption, the dose did not result in a cancer risk estimate of concern. Therefore the cancer estimates from each route can be aggregated.

5.5.2 Cancer DWLOC Calculations

The estimated DWLOC for cancer from food, drinking water, and residential exposure is <0.1 ppb. The Tier 2 PRZM/EXAMS 37 year mean concentration estimates range from less than 1 ppb to 4.3 ppb. The available USGS surface and groundwater monitoring data ranged from 0.0037 to 0.365 ppb in surface water, and from 0.82 - 0.005 ppb in ground water. Further refinement of the drinking water modeling estimates and/or detailed analysis of water monitoring data might be useful for risk assessment and risk management decisions, once the final disposition of residential/recreational uses is known..

Table 7c. Cancer DWLOC Calculations									USGS SW / GW Monitoring[6] (µg/L)
Population	Target Max Exposure[2] mg/kg/day	Chronic Food Exposure mg/kg/day	Residential Exposure (LADD) mg/kg/day	Aggregate cancer risk (food and residential)	Max Water Exposure[3] mg/kg/day	Cancer DWLOC[5] (µg/L)	Ground Water EEC[4] (µg/L)	PRZM-EXAMS Cancer (µg/L)	
U.S. Pop	3.86 e-05	4 e-06	3.2 e-05	9.3 e-07	2.6 e-06	<0.1	3	0.535 - 4.35	SW: 0.0037 - 0.365 GW: 0.005 - 0.82

[1] EPA's goal is to mitigate cancer risk to 1 x 10^{-6}.
[2] Target Maximum Exposure (mg/kg/day) = [negligible risk/Q*] ; negligible risk = 1.0 e-06; Q_1* = 0.0259
[3] Maximum Water Exposure (mg/kg/day) = [Target Maximum Exposure - (Chronic Food Exposure + Residential Exposure (Lifetime Average Daily Dose))]
[4] The crop producing the highest level was used.
[5] Cancer DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}^2}$

Body weight = 70 kg for U.S. Population
Consumption = 2L/day for Adults and 1L/day for infants and children
[6] USGS - NAWQA Data Retrieval; Maximum ground water detection at Benton Ozark, AK at 0.82 ppb on April 13, 1994, data ranging form 0.82 - 0.005 ppb (ground water).

The estimated cancer risk from one day per year of postapplication (high or low contact) exposure to pronamide treated turf did not exceed the Agency's level of concern of 1.0 x 10^{-6} (one in a million). However, more than one day's exposure to treated turf while golfing could result in a cancer risk estimate greater than 1.0 x 10^{-6} . For average dietary consumption, the dose did not result in a cancer risk estimate of concern. However, when the golfing exposure is added to the chronic food exposure, the estimated DWLOC for cancer is <0.1 ppb, which is below most of the screening level drinking water concentrations estimated by EFED, and therefore exceeds the level of concern. Some of the surface and groundwater monitoring data are greater than the DWLOC, which generates a concern for cancer.

Therefore, HED has some concerns for exposures to pronamide in drinking water for cancer risk. The model estimates for Northwest pears and apples, and alfalfa grown in CA indicate that an extreme case using highest label rates might present a concern for cancer. Typical rates for the fruit are one-half , and alfalfa is one-quarter the rates used in the model, according to the latest QUA report. The model estimates

would therefore be decreased proportionately for those crops if pronamide were applied at the lower or more typical use rate.

The registrant for pronamide has requested cancellation of the turf use in a letter dated January 14, 2002. If the turf use is canceled, there will be no residential or recreational non-dietary exposures, and the only remaining risk of concern will be the aggregate food and drinking water cancer estimate. Without residential/recreational exposure, the cancer DWLOC will be 1.2 ppb. Additional monitoring data, targeted at water sources near pronamide high use sites, such as lettuce fields in Monterey County, CA, could help refine the cancer risk assessment.

Uncertainties

Aggregate risk estimates as conducted in this document are considered to be high-end or conservative estimates, and can generally be refined, if necessary, with chemical-specific data. The postapplication dermal risk estimates were based on the Office of Pesticide's Residential SOPs (1997, 2001), which utilize both central tendency and upper-percentile assumptions (i.e., duration of exposure and maximum application rate for short-term assessments) and are considered to be representative of high end exposures. The adult and children's transfer coefficients are based on the Jazzercise protocol and an upper percentile exposure duration value. Where study data were used with the SOP formulae, these risk estimates were better refined, and hence, less conservative. Therefore, the exposure estimates related to turf skin contact (which were based on study data) are more refined than the estimates of incidental ingestion In addition, dermal doses assumed a 100% dermal absorption factor, and exposures are assumed to occur on the day of treatment (highest residue).

6.0 CUMULATIVE EXPOSURE TO SUBSTANCES WITH A COMMON MECHANISM OF TOXICITY

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this risk assessment for pronamide because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of pronamide. For purposes of this tolerance reassessment review, EPA has assumed that pronamide does not have a common mechanism of toxicity with other substances.

7.0 INCIDENT DATA

A review of incident data sources found that relatively few incidents of pronamide poisonings were reported (J. Blondell, M. Spann, August 10, 2001). There are only two Poison Center reports, no incident reports in OPPs Incident Data System and only two reports from the California Pesticide Illness Surveillance Program. On the list of the top 200 chemicals for which National Pesticide Telecommunications Network (NPTN) received calls from 1984-1991 inclusively, pronamide was not reported to be involved in human incidents.

8.0 TOLERANCE REASSESSMENT RECOMMENDATIONS

8.1 Tolerance Reassessment Recommendation

Pronamide tolerances are established under 40 CFR §180.317(a), (b), and (c). The tolerance expression, listed in (a) and (c), is in terms of the combined residues of the herbicide propyzamide and its metabolites (containing the 3,5-dichlorobenzoyl moiety and calculated as 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide). The tolerance expression, listed in (b), is in terms of the parent only. HED recommends that the tolerance expression under (b) be modified to include the metabolites (containing the 3,5-dichlorobenzoyl moiety and calculated as 3,5-dichloro-*N*-(1,1-dimethyl-2-propynyl)benzamide).

A summary of pronamide tolerance reassessments is presented in Table 8. For a full discussion of tolerances see the HED Residue Chemistry Chapter (J. Morales, February 28).

Tolerances for inadvertent residues of pronamide and its metabolites containing the 3,5-dichlorobenzoyl moiety should be proposed for: (1) the forage of cereal grains crop at 0.6 ppm; (2) the straw of cereal grains crop at 0.3 ppm; and (3) the hay of cereal grains crop at 0.2 ppm. The required tolerance proposal is concomitant with a recommendation for a label revision to establish a 180-day plantback interval for Crop Group 16.

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Table 8. Tolerance Reassessment Summary for Pronamide

Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity Definition*
Tolerances Listed Under 40 CFR §180.317(a)			
Apples	0.1	0.1	*Apple*
Artichokes	0.1	0.051	*Artichoke*
Blackberries	0.05	0.05	*Blackberry*
Blueberries	0.05	0.05	*Blueberry*
Boysenberries	0.05	0.05	*Boysenberry*
Cattle, fat	0.02	0.20	
Cattle, kidney	0.4	0.4	
Cattle, liver	0.4	0.4	
Cattle, mbyp (except kidney, liver)	0.02	0.02	
Cattle, meat	0.02	0.02	
Eggs	0.02	0.02	

Table 8. Tolerance Reassessment Summary for Pronamide

Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity Definition*
Endive (escarole)	1.0	1.0	
Goats, fat	0.02	0.20	
Goats, kidney	0.4	0.4	
Goats, liver	0.4	0.4	
Goats, mbyp (except kidney, liver)	0.02	0.02	
Goats, meat	0.02	0.02	
Grapes	0.1	0.1	*Grape*
Hogs, fat	0.02	0.20	
Hogs, kidney	0.4	0.4	
Hogs, liver	0.4	0.4	
Hogs, mbyp (except kidney, liver)	0.02	0.02	
Hogs, meat	0.02	0.02	
Horses, fat	0.02	0.20	
Horses, kidney	0.4	0.4	
Horses, liver	0.4	0.4	
Horses, mbyp (except kidney, liver)	0.02	0.02	
Horses, meat	0.02	0.02	
Lettuce	1.0	1.0	*Lettuce, head* Only head lettuce is supported by acceptable data; leaf lettuce uses must be removed from the label. Alternatively, the label may be revised to specify a practical PHI (35-day) for leaf lettuce and supporting data be submitted.
Milk	0.02	0.02	
Nongrass animal feeds	10.0	10.0	*Nongrass animal feeds (forage, fodder, straw, and hay) group*
Pears	0.1	0.1	*Pear*
Poultry, fat	0.02	0.02	
Poultry, kidney	0.2	Revoke	Tolerances are typically not established for poultry kidneys.
Poultry, liver	0.2	0.2	
Poultry, mbyp (except kidney, liver)	0.02	0.02	*Poultry, mbyp (except liver)*
Poultry, meat	0.02	0.02	
Radicchio, greens (tops)	2.0	2.0	
Raspberries	0.05	0.05	*Raspberry*
Sheep, fat	0.02	0.20	
Sheep, kidney	0.4	0.4	
Sheep, liver	0.4	0.4	

Table 8. Tolerance Reassessment Summary for Pronamide			
Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *Correct Commodity Definition*
Sheep, mbyp (except kidney, liver)	0.02	0.02	
Sheep, meat	0.02	0.02	
Stone fruits	0.1	0.1	*Stone fruits group*
Tolerances To Be Proposed Under 40 CFR §180.317(a)			
Alfalfa, seed	--	10.0	Tolerance recommendation is contingent upon required label revision to specify a 50-day PHI and a maximum seasonal rate of 2.0 lb ai/A.
Tolerances Listed Under 40 CFR §180.317(b)			
Cranberries	0.05 [with 12/31/01 expiration date]	0.05	*Cranberry*
Grass, forage	1.0 [with 12/31/01 expiration date]	1.0	Additional data are required for the establishment of permanent tolerances on grass forage and hay.
Grass, hay	0.5 [with 12/31/01 expiration date]	0.5	
Tolerances Listed Under 40 CFR §180.317(c)			
Peas, dried (winter)	0.05	TBD	*Pea, field, seed*
Rhubarb	0.1	0.1	
Tolerances To Be Proposed Under 40 CFR §180.317(c)			
Pea, field, hay	--	TBD	
Pea, field, vines	–	TBD	

CODEX HARMONIZATION

No Codex MRLs have been established or proposed for residues of pronamide. Therefore, issues of compatibility with respect to U.S. tolerances and Codex MRLs do not exist.

9.0 DATA NEEDS

Product Chemistry

Most pertinent product chemistry data requirements are satisfied for the Rohm and Haas 94.6% T/TGAI, except additional data are required concerning the materials used to produce the product and UV/Visible absorption (OPPTS 830.1600 and 7050). Additional data are also required for the Rohm and Haas 51% FI concerning oxidation/reduction, explodability, storage stability, and corrosion characteristics (OPPTS 830.6314, 6316, 6317, and 6320). Provided that the registrant submits the data required in the attached data summary tables for the pronamide T/TGAI and FI, and either certifies that the suppliers of beginning materials and the manufacturing processes have not changed since the last comprehensive product chemistry reviews or submits complete updated product chemistry data packages, HED has no

objections to the reregistration of pronamide with respect to product chemistry data requirements.

Toxicology

Although there is confidence in the overall scientific quality of the available toxicity data, several data gaps were identified: a developmental toxicity study in rats, a 21-day dermal toxicity study, 28-day inhalation toxicity study, a dermal penetration study and a comparative thyroid rat assay in adult animals and offspring.

Residue Chemistry

A review of the product labels and the supporting residue data indicate the following label amendments and data submissions are required:

- additional residue data are required for: use on grasses, dried winter peas (outstanding), the vines and hay of winter peas, grass forage, and hay.
- label amendments are required for alfalfa grown for seed, lettuce, and peas (winter); see chemistry chapter for details;
- label revisions should be made for rotational crops as listed:
  1. 30-day plantback interval for leafy vegetables (except *Brassica* vegetables) (Crop Group 4);
  2. 90-day plantback interval for root and tuber vegetables (Crop Group 1);
  3. 360-day plantback interval for cereal grains (Crop Group 15) and the forage, fodder, and straw of cereal grains (Crop Group 16).

For purposes of reregistration, no additional plant metabolism studies are required; however, because the available metabolism studies were only conducted on alfalfa and lettuce, the Agency may require additional metabolism studies in the future should the registrants seek for additional uses on other crop groups.

The registrant is required to further optimize/improve the revised animal enforcement method (TR 34-91-68) to yield acceptable recoveries at a fortification level equal to established animal tolerances. Following method improvement, the registrant is required to submit bridging independent laboratory validation data; the required ILV data should include two control samples fortified at 0.4 ppm, the reassessed tolerance level for the kidney and liver of ruminants.

Additional confirmatory storage stability data for the regulated pronamide metabolites on alfalfa, apples, grapes, lettuce, and peaches or plums are required.