UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 13, 2005

MEMORANDUM

SUBJECT: Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision Document (TRED) which includes a New Use on Grain Sorghum. PC Code: 080808, DP Barcode: D323271.

Regulatory Action: Phase One Tolerance Reassessment Eligibility Decision
Risk Assessment Type: Single Chemical/Aggregate

FROM: Jose Morales, Chemist
John Liccione, Toxicologist
Jose Morales, Chemist (Dietary Exposure Assessment)
Steve Weiss, ORE
Reregistration Branch 3
Health Effects Division (7509C)

THROUGH: Catherine Eiden, Branch Chief
Reregistration Branch 3
Health Effects Division (7509C)

TO: Diane Sherman, Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division (7508C)

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1.0 Executive Summary

Use Profile

Propazine is a chlorinated triazine herbicide. It acts by inhibiting photosynthesis and is considered to be a selective herbicide. It is usually applied as a pre-emergent herbicide to soil, absorbed through leaves and roots and translocated to other plant parts. It is systemic. Tolerances are expressed currently as propazine, per se. Under tolerance reassessment, it is recommended that tolerances be expressed as propazine plus desisopropyl (or des-ethyl atrazine) and diaminochlorotriazine (DACT).

Propazine controls many braodleaf weeds and grasses such as pig-weed, devil's claw, carpetweed, smartweed, kochia, morningglory, lambsquarter, ragweed, purslane, and Russian thistle. Propazine is currently registered for use on container-grown greenhouse ornamentals. The method of application for propazine to ornamentals is through flood or drench nozzles only. The REI for the registered use on ornamentals is 24 hours.

There is also a proposed use on grain sorghum, stover and forage. There are no residential uses of propazine. The proposed use of propazine on sorghum recommends 1.2 lbs. a.i./acre and 1 application per season. The method of application of propazine to sorghum is through ground and aerial application. Applications are made to sorghum at pre-plant and pre-emergence. The proposed REI and PHI for sorghum are 24 hours and 60 days, respectively.

Hazard Characterization

Propazine is not acutely toxic. Propazine shares a common mechanism of toxicity with atrazine and 4 other chlorinated triazine compounds: simazine, atrazine, and the 3 chlorinated degradates common to these compounds. All exhibit a Central Nervous System (CNS) toxicity resulting in neuroendocrine effects seen across a variety of species. Based on propazines' inclusion in the common mechanism of toxicity determined for the chlorinated triazines listed above, propazine can alter hormone levels in rats that may result in developmental and reproductive consequences. These neuroendocrine effects are the primary toxicological effects of regulatory concern. These effects are time and dose dependent. The neuroendocrine effects resulting in reproductive and developmental consequences seen in the test animals are believed to be relevant to humans.

Although previously classified as a Group C (possible human carcinogen), propazine has been reclassified as "Not Likely to be a Human Carcinogen". Like atrazine and simazine, propazine was shown to induce mammary tumors in Sprague-Dawley rats, and like atrazine, the mechanism associated with this tumor formation in the Sprague-Dawley rat is based on a CNS mechanism involving the neuroendocrine system. However, the mechanism responsible for tumor formation is believed to be species/strain-specific to the Sprague-Dawley rat as it has not been observed in any other species or rat strain tested. In June 2000, the Scientific Advisory Panel (SAP) concluded that the CNS mechanism of toxicity shared by atrazine, simazine, and propazine and their common degradates leading to tumor formation in the Sprague-Dawley rat is not operative in humans.

Because of propazine's similarity to atrazine, propazine is considered to be of equal potency to atrazine and the chlorinated degradates with respect to their common mechanism of toxicity. It was concluded that atrazine data can be used as bridging data for propazine, because propazine and atrazine share a common mechanism of toxicity based on neuroendocrine effects, the database for propazine's potential neuroendocrine effects is less robust than the atrazine database, and neuroendocrine effects are the effects of primary regulatory concern.

Therefore, for endpoint selection, the team considered atrazine endocrine-related data for selection of endpoints for propazine. Atrazine's neuroendocrine-related endpoints were selected for all risk assessment scenarios for propazine, except for the acute reference dose which was based on a study conducted with propazine which found a developmental effect (decreased ossification), the nature of which is not clearly linked to an endocrine mechanism. Further rationale to support the endpoint selection is provided in the remainder of this chapter.

Because the FQPA decision for atrazine was based on its neuroendocrine effects, the propazine team considered the FQPA decisions for atrazine as relevant to propazine. Thus similar rationales were used in determining the need for FQPA safety factors for propazine. In particular, it was noted for atrazine that the focus of testing in young rats had been limited to short-term dosing of specific developmental periods (e.g., postnatal 20-50 days in the rat pubertal assays) which raised two issues: the uncertainty associated with the apparent sensitivity during earlier developmental periods, and the uncertainty of the consequence of a longer duration of dosing throughout development. From a review of the literature on endocrine disruptors (EPA 1997 Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis by Crisp et al., and the 1999 NAS Report on Hormonally Active Agents in the Environment), an increased sensitivity can be found with exposures to early developmental periods with other endocrine disruptors. Therefore, it is important for any chemical that is an endocrine disruptor to evaluate critical periods throughout development. This same rationale has been applied to potential effects of propazine on the young during development.

Dietary Risk Estimates (Food + Water)

Residues of concern for dietary risk assessment are propazine and the des-isopropyl propazine and diaminochlorotriazine (DACT). The residue of concern for drinking water is propazine, per se. Combined acute exposures through water and food are below HED's level of concern for females 13-49 years of age, the population of interest. Combined chronic exposures through water and food are below HED's level of concern for all subpopulations. Drinking water exposures are the dietary risk drivers accounting for 100% of the aPAD and cPAD, respectively. Dietary exposures through food only are zero because there is no exposure to grain sorghum commodities reported in the diet.

Residential Exposure Estimates

There are no residential uses of propazine.

Aggregate Risk Estimates

As there are no residential uses of propazine, aggregate risk estimates are the same as described above under *Dietary Risk Estimates*.

Occupational Exposure Estimates

Occupational exposure and risk estimates were not assessed as this document supports a TRED.

Uncertainties

All risk estimates presented in this document are considered conservative and protective. Uncertainties associated with this assessment include the use of predictive models (PRZM/EXAMS) to estimate drinking water concentrations of propazine.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

Propazine is a triazine herbicide that is applied before planting, at planting, and after crop emergence for preemergence control of broadleaf weeds such as pigweed, devil's claw, carpetweed, smartweed, kochia, morningglory, lambsquarter, ragweed, purslane, and Russian thistle. Propazine can also be applied after removal of existing weeds. It is currently registered for use on container grown ornamentals in greenhouses, however, use on sorghum has been proposed and will be included in the propazine risk assessments. Propazine is formulated as a flowable concentrate.

Usage information on propazine can be found in the attached tables. The A2 table contains information on food/feed use patterns and the A3 table contains information on non-food/non-feed use patterns.

TABLE A2. FOOD/FEED USE PATTERNS SUMMARY FOR PROPAZINE

SITE NAME	LIMITATIONS					
Application Timing (for any Reg.# at any rate) Application Type (for any Reg.# at any rate) Application Equipment (for any Reg.# at any rate)	Max. Single Appl. Rate to a Single Site	Max. Seasonal Rate	Max. # Apps/ cc & yr	M R I	R E I	PHI/PGI/PSI Use Limitations (May not apply to all Reg. #s)
SORGHUM	60 day PHI Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not apply through any type of irrigation system. Do not contaminate water by cleaning of equipment or disposal of equipment wash waters. Do not contaminate water, food, or feed by storage or disposal.					
Preemergence Ground Aerial	1.2 lb a.i./acre	NS (1/cc)	1/cc NS	NS	24 h	
Preplant Ground Aerial	1.2 lb a.i./acre	NS (1/cc)	1/cc NS	NS	24 h	

HEADER ABBREVIATIONS
Site Name - The site name refers to the entity (crop, building, surface or article) where a pesticide is applied and/or which is being protected.
Limitations - Precautionary statements related to the use of the product(s).
Application Timing - The timing of pesticide application and is the primary application sort (not aggregated).
Application Type - The type of pesticide application (aggregated).
Application Equipment - The equipment used to apply pesticide (aggregated).
Max. Single Appl. Rate to a Single Site - Maximum Dose for a single application to a single site. System calculated.
Max Seasonal Rate - The maximum amount of pesticide that can be applied to a site in one growing season (/cc) and during the span of one year (/yr).
Max. # Apps/cc & yr - Maximum Number of Applications per crop cycle and per year.
M R I - Minimum Retreatment Interval (days) (at any rate). The minimum interval between pesticide application (days).
R E I - ReEntry Interval - The minimum amount of time that must elapse before workers can reenter a treated area.
PHI/PGI/PSI Use Limitations (May not apply to all Reg.#s) - Preharvest/Pregrazing/Preslaughter Interval use limitations pertinent to the application.
Current As Of: - The label data for the listed products in this report is current of this date.

ABBREVIATIONS
NS - Not Specified (on label)

SITE NAME	LIMITATIONS					
Application Timing (for any Reg.# at any rate) Application Type (for any Reg.# at any rate) Application Equipment (for any Reg.# at any rate)	Max. Single Appl. Rate to a Single Site	Max. Seasonal Rate	Max. # Apps/ cc & yr	M R I	R E I	PHI/PGI/PSI Use Limitations (May not apply to all Reg. #s)
ORNAMENTAL AND/OR SHADE TREES, ORNAMENTAL HERBACEOUS PLANTS, ORNAMENTAL NONFLOWERING PLANTS, ORNAMENTAL WOODY SHRUBS AND VINES	Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not apply through any type of irrigation system. Do not contaminate water by cleaning of equipment or disposal of equipment wash waters. Do not contaminate water, food, or feed by storage or disposal.					
At planting Flood or Drench nozzles	.03516 lb a.i./ 1000 sq. ft.	NS	1/cc NS	NS	24 h	
Postemergence Flood or Drench nozzles	.03516 lb a.i./ 1000 sq. ft.	NS	1/cc NS	NS	24 h	
Preplant Flood or Drench nozzles	.03516 lb a.i./ 1000 sq. ft.	NS	1/cc NS	NS	24 h	

PRODUCT NUMBERS CONTAINED IN THIS REPORT
001812-00352

HOMEOWNER PRODUCTS CONTAINED IN THIS REPORT
None

HEADER ABBREVIATIONS
Site Name - The site name refers to the entity (crop, building, surface or article) where a pesticide is applied and/or which is being protected.
Limitations - Precautionary statements related to the use of the product(s).
Application Timing - The timing of pesticide application and is the primary application sort (not aggregated).
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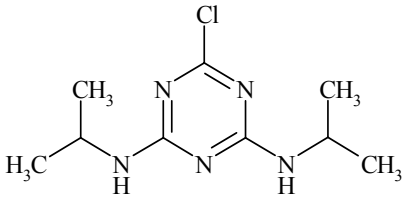
Max. Single Appl. Rate to a Single Site - Maximum Dose for a single application to a single site. System calculated.
Max Seasonal Rate - The maximum amount of pesticide that can be applied to a site in one growing season (/cc) and during the span of one year (/yr).
Max. # Apps/cc & yr - Maximum Number of Applications per crop cycle and per year.
M R I - Minimum Retreatment Interval (days) (at any rate). The minimum interval between pesticide application (days).
R E I - ReEntry Interval - The minimum amount of time that must elapse before workers can reenter a treated area.
PHI/PGI/PSI Use Limitations (May not apply to all Reg.#s) - Preharvest/Pregrazing/Preslaughter Interval use limitations pertinent to the application.
Current As Of: - The label data for the listed products in this report is current of this date.

ABBREVIATIONS
NS - Not Specified (on label)

2.2 Structure and Nomenclature

Propazine Nomenclature.	
PC Code 006308	
Chemical structure	
Common name	Propazine
Molecular Formula	$C_9H_{16}N_5Cl$
Molecular Weight	229.7
IUPAC name	6-chloro-N^2,N^4-di-isopropyl-1,3,5-triazine-2,4-diamine
CAS name	2-chloro-4,6-bis(isopropylamino)-1,3,5-triazine OR 6-chloro-*N*,*N*'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine
CAS #	139-40-2

2.3 Physical and Chemical Properties

Propazine is a colorless crystalline solid. It is stable in neutral, slightly acid, or alkaline media, but is hydrolyzed by stronger acids and alkalis. It is nonflammable and noncorrosive under normal use conditions, however may burn if exposed to heat or flame. Thermal decomposition may produce toxic oxides of carbon and nitrogen, and toxic and corrosive fumes of chlorides.

Physicochemical Properties of Propazine.		
Parameter	Value	Reference
Melting point	217.7 °C	RD D219079, 9/26/95, S. Malak
pH	5.66	
Density, bulk density, or specific gravity	0.46 g/mL	
Water solubility	3.8 ppm at 25 °C	
Solvent solubility (at 25 °C)	14,252 ppm in acetone 4,696 ppm in 1-octanol	
Vapor pressure	2.9×10^{-8} mm Hg at 20 °C 2.98×10^{-5} Torr at 45 °C	Product Chemistry Chapter of the Propazine Reregistration Standard, 5/19/87 RD D219079, 9/26/95, S. Malak
Dissociation constant, pK	Not applicable; practically insoluble in water.	RD D219079, 9/26/95, S. Malak
Octanol/water partition coefficient	P = 1234.7 Log P = 3.08	
UV/visible absorption spectrum	Not available	

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Propazine is metabolized and excreted in the rat within 48 hours of dosing. Most of the excreted propazine residues were detected in the urine and feces (with most of the residue recovered in the urine) with minor amounts respired as CO_2. Propazine is metabolized in the rat through the removal of alkyl side chains and conjugation of the triazine ring with glutathione-S-transferase. The mono- and di-dealkylated compounds, 2-chloro-4-ethylamino- 6-amino-s-triazine and diaminochlorotriazine (DACT), respectively, are the major rat degradates. Conjugated mercapturates of hydroxy propazine were also detected.

The metabolic pathway in plants is similar to that in rats. The submitted sorghum metabolism study indicates that propazine is rapidly and extensively metabolized in sorghum via: (i) N-dealkylation; (ii) replacement of chlorine by hydroxy; and (iii) glutathione conjugation. The results suggest that the metabolism of propazine in sorghum is similar to published and available plant metabolism studies for other triazine herbicides. Plant metabolism occurs via several competing routes. In one major route the N-ethyl groups are cleaved leaving the bare amine attached to the ring. First one ethyl group is lost, then both are lost, ultimately leaving diaminochlorotriazine (DACT). DACT can subsequently proceed to replacement of the chlorine with a proline group, which is attached to the triazine via the proline nitrogen. In a second major route of metabolism, the chloro group on propazine is replaced by a hydroxy group to hydroxy-propazine, which can proceed by loss of the isopropyl groups to diaminohydroxytriazine, the hydroxy equivalent of DACT. The diaminohydroxytriazine can then under go replacement of one or both amines by hydroxy groups ultimately leading to cyanuric acid. Alternatively, the chlorine in propazine can be replaced by glutathione and through a variety of intermediate conjugates can be eventually lysed to NH2-propazine, and then presumably loss of one or both isopropyl groups.

The metabolic pathway in livestock is also similar to that in plants and rats. The nature of propazine residues in livestock is adequately understood based on adequate metabolism studies with goats and hens. Propazine metabolism in animals is similar to that in plants, involving dealkylation and conjugation, with the triazine ring remaining intact. There is one exception to propazine metabolism in animals; animals do not metabolize propazine directly to hydroxy-propazine, but animals may receive hydroxy propazine through feeds. Several studies have been performed on the metabolism of propazine in livestock and poultry. In animals, in general, propazine residues tend to lose one or both isopropyl groups to form the chloro-metabolites or to replace the chloro- group with a hydroxy- group and then to lose one or both isopropyl groups. Feeding with hydroxy-propazine leads to formation, through loss of one or both isopropyl groups of hydroxy-metabolites only. A glutathione conjugate is also formed from the hydroxy-propazine.

The team concluded that based on the above descriptions, plant, animal, and rat metabolism are similar across all these metabolic pathways. The team further concludes that the metabolic pathway for propazine is also similar to that for simazine and atrazine.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

The nature of propazine residues in sorghum is adequately understood. Total radioactive residues (TRR) were 0.126, 0.133 and 2.344 ppm in/on sorghum forage, grain and fodder (stover), respectively, following one preemergence application of [^{14}C]propazine at 1.96 lb ai/A (1.6x the proposed single application rate). The parent propazine was identified at a range of <0.001-0.011 ppm (0.5-0.8% TRR) in sorghum matrices. The chlorometabolites G-30033 and G-28273 were not detected in grain but were identified as minor residue components in forage (8.7% TRR, 0.011 ppm) and stover (3.9% TRR, <0.091 ppm). Several free hydroxymetabolites (propazine 2-hydroxy; atrazine des-ethyl 2-hydroxy; and ammeline) were identified at slightly

higher combined levels in forage (22.2% TRR, 0.028 ppm), grain (12.6% TRR, <0.016 ppm), and stover (8.2% TRR, <0.193 ppm).

In a Memorandum of Understanding between HED and Griffin Corporation for Propazine (see 1/11/96 memo of M. Metzger), HED has indicated that if the metabolism of propazine is shown to be similar to the metabolism of chloro-triazines in sorghum, and toxicity of propazine is also similar, establishment of tolerances and risk assessment would be the same as for other triazines. As is discussed more fully below, although in many cases propazine and its chloro-metabolites are not the highest residues in crops, HED has concluded that they are the residues of interest and the residues to be used in the tolerance expression and for risk assessment. This decision is based largely upon toxicological considerations.

3.2.2 Description of Livestock Metabolism

Ruminants. The nature of propazine residues in ruminants is understood. In a goat metabolism study where [^{14}C]propazine was administered orally to a lactating goat at 9.9 ppm (~20x the estimated dietary burden of 0.5 ppm) in the diet for seven consecutive days, TRR were 0.080-0.238 ppm in milk, 1.123 ppm in liver, 1.041 ppm in kidney, 0.209 ppm in muscle, and 0.160 ppm in fat. The parent propazine was not detected in goat milk or tissues. The chlorometabolite G-28273 (DACT) was the principal residue identified in milk (63.4% TRR, 0.141 ppm), fat (50.4% TRR, 0.080 ppm), muscle (26.1% TRR, 0.054 ppm), and liver (2.7% TRR, 0.031 ppm). The metabolite G-30033 was identified in milk (9.4% TRR, 0.021 ppm) but not in tissues. The remaining radioactivity in goat milk and tissues was characterized to be comprised of up to six unknown metabolites. Although each unknown accounted for <7% TRR in milk, several unknowns were present at significant levels in goat tissues. None of these unknown residues co-chromatographed with the 17 reference standards including standards of known chloro- and hydroxy-metabolites of triazine herbicides.

Another goat metabolism study was performed using a radiolabeled hydroxymetabolite of propazine as the test substance. TRR were 0.025-0.029 ppm in milk, 0.006 ppm in muscle, 0.001 ppm in fat (renal and omental), 0.110 ppm in kidney, and 0.036 ppm in liver taken/collected from a lactating goat administered orally with [U-^{14}C]2-hydroxypropazine at 10.9 ppm in the diet for three consecutive days. Residue characterization was not conducted in muscle and fat tissues because of low radioactivity (<0.010 ppm). The test substance, 2-hydroxypropazine, was the major residue identified in all matrices accounting for 63.5% TRR (0.069 ppm) in kidney, 77.2% TRR (0.028 ppm) in liver, and 65.0-69.4% TRR (0.017-0.020 ppm) in milk. The only other metabolite identified was desisopropyl hydroxypropazine, which was detected in minor amounts in all matrices: 2.9% TRR (0.003 ppm) in kidney, 3.6% TRR (0.001 ppm) in liver and 8.2-8.5% TRR (0.002 ppm) in milk.

When the residue level in milk, which shows the highest residue from the study, is interpolated to 1x of the MTDB, the anticipated residue of G-28273 is about 0.004 ppm. In fat, the anticipated residue is 0.0023 ppm, in meat it is 0.0015 ppm, and in liver it is 0.00089 ppm.

Poultry. The nature of propazine residues in poultry is understood. TRR were 0.019-0.448 ppm in whole egg, 0.010-0.669 ppm in egg yolk, 0.024-0.327 ppm in egg white, 1.196 ppm in liver, 0.961 ppm in composite muscle, and 0.172 ppm in composite fat taken/collected from laying hens orally administered with [^{14}C]propazine at 20.3 ppm (~102x the dietary burden MTDB of 0.2 ppm) in the diet for 14 consecutive days. The parent propazine was not identified in poultry eggs or tissues. The only residue component identified was G-28273 which was quantitated in poultry matrices as follows: liver (4.3% TRR, 0.171 ppm), muscle (18.3% TRR, 0.212 ppm), fat (48.1% TRR, 0.083 ppm), egg yolk (35.3% TRR, 0.236 ppm), and egg white (51.9% TRR, 0.170 ppm). Seven unknown compounds were detected in select matrices some of which were observed at >10% TRR. The petitioner characterized these unknown metabolites to be relatively more polar than propazine based on the chromatographic profiles.

When the residue level in egg yolk, which shows the highest residue from the study, is interpolated to 1x of the MTDB, the expected residue of G-28273 is about 0.002 ppm.

Anticipated residues at the MTDB (1X) in meat byproducts, meat, fat, and egg whites are the same or less: 0.0017 ppm, 0.002 ppm, 0.002 ppm, and 0.0017 ppm, respectively.

Sorghum grain, forage, and stover, and soybean meal as a source of protein are the livestock feed items included in the maximum theoretical dietary burden (MTDB) given below. Following tolerance reassessment, the maximum theoretical dietary burden of propazine has been calculated (see Table 3) as follows: 0.29 ppm for beef cattle and dairy cattle, 0.16 ppm for swine, and 0.14 ppm for poultry.

Table 3. Calculation of Maximum Dietary Burdens of Propazine to Livestock.

Feedstuff	% Dry Matter [1]	% Diet [1]	Estimated Tolerance (ppm)	Dietary Contribution (ppm) [2]
Dairy & Beef Cattle				
Soybean, meal	89	15	0	0
Sorghum grain	86	35	0.15	0.061
Sorghum forage	35	35	0.20	0.200
Sorghum stover	88	15	0.15	0.025
TOTAL BURDEN	--	100	--	**0.29**
Swine				
Sorghum grain	86	90	0.15	0.157
TOTAL BURDEN	--	90	--	**0.157**
Poultry				
Sorghum grain	86	80	0.15	0.140
TOTAL BURDEN	--	80	--	**0.140**

[1] Table 1 (OPPTS Guideline 860.1000) & personnel communication B. Schneider.
[2] Contribution = ([tolerance /% DM] x % diet) for beef and dairy cattle; contribution = (tolerance x % diet) for poultry and swine.

Although there are no submitted feeding studies, the results of animal metabolism studies suggest a Category 3 situation with regard to the need for animal commodity tolerances as per 40 CFR §180.6(a)3. Based on the metabolism study results in the goat, there is no expectation of finite residues of propazine and its chlorometabolites in animal commodities as a result of the proposed use on grain sorghum.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

The nature of propazine residues in rotational crops is adequately understood. The study was initiated by applying [^{14}C]propazine to bare sandy loam soil at 2.39 lb ai/A (2.0x the proposed single application rate for sorghum). Lettuce, turnip, and spring wheat were then planted in the treated soil as rotational crops at plantback intervals (PBIs) of 29, 120, and 365 days. At the 29-PBI, total radioactive residues were 1.298 ppm for wheat forage, 5.787 ppm for wheat straw, and 1.680 ppm for wheat grain heads. At the 120-day PBI, TRR were 0.103 ppm for lettuce, 0.179 ppm for turnip tops, 0.057 ppm for turnip roots, 0.355 ppm for wheat forage, 1.987 ppm for wheat straw, and 0.928 ppm for wheat grain heads. At the 365-day PBI, TRR were 0.209 ppm for lettuce, 0.450 ppm for wheat forage, 1.028 ppm for wheat straw, and 0.245 ppm for wheat grain heads. Propazine was identified (<1-43% TRR) in all rotational crop matrices from all plantback intervals, but appears to decrease with longer plantback intervals. In addition to the parent, the following metabolites were identified: atrazine des-ethyl (G-30033); propazine 2-hydroxy (GS-11526); and atrazine des-ethyl 2-hydroxy (GS-17794). Quantitative data pertaining to the level of metabolite identification is presented in the topical section for OPPTS 860.1850. The primary metabolic products in rotational crops are similar to those found in the sorghum metabolism study. The propazine residues of concern in rotational crops, for the purposes of tolerance establishment and risk assessment, are the parent compound and its 2 chlorinated metabolites.

Two limited field rotational crop trials with propazine were conducted in NC and TX. At each site, a 4 lb/gal flowable concentrate formulation of propazine was applied as a preemergence ground spray to grain sorghum, the primary crop, at a nominal rate of 1.2 lb ai/A (1.0x the proposed single application rate). The primary crop was removed (by cutting) from the plots approximately 90 days after the test substance application. The following rotational crops were then planted at each field site: radish or turnip (a root vegetable), lettuce or mustard (a leafy vegetable), and winter or spring wheat (a cereal grain). The plantback intervals used in the study were 94, 127, and 242/280 days for the NC field site and 97, 120, 195, and 239 days for the TX field site.

The results of the NC trial indicate that residues of propazine, G-30033, and G-28273 were each below the LOQ of 0.0500 ppm in/on all samples of rotational crop commodities (mustard leaves, turnip tops/roots, and spring/winter wheat forage, hay, straw, and grain) at all PBIs (94, 127, and 242/280 days). The results of the TX trial indicate that residues of propazine, G-30033, and G-28273 were each below the LOQ of 0.0500 ppm in/on the following rotational crop commodities and plantback intervals: (i) lettuce leaves at a 97-day PBI; (ii) radish root at PBIs of 97 and 239 days; (iii) wheat forage at PBIs of 120 and 195 days; (iv) wheat hay, straw, and grain at PBIs of 97, 120, and 195 days. A few rotational crop commodities from the TX trial showed quantifiable residues including: (i) lettuce leaves at the 239-day PBI (propazine was detected at 0.0505-0.0510 ppm, G-30033 at 0.137-0.139 ppm, and G-28273 at 0.139 ppm); (ii) radish tops at the 97-day PBI (propazine was detected at 0.051-0.052 ppm); and (iii) wheat forage at the 97-day PBI (G-30033 was detected at 0.102-0.107 ppm). These data trigger the need for extensive field rotational trial data, as described under OPPTS 860.1900, to determine appropriate plantback intervals and tolerances for inadvertent residues of propazine and its chlorometabolites.

3.3 Environmental Degradation

Persistence: Existing laboratory studies indicate that propazine is resistant to breakdown by hydrolysis and photolysis (both aqueous and in soils). However, published literature on propazine and related chloro-s-triazines indicate that the chemical may be susceptible to hydrolysis after adsorption onto the surface of soil colloids (a surface catalysis effect). Propazine resists degradation under laboratory aerobic soil conditions with half-lives ranging from 15 weeks in loamy sand soil and to 41 weeks in sandy loam soil. The major soil metabolite is 2-hydroxy propazine (2-hydroxy-4,6-bis(isopropylamino)-s-triazine), which comprised a maximum of 31% of the total applied radioactivity (TAR) after one year. Minor degradates (less than 10% of TAR) consist of des-isopropyl propazine and 2-hydroxy des-isopropyl propazine.

Propazine is not likely to volatilize from near surface soils or surface waters under normal environmental conditions, due to its low vapor pressure (2.9 x 10-8 Torr at 20C). If released to water, propazine will not be expected to bioconcentrate in aquatic organisms, adsorb to sediment and/or suspended particulate matter, or to volatilize. Slow biodegradation of propazine may occur in natural water based upon its biodegradation in soil.

Mobility: Propazine does not adsorb as strongly to soil particles as other triazine herbicides. In most soils used in batch equilibrium studies, especially sand and sandy loam soils, it binds weakly to soil particles (Koc-ads = 268 and 128 mL/g, respectively). Literature studies also showed that depending on soil temperature, moisture, and pH, it can become unbound ("Worthing, C.R., ed., 1983. The pesticide manual: A world compendium. Croydon, England: The British Crop Protection Council."). The major degradate, hydroxypropazine is slightly less mobile, with Koc-ads values ranging from 78 (loam) to 342 (silty clay) mL/g. In sand and sandy loam soils, the Koc-ads values are 329 and145 mL/g, respectively.

Based on the information summarized above, propazine is expected to be moderately persistent and mobile in most soils, and it is resistant to breakdown by hydrolysis, photolysis, or biodegradation. The mobility of propazine is also noted in the fields, where supplemental terrestrial field dissipation studies suggest that propazine dissipates slowly from the upper 6 inches (half-lives of 51 days in TX, and 7 to 58 days in NC, <30 to 149 days in NY, <31 days in CA, and 60 to >357 days in NE) to leach to ground water. It has also been reported in the literature that if released to soil, propazine will persist longer in dry or cold conditions or other

conditions which inhibit biological and chemical activity (Worthing). It is therefore very likely that in areas where soils are highly permeable, the water table is shallow, or where there is irrigation and/or high rainfall, the use of propazine may result in ground water contamination.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4.1. Names and Structures of Important Metabolites of Propazine in Plants and Animals

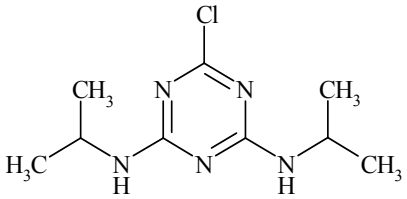
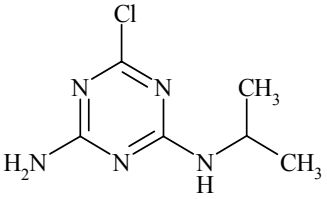
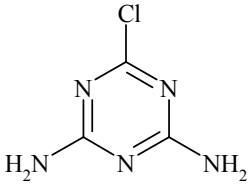
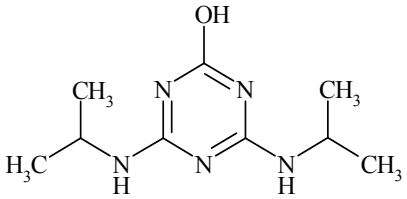
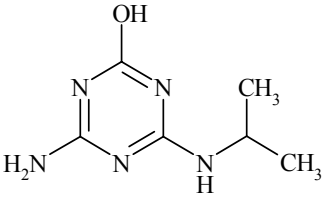
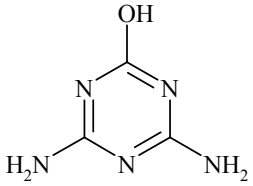
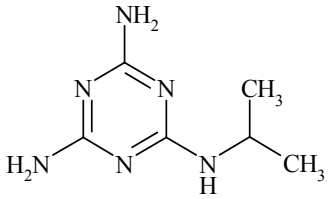
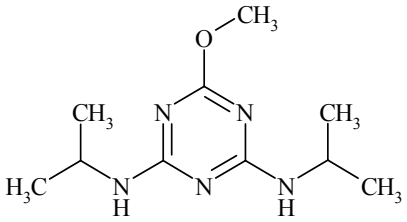
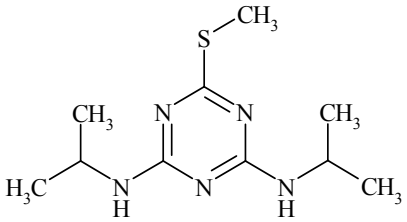
Table 3.4.1. Propazine and its Metabolites in Plants and Animals.		
Common Name (Code) Chemical Name	Substrate	Chemical structure
Propazine (G-30028) 2-chloro-4,6-bis(isopropylamino)-s-triazine	Sorghum forage, grain, and stover 120- and 365-day PBI lettuce; 120-day PBI turnip tops and roots; and 29-, 120- and 365-day PBI wheat forage, grain and straw.	
Propazine des-ethyl (G-30033) 2-amino-4-chloro-6-(1-methylethyl-amino)-s-triazine or 2-amino-4-chloro, 6-isopropylamino-s-triazine)	Sorghum forage and stover Goat milk 120- and 365-day PBI lettuce; 120-day PBI turnip tops and roots; 29-, 120- and 365-day PBI wheat forage; and 29- and 120-day PBI wheat grain and straw.	
DACT (G-28273) 2,4-diamino-6-chloro-*s*-triazine	Sorghum stover Goat milk, liver, muscle, and fat Poultry liver, muscle, fat, egg yolk, and egg white	
Propazine 2-hydroxy or **2-hydroxypropazine** (G-S11526) 2-hydroxy-4,6-bis-(1-methylethyl-amino)-s-triazine or 2-hydroxy-4,6-bis (isopropylamino)-s-triazine	Sorghum forage, grain, and stover Goat kidney, liver, and milk (from the goat metabolism study using [U-^{14}C]2-hydroxypropazine as the test substance) 120-day PBI turnip tops; 29-day PBI wheat forage and straw; and 29- and 120-day PBI wheat grain.	
Desisopropyl hydroxypropazine 4-amino-2-hydroxy-6-isopropylamino-triazine	Goat kidney, liver, and milk (from the goat metabolism study using [U-^{14}C]2-hydroxypropazine as the test substance). Sorghum forage, grain, and stover 120- and 365-day PBI lettuce; 120-day PBI turnip tops and roots; and 29-, 120- and 365-day PBI wheat forage, grain and straw.	

Table 3.4.1. Propazine and its Metabolites in Plants and Animals.		
Common Name (Code) Chemical Name	Substrate	Chemical structure
Ammeline (GS-17791) 2,4-diamino-6-hydroxy-*s*-triazine	Sorghum stover	
Triazine-methyl-triamine (CGA-101248) N-(1-methyl)-1,3,5-triazine-2,4,6-triamine	Sorghum stover	
Prometon (G-31435) 2-methoxy-4,6-bis (1-methylethylamino)-*s*-triazine	Sorghum stover	
Propazine-2-methyl-sulfinyl (GS-16141) 2,4-bis (1-methylethylamino)-6-methylsulfinyl-*s*-triazine	Sorghum stover	

3.5 Toxicity Profile of Major Metabolites and Degradates

Propazine toxicity has been bridged to atrazine toxicity and the toxicity of metabolites des-isopropyl propazine (G-30033) and DACT (G-28273) are taken to be the same as the parent, as they are for atrazine. Specific toxicity information exists for DACT allowing it to be bridged to atrazine, and hence to propazine. Although no toxicity information exists for the hydroxy propazine metabolites, it does exist for the hydroxy-atrazine metabolites, and the hydroxy-propazine metabolites are likewise taken to have the same toxic properties as the hydroxy-atrazine metabolites. Toxicity studies conducted in the rat were submitted for sub chronic, chronic/carcinogenic, and developmental effects of hydroxy atrazine. Results indicate that the kidney is the primary target organ associated with hydroxy atrazine toxicity. Hydroxy atrazine crystals appeared in the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorinated metabolites of atrazine. Hydroxy atrazine is not a chlorinated metabolite of atrazine and is not expected to be associated with any of the effects attributed to atrazine or its chlorinated metabolites.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

In a Memorandum of Understanding between HED and Griffin Corporation for Propazine (see 1/11/96 memo of M. Metzger), HED has indicated that if the metabolism of propazine is shown to be similar to the metabolism of chloro-triazines in sorghum, and toxicity of propazine is also similar, establishment of tolerances and risk assessment would be the same as for other triazines.

Tolerances have been reassessed for propazine; the reassessment table can be found in Appendix 3.0.

3.6.1 Tabular Summary

Table 3.6.Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Propazine and its 2 Chloro-metabolites	Propazine and its 2 Chloro-metabolites
	Rotational Crop	Propazine and its 2 Chloro-metabolites	Propazine and its 2 Chloro-metabolites
Livestock[a]	Ruminant	N/A	N/A
	Poultry	N/A	N/A
Drinking Water		Propazine	NA

[a] Meat, meat byproducts, fat, milk and eggs are expected to be covered by 40CFR180.6(a)3 as having no reasonable expectation of residues.

3.6.2 Rationale for Inclusion of Metabolites and Degradates

Propazine and the chlorinated degradates are recommended by the team as the compounds for risk assessment and for the tolerance expression in plants and animals. Propazine and its chloro-metabolites, des-isopropyl propazine and DACT all share a neuroendocrine mechanism of toxicity that is of primary regulatory concern. They are considered to have equal potency toxicologically. Propazine and the chlorinated metabolites are detected in plants and animal tissues. But in plants they are mainly detected in stems and leaves of plants (as the forages of grains) rather than the fruiting portions of plants (i.e., fruits, nuts, grain seeds, etc). This is because propazine is primarily translocated after pre-plant and pre-emergence applications directed to the ground, rather than being foliarly applied. As seems to be common for many herbicides, propazine residues are generally poorly translocated to the fruiting parts of the plant. The only foliar applications for propazine are to ornamentals, non-food uses. Therefore, although infrequent and low detection of propazine and the chlorinated degradates is the rule, the use of propazine and the chlorinated metabolites for the tolerance expression should be sufficient to detect any illegal and misuses of propazine products.

Hydroxy-atrazine has a different toxicological profile from atrazine (see Tables 4.1.b & c), and although no toxicological data are available for hydroxy-propazine, by analogy, the hydroxy-propazine metabolites are expected to have a different toxicological profile from propazine and the chlorinated degradates. Although hydroxy-propazine residues are present in plants, exposure to hydroxy-propazine metabolites is mainly expected to be through livestock products from eating feed items made of the stems and leaves of treated plants (transfer from animals commodities is not expected from the proposed use in sorghum). An assessment for hydroxy-atrazine with a wide use of atrazine on corn (>75% crop-treated), led to exposures and risk estimates that were <1% of the cPAD for hydroxy-atrazine. From this it is anticipated that the exposure to hydroxy-propazine in the diet would be very small, and of very low risk. Therefore the propazine team recommends against risk assessments, or tolerance expressions including the hydroxy-propazine metabolites.

The drinking water assessment for this risk assessment was based on parent propazine only, as insufficient data exist to fully assess the persistence and mobility of propazine's major degradate, hydroxy-propazine [2-hydroxy-4,6,bis(isopropylamino)-s-triazine] in the

environment. Furthermore, based on the risk assessment of the atrazine and simazine, this hydroxy-propazine [2-hydroxy-4,6,bis(isopropylamino)-s-triazine] was not considered to be of toxicological concern to human health. The minor degradates DEA and DACT, although of equal potency toxicologically compared to parent propazine, were also not included in this assessment mostly based on their low detection in the laboratory soil metabolism studies and in the terrestrial field studies (less than 5% of Total Applied Radioactivity (TAR)) . For atrazine and simazine, these chlorinated degradates were formed at much higher percentage, and ample monitoring data were available to adequately estimate their concentrations versus those of the parents. For propazine, minimal monitoring data exist for an adequate quantitative assessment of the chlorinated degradates. Additionally, as mentioned above, laboratory and field studies indicate that DEA and DACT, if formed in the environment, would not be present nor would persist at any significant concentration compared to parent propazine to adversely impact the results of the drinking water assessment, as presented in this document.

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

The toxicity database for propazine is considered complete for the assessment of toxicological endpoints for risk assessment purposes.

In a thorough weight-of-evidence analysis, the EPA has determined that the available scientific evidence indicates that a common mechanism of toxicity exists among certain triazine-containing pesticides (U.S. EPA 2002. The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity). Propazine has been grouped with several structurally-related, chlorinated triazines (e.g., atrazine, simazine, and 3 chlorotriazine degradates common to atrazine, simazine and propazine) on the basis of a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis. As a result of their common mechanism of toxicity, exposure to propazine, like exposure to atrazine, results in reproductive and developmental effects and consequences that are considered relevant to humans. These effects form the basis of the regulatory endpoint selection for both compounds. This mechanism involves a central nervous system (CNS) toxicity, specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus, which cause cascading changes to hormone levels, e.g., suppression of the luteinizing hormone surge prior to ovulation resulting in prolonged estrus in adult female rats (demonstrated with atrazine and propazine), and developmental delays, i.e., delayed vaginal opening and preputial separation in developing rats (studied in atrazine and propazine). These neuroendocrine effects are considered the primary toxicological effects of regulatory concern. The NOAEL for endocrine changes is protective of systemic toxicity.

This CNS mechanism of toxicity also results in mammary tumors specific to female Sprague-Dawley rats exposed to propazine, simazine and atrazine; however, the particular cascade of events leading to tumor formation in this specific strain of rat is not considered to be operative in humans. Consequently, atrazine has been classified as “Not Likely to be Carcinogenic to Humans”, as per the June 2000 Scientific Advisory Panel (SAP) report. Similarly, propazine has been reclassified as “ “Not Likely to be Carcinogenic to Humans” by the HED Cancer Assessment Review Committee (CARC) as per HED memo TXR No. 0053936, J. Kidwell, 12/8/05.

Propazine is considered to be of equal potency to atrazine, simazine and the chlorinated degradates with respect to their common mechanism of toxicity, based on the available data on simazine and propazine, which indicate comparable endocrine effects to atrazine. It was concluded that atrazine data can be used as bridging data for propazine because propazine, simazine and atrazine share a common mechanism of toxicity based on neuroendocrine effects, the database for propazine’s potential neuroendocrine effects is less robust than the atrazine database, particularly for the young, and neuroendocrine effects are the effects of primary regulatory concern.

Therefore, for endpoint selection, the team considered atrazine endocrine-related data for selection of endpoints for propazine. Atrazine’s neuroendocrine-related endpoints were selected

for all risk assessment scenarios for propazine, except for the acute reference dose which was based on a study conducted with propazine which found developmental effect (incomplete ossification), the nature of which is not clearly linked to an endocrine mechanism. Further rationale to support the endpoint selection is provided in the remainder of this chapter.

Because the FQPA decision for atrazine was based on its neuroendocrine effects, the propazine team considered the FQPA decisions for atrazine as relevant to propazine. Thus similar rationales were used in determining the need for FQPA safety factors for propazine. In particular, it was noted for atrazine that the focus of testing in young rats had been limited to short-term dosing of specific developmental periods (e.g., postnatal 20-50 days in the rat pubertal assays) which raised two issues: the uncertainty associated with the apparent sensitivity during earlier developmental periods, and the uncertainty of the consequence of a longer duration of dosing throughout development. From a review of the literature on endocrine disruptors (EPA 1997 Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis by Crisp et al., and the 1999 NAS Report on Hormonally Active Agents in the Environment), an increased sensitivity can be found with exposures to early developmental periods with other endocrine disruptors. Therefore, it is important for any chemical that is an endocrine disruptor to evaluate critical periods throughout development. This same rationale has been applied to potential effects of propazine on the young during development.

Acute Toxicity: The acute toxicity database for propazine is considered complete for acute oral, acute dermal, acute inhalation, dermal and eye irritation, and dermal sensitization. Propazine has a low order of toxicity via the oral (Category IV), dermal (Category IV) and inhalation (Category III) routes of exposure. It is not an eye or skin irritant, or a dermal sensitizer. The acute toxicity data for propazine are summarized below in Table 4.1a.

Table 4.1 a. Acute Toxicity Profile - Propazine technical

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.11	Acute Oral	43474101	LD_{50} > 5050 mg/kg	IV
870.12	Acute Dermal	43474102	LD_{50} > 5050 mg/kg	IV
870.13	Acute Inhalation	43474103	LC_{50} > 1.22 mg/L	III
870.24	Primary Eye Irritation	43474104	Slight irritant	IV
870.25	Primary Dermal Irritation	43474105	Negative	IV
870.26	Dermal Sensitization	43474106	Negative	N/A

Chronic Toxicity: The chronic toxicity database for propazine is considered complete for assessment of chronic toxicity in the rodent. A chronic dog study is in progress.

In a two-year dietary study in rats treated with propazine, decreased body weights were evident in the high-dose males (51 mg/kg/day) and females (68 mg/kg/day). There were no treatment-related effects on food consumption, clinical chemistry, hematology and urinalysis. The NOAELs were 5.2 mg/kg/day for males and 6.4 mg/kg/day for females.

In a carcinogenicity study, female mice administered 450 mg/kg/day propazine exhibied myocardial degeneration. The NOAEL in females is 150 mg/kg/day. The NOAEL in males is 450 mg/kg/day.

Developmental/Reproductive Toxicity: Available developmental toxicity data provided no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits to *in utero* and/or postnatal exposure to propazine. Developmental effects (incomplete ossification) in the rat were observed in the presence of maternal toxicity (decreased body weight and food consumption at 100 mg/kg/day). Maternal and developmental NOAELs are 10 mg/kg/day. In the rabbit, maternal effects (decreased body weight gain, food consumption and defecation) were

noted at 50 mg/kg/day (high dose tested). The NOAEL is 10 mg/kg/day. There were no developmental effects.

Body weight decrement in rat offspring was reported in the three-generation reproduction study (LOAEL = 50 mg/kg/day; NOAEL = 5 mg/kg/day). Maternal body weight decrement was also observed at 50 mg/kg/day.

Special Studies: Special studies were conducted to measure hormone level changes as a result of exposure to atrazine and simazine, triazines similar in struture to propazine. These studies are the basis for using atrazine endpoints and points of departure (NOAELs and LOAELs) in the propazine risk assessment. These studies were also used in a recent risk assessment for simazine. The results of these studies showed similar effects at equivalent doses in the short-term studies, i.e., the 28-day and 14-23 day studies between atrazine and simazine or that atrazine's endpoints were protective of simazine's toxic effects. Unfortunately, a comparison of LH-surge effects for the longer-term studies could not be made because of the inadequacy of the 6-month simazine study with regard to evaluation of endocrine effects. These studies are summarized below:

Simazine	**Atrazine**
Special Study - LH surge in rats (SD) (gavage - 4 weeks) **MRID 45471002**	**Special Study - LH surge in rats (SD) (gavage - 4 weeks)** **MRID 45471002**
LOAEL for systemic toxicity: 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects.	LOAEL for systemic toxicity: 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects.
NOAEL for all three compounds is 5 mg/kg/day.	NOAEL for all three compounds is 5 mg/kg/day.
LOAEL for endocrine effects : 40 mg/kg/day for simazine, atrazine, and DACT, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels).	LOAEL for endocrine effects : 40 mg/kg/day for simazine, atrazine, and DACT, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels).
NOAEL for endocrine effects: 5.0 mg/kg/day for simazine, atrazine, and DACT.	NOAEL for endocrine effects: 5.0 mg/kg/day for simazine, atrazine, and DACT.
Special Study - 6-month LH surge study in the rat (SD) **MRID 45622309**	**Special Study - 6-month LH surge study in the rat (SD)** **MRID 44152102**
An unacceptable study was available, and not useful for risk assessment.	LOAEL: 3.65 mg/kg/day, based on estrous cycle alterations and LH surge attenuation.

Simazine	Atrazine
Special Study - in vivo endocrine effects in rats (SD). (14-23 days) MRID 43598614	**Special Study - in vivo endocrine effects in rats (SD). (14-23 days) MRID 43598614**
LOAEL for systemic toxicity: 100 mg/kg/day for both atrazine and simazine, based on body weight effects and organ weight effects for atrazine.	LOAEL for systemic toxicity: 100 mg/kg/day for both atrazine and simazine, based on body weight effects and organ weight effects for atrazine.
NOAEL for toxicity: cannot be determined.	NOAEL for toxicity: cannot be determined.
LOAEL for endocrine effects : 300 mg/kg/day based on organ weight effects and vaginal cytology.	LOAEL for endocrine effects: 100 mg/kg/day based on organ weight effects, plasma hormone changes (estradiol), estrus cycle lengthening, and vaginal cytology.
NOAEL for endocrine effects: 100 mg/kg/day.	NOAEL for endocrine effects: cannot be determined.

In addition to the special studies, there are published data (Laws et al. 2003) on the pubertal effects of propazine in the female rat. These data demonstrated that propazine can delay the onset of puberty in the female rat at doses equimolar to atrazine. Unpublished EPA research data also have demonstrated that propazine can affect LH surge in a similar manner as atrazine and simazine.

Carcinogenicity/Mutagenicity: In 1989, the HED Cancer Peer Review Committee (CPRC) classified propazine as a **Group C Carcinogen (possible human carcinogen)** with a linear low-dose approach (Q_1*) based on mammary tumors in Sprague-Dawley rats for human risk characterization. However, this classification preceded the carcinogenicity evaluation of atrazine, a structurally similar triazine that is now considered "not likely to be carcinogenic to humans", because the mechanism of toxicity leading to mammary tumor formation in the female Sprague-Dawley rat is not operative in humans. Since propazine has been grouped with atrazine and other triazines on the basis of common mechanism of action of carcinogenicity, propazine has been reclassified by CARC (December 2005) as "not likely to be carcinogenic to humans."

Propazine was negative in gene mutation and structural chromosomal aberration assays in chinese hamster cells. Propazine produced a dose-related positive response without metabolic activation. Propazine was negative in a chromosomal aberration assay in spermatogonial cells in the mouse.

The following table is the complete toxicity profile for propazine.

Subchronic and chronic toxicity data for propazine are summarized in Table 4.1b.

Table 4.1.b. Subchronic, Chronic and Other Toxicity Profile for Propazine

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3150 13-Week dietary toxicity (dog)	00111680 0, 1.25, 5.0, or 25 mg/kg/day	Unacceptable - not upgradable
870.3200 21/28-Day dermal toxicity (rat)	44127401 0, 10, 100 or 1000 mg/kg/day	systemic NOAEL = 100 mg/kg/day systemic LOAEL = 1000 based on decreased body weight gain
870.3700a Prenatal developmental in Rat	00150242 0, 10, 100 or 500 mg/kg/day	Maternal NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight and food consumption. Developmental NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on decreased ossification.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Prenatal developmental in Rabbit	44153401 0, 2, 10 or 50 mg/kg/day	Maternal NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on decreased body weight gain, decreased food consumption, and decreased defecation. Developmental NOAEL $\geq$ 50 mg/kg/day (hdt) LOAEL : not identified.
870.3800 Reproduction and fertility effects (Rat)	00041409 0, 3, 100, or 1000 ppm (0, 0.15, 5, or 50 mg/kg/day)	Parental/Systemic NOAEL = 5.0 mg/kg/day (M&F) LOAEL = 50 mg/kg/day based on decreased body weight.(M&F) Offspring NOAEL $\geq$ 50 mg/kg/day LOAEL: not identified)
870.4100b Chronic toxicity (dog)	Study recently submitted and in review	Study recently submitted and in review
870.4200 Carcinogenicity (rat)	00041408 Acceptable-guideline 0, 3, 100, or 1000 ppm M: 0, 0.1, 5.2, or 51 mg/kg/day F: 0, 0.2, 6.4, or 68 mg/kg/day	NOAEL = 5.2 mg/kg/day (M); 6.4 mg/kg/day (F) LOAEL = 51 mg/kg/day (M) based on decreased body weight; 68 mg/kg/day (F), based on decreased body weight. Carcinogenicity -treatment-related increase in mammary gland tumors (adenocarcinomas and adenomas)
870.4300 Carcinogenicity (mouse)	00044335 Acceptable-guideline 0, 3, 1000 or 3000 ppm (0, 0.45, 150 or 450 mg/kg/day)	NOAEL = 450 mg/kg/day (M); 150 mg/kg/day (F) LOAEL = 450 mg/kg/day based on myocardial degeneration (F) . No evidence of carcinogenicity.
Gene Mutation: Chinese Hamster Cells	00163222 Acceptable-guideline 100-1000 µg/ml in the in the presence and absence of mammalian metabolic activation	Propazine produced a dose-related positive response without metabolic activation . A lesser and non-dose-related response was observed in presence of metabolic activation.
Structural Chromosomal Aberration: Chinese Hamster Cells	00150622 Acceptable-guideline 1250, 2500 or 5000 mg/kg	Negative
DNA Damage: Primary Rat Hepatocytes	00150623 0, 0.5, 2.5, 12.5, pr 62.5 µg/ml	Negative
Chromosomal Aberration: Mouse Spermatogonial Cells	46171701 0, 500, 1000, or 2000 mg/kg	Negative
870.6200a Acute neurotoxicity screening battery	Not available.	N/A
870.6200b Subchronic neurotoxicity screening battery	Not available.	N/A

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics (rat)	4368901 Acceptable-guideline	Propazine (2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine, unlabeled 98.2% a.i. or as [ring-UL-^{14}C]-Propazine, 99.6% a.i.) was administered to Sprague Dawley rats (5/sex/dose group) as a single gavage dose of 1.0 or 100 mg/kg labeled Propazine or as 14-daily doses of unlabeled 1.0 mg/kg Propazine followed by a single 1.0 mg/kg labeled dose. Corn oil was the vehicle for all treatments. Absorption from the gastrointestinal tract was rapid and similar for all study groups and no apparent sex-related differences were found. Based on recoveries from urine/cage wash and tissues, absorption was ≥73%. Within 48 hours of treatment, 82-95% of the administered dose was recovered from excreta, predominately the urine. No specific target organs were identified. Labeled Propazine was recovered only in the feces of male and female rats in the single high-dose group and female rats in the single low-dose group. As presented, it cannot be determined if this represents unabsorbed material or material that underwent enterohepatic circulation. Less than 0.1% of the administered dose was detected as CO_2 during a pilot study. Thirteen metabolites were recovered; three of which were identified. The predominant, G 28273, accounted for 20-30% of the administered dose while the other two contributed <5%. Of 10 unidentified metabolites detected, the combined contribution of six was <15% of the administered dose. Unidentified Metabolite 5 was predominant and contributed 18-24% of the administered dose for all study groups with unidentified Metabolites 4 and 8 next abundant. Although unidentified Metabolite 1 was found at <3% of the administered dose for most treatment groups, it accounted for 11% of the dose from male rats in the single high-dose group. Based on the results and literature review of other 2-chloro-*s*-triazines, the study author proposed that Phase I metabolism proceeded by dealkylation at the 4 and 6 amin positions to ultimately form G 28273 while Phase II metabolism involved glutathione conjugation. Although glucuronidation could not be ruled out, the author suggested that unidentified Metabolites 4 and 5 were glutathione conjugates.
Dermal Absorption - rat	Not available	Not available

Hydroxy-propazine and Hydroxy-atrazine:

For this assessment, the team assumes that hydroxy-propazine has a toxic profile and exhibits similar toxic effects as hydroxy-atrazine. Toxicity studies conducted in the rat were submitted for sub chronic, chronic/carcinogenic, and developmental effects of hydroxy atrazine. Results indicate that the kidney is the primary target organ associated with hydroxy atrazine toxicity. Hydroxy atrazine crystals appeared in the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorinated metabolites of atrazine. Hydroxy atrazine is not a chlorinated metabolite of atrazine and is not expected to be associated with any of the effects attributed to atrazine or its chlorinated metabolites. Subchronic and chronic toxicity data for Hydroxy-atrazine are summarized in Table 4.1.c.

Table 4.1. c. Subchronic, Chronic and Other Toxicity Profile for Hydroxy-atrazine		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
870.3100 90-Day oral toxicity rodents	MRID 41293501 (1989) 0, 10, 100, 300, 600 ppm 0, 0.6, 6.3, 18.9, 37.5 mg/kg/day - males 0, 0.8, 7.4, 22.8, 45.6 mg/kg/day - females	NOAEL = 6.3 mg/kg/day in males and 7.4 mg/kg/day in females LOAEL = 18.9 mg/kg/day in males and 22.8 mg/kg/day in females based on kidney alterations .
870.3700a Prenatal developmental in rodents	MRID 41065202 (1989) 0, 5, 25, or 125 mg/kg/day	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 125 mg/kg/day based on decreased food consumption during the dosing period and enlarged and mottled kidneys. Developmental NOAEL = 25 mg/kg/day. Developmental LOAEL = 125 mg/kg/day based on increased incidence of partially ossified interparietal and hyoid bones and decreased fetal body weight.
870.4100a (870.4300) Combined Chronic Toxicity/ Oncogenicity – Rat	MRID 43532001 (1995) 0, 10, 25, 200, 400 ppm 0, 0.39, 1.0, 7.8, 17.4 mg/kg/day - males 0, 0.5, 1.2, 9.4, 22.3 mg/kg/day - females	NOAEL = 1.0 mg/kg/day for males and 1.2 mg/kg/day for females LOAEL = 7.8 mg/kg/day for males and 9.5 mg/kg/day for females based on gross and histopathological effects in the kidneys
870.5100 Bacterial reverse mutation assay	MRID 40722304 (1988) 0, 20, 78, 313, 1250, 5000 µg/0.1 ml	No increases in revertant colonies in TA 98, 100, 1535, and 1537 Salmonella strains exposed to precipitating concentrations (313 µg/plate and above) both with and without activation system.
870.5375 Micronucleous assay	MRID 41479401 (1988) 0, 1250, 2500, 5000 mg/ml	No increase in micronuclei in mice treated with acute intubated doses up to the limit dose of 5000 mg/ml.
870.5550 UDS assay	MRID 40722305 (1988) 0, 13.9, 41.7, 125, 375, 750, 1500 µg/ml	No evidence of unscheduled DNA synthesis was found up to the limits of solubility (increasing precipitation from 500 µg/ml) and at concentrations approaching toxicity (1500 µg/ml) in primary hepatocyte cultures treated *in vitro*.
870.5550 UDS assay	MRID 40888101 (1988) 0, 13.9, 41.7, 125, 375, 750, 1500 µg/ml	Negative up to the limits of solubility (increasing precipitation from 500 µg/ml) and severe cytotoxicity (1500 µg/ml) in human fibroblast cells

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database for propazine is adequate for the evaluation of risks to infants and children. Relevant studies include developmental toxicity studies in the rat and rabbit and a 2-generation reproductive toxicity study in the rat. In addition, there are several non-guideline studies on propazine that assess endocrine-related toxicity. Also, endocrine toxicity studies on atrazine were used as bridging data on the basis of a common mechanism of toxicity.

4.2.2 Evidence of Neurotoxicity

Acute and subchronic neurotoxicity studies are not available. Effects commonly associated with neurotoxicity, i.e., staggered gait, excessive salivation, twitching, disorientation) were not observed in the available database. Based on the weight-of-evidence, propazine has been grouped along with atrazine, simazine and several degradants by a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis. Data indicate that propazine treatment is associated with neuroendocrine-related effects, e.g., attenuation of the LH pituitary surge and disruption of the estrus cycle and these effects are indicative of neuroendocrine toxicity. Studies with the structurally similar triazine, atrazine, have revealed neuroendocrine effects including decreased secretion of hypothalamic catecholamine levels and gonadotgrophin releasing hormone.

4.2.3 Developmental Toxicity Studies

Developmental Rat Study

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00150242), propazine (99.1%) was administered to 25/dose female Sprague-Dawley rats by gavage at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 6 through 15.

Salivation, described as "clear" was reported in 15 of the pregnant females in the 500 mg/kg/day group; salivation also occurred in 2/7 females in the range-finding study at the HDT of 1000 mg/kg/day. Maternal body weights were decreased in the 100 mg/kg/day group (-7% compared to controls on day 13 of gestation) and in the 500 mg/kg/day group (-14% on day 13). The decreased body weights were accompanied by decreased food consumption in the 100 mg/kg/day group (-18% on day 6) and the 500 mg/kg/day group (-40% on day 6). **The maternal NOAEL is 10 mg/kg/day and the maternal LOAEL is 100 mg/kg/day based upon decreased body weights and food consumption.**

The litter incidences of corpora lutea, implantation sites, resorptions, and viable and dead fetuses were similar between dose groups. Statistically significant decreases in fetal body weights occurred in the 500 mg/kg/day group (-6% compared to controls for males and females). The 100 mg/kg/day group had increased litter incidence in comparison to controls of incomplete ossification of interparietals. In addition, the 500 mg/kg/day group had increased litter incidence of 14th rib, non-ossified hyoid, and incomplete ossification of frontals/parietals, occipitals/interparietals, hyoid, and sacral vertebra(e). The developmental NOAEL is 10 mg/kg/day and the developmental LOAEL is 100 mg/kg/day based on decreased ossification.

Developmental Rabbit Study

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44153401), propazine technical (98% a.i., Lot #309027C) was administered to 20 New Zealand White rabbits/dose level by gavage in corn oil at dose levels of 0, 2, 10 or 50 mg/kg/day from day 6 through 19 of gestation.

Decreased defecation was observed in the 50 mg/kg/day group. Body weight gain was decreased by 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased by 28% in the 50 mg/kg/day group during the treatment period. **The**

maternal LOAEL is 50 mg/kg/day, based on decreased defecation and decreased body weight gain and food consumption during the treatment period. The maternal NOAEL is 10 mg/kg/day.

Live litter size, mean fetal weight, fetal sex ratios, mean number of corpora lutea and implantation sites and postimplantation loss were unaffected by treatment. There were no treatment related effects in developmental parameters. **The developmental LOAEL is > 50 mg/kg/day and the developmental NOAEL is ≥ 50 mg/kg/day.**

4.2.4 Reproductive Toxicity Study

EXECUTIVE SUMMARY: In a 3-generation reproductive study (MRID 00041409), technical propazine (% a.i. unspecified) was administered in diet to 10 males and 20 females/group Charles River CD rats at concentrations of 0, 3, 100, or 1000 ppm (0, 0.15, 5, or 50 mg/kg/day). There were 2 litters per generation.

Parental toxicity was manifested as significant body weight decrements for males and females in comparison to controls for the high-dose group of 1000 ppm. Weight decrements at termination were greater for males (-12 to -18%) than for females (-7 to -8%). Statistical significance for body weight decrements in females was reported at termination and also after approximately 10 weeks of treatment in each generation.

Offspring toxicity was manifested as body weight decrements of approximately -10% on gestation day 21 in male and female pups of the F1b, F2a, F2b, F3a, and F3b generations of the 1000 ppm dose group. Parental organ weights showed inconsistent effects at the high-dose group in comparison to controls with no histological correlates and were not considered treatment related effects. **The parental/offspring NOAEL is 100 ppm (5 mg/kg/day) and the parental/offspring LOAEL is 1000 ppm (50 mg/kg/day) based on body weight decrements in males and females.**

No reproductive toxicity occurred. Male and female fertility, gestation length, pup viability, and pup survival were similar in all groups. **The reproductive NOAEL is ≥ 1000 ppm (50 mg/kg/day) and the reproductive LOAEL is > 1000 ppm (50 mg/kg/day).**

4.2.5 Additional Information from Literature Sources

There is a published study (Laws et al. 2003) on the pubertal effects of propazine in the female rat. The results demonstrated that propazine can delay the onset of puberty (vaginal opening as an indicator) in the female rat in a dose-dependent manner. Female rats were dosed daily by oral gavage, beginning on PND 22 and continuing through PNDs 41-42. Doses selected were 13, 26.7, 53, 106.7 and 213 mg/kg/day. The LOAEL was 106.7 mg/kg/day, and the NOAEL was 53 mg/kg/day.

4.2.6 Pre-and/or Postnatal Toxicity

Based on the results of the traditional developmental and reproduction studies, in 1997, the HIARC concluded that there is no concern for pre-and/or postnatal toxicity resulting from exposure to propazine. However, residual concerns remain related to potential neuroendocrine

effects on the developing organism were identified. See section 4.5 for discussion on special FQPA factor.

4.2.6.1 Determination of Susceptibility

The HIARC concluded that there was no indication of increased sensitivity of rats or rabbits to *in utero* and post-natal exposure to Propazine. In the prenatal developmental toxicity studies in rats and rabbits, evidence of developmental toxicity was seen only in the presence of maternal toxicity at the highest dose tested. There were no treatment-related effects in the offspring in the two-generation reproduction study in rats (see section 4.5 for rationale).

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

No quantitative or qualitative sensitivity was observed in the rat and rabbit developmental studies or in the 2-generation reproduction study in the rat. There is no concern and there are no residual uncertainties for pre-and/or postnatal toxicity conventionally tested for in the developmental and reproduction studies. However, residual concerns remain related to potential neuroendocrine effects on the developing organism were identified. See section 4.5 for discussion on special FQPA factor.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Acute and subchronic neurotoxicity studies are not available for propazine. Special studies on atrazine, a triazine similar in structure to propazine, have provided evidence of atrazine-associated neuroendocrine effects. Central nervous system (CNS) effects (specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus) have been observed. Special endocrine studies on simazine, a triazine also similar in structure to propazine, have provided further support for endocrine effects. Based on available evidence, Propazine has been grouped with several triazines (e.g., atrazine and DACT) on the basis of a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

Based on available evidence, Propazine has been grouped with several triazines (e.g., atrazine, simazine and DACT) on the basis of a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis. In 2002, HIARC concluded that a developmental neurotoxicity study was not required for atrazine, a triazine similar in structure to propazine. A standard DNT was not recommended because atrazine's CNS mode of action primarily affects pituitary endocrine function, and the parameters measured in the DNT, i.e., the functional endpoints (motor activity tests, auditory startle tests, and learning and memory tests) may not be sensitive to detect behavioral consequences of this hypothalamic disruption. Certain measures performed in the DNT (such as determination of onset of developmental landmarks and neuropathology) would be useful in examining this CNS neuroendocrine toxicity. However, special studies designed specifically to examine these endpoints would be much more useful in this regard.

Based on the above rationale applied to atrazine and the common mode of toxicity for chlorinated triazines applied to propazine, a DNT study for propazine is not recommended.

4.3.2.1 Rationale for the UF_{DB} (when a DNT is recommended)

Not applicable.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

In a developmental toxicity study (MRID 00150242), propazine (99.1%) was administered to 25/dose female Sprague-Dawley rats by gavage at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 6 through 15.

Salivation, described as "clear" was reported in 15 of the pregnant females in the 500 mg/kg/day group; salivation also occurred in 2/7 females in the range-finding study at the HDT of 1000 mg/kg/day. Maternal body weights were decreased in the 100 mg/kg/day group (-7% compared to controls on day 13 of gestation) and in the 500 mg/kg/day group (-14% on day 13). The decreased body weights were accompanied by decreased food consumption in the 100 mg/kg/day group (-18% on day 6) and the 500 mg/kg/day (-40% on day 6).

The maternal NOAEL is 10 mg/kg/day and the maternal LOAEL is 100 mg/kg/day based upon decreased body weights and food consumption.

The litter incidences of corpora lutea, implantation sites, resorptions, and viable and dead fetuses were similar between dose groups. Statistically significant decreases in fetal body weights occurred in the 500 mg/kg/day group (-6% compared to controls for males and females). The 100 mg/kg/day group had increased litter incidence in comparison to controls of incomplete ossification of interparietals. In addition, the 500 mg/kg/day group had increased litter incidence of 14th rib, non-ossified hyoid, and incomplete ossification of frontals/parietals, occipitals/interparietals, hyoid, and sacral vertebra(e).

The developmental NOAEL is 10 mg/kg/day and the developmental LOAEL is 100 mg/kg/day based on decreased ossification.

Dose and Endpoint for Risk Assessment: The developmental NOAEL was 10 mg/kg/day based on based upon incomplete ossification observed at 100 mg/kg/day. At 500 mg/kg/day, 14th rib and further incomplete ossification were observed. The maternal NOAEL was 10 mg/kg/day based upon decreased body weights and food consumption observed at 100 mg/kg/day.

Comments about Study/Endpoint: The team selected this study as most suitable for this endpoint. This study was also selected previously by HIARC. The developmental effects are presumed to occur after a single exposure, and were, thus, considered to be appropriate for the acute risk assessment. This dose/endpoint is applicable only to Females 13+. In addition, this endpoint selection is supported by the Stoker et al. Study (1999) in which atrazine caused the suppression of suckling-induced prolactin release in female rats (dams) who were exposed to atrazine during PND 1 through 3. This suppression of prolactin led to lateral prostate inflammation in male offspring via lactation. The critical period of exposure for this effect was PND 1 through 9. The

NOAEL for this effect was 12.5 mg/kg/day; the LOAEL was 25 mg/kg/day. This study along with standard, guideline developmental studies were used in a weight-of-the-evidence approach to select an appropriate endpoint for the acute risk assessment for atrazine. To the extent that atrazine's toxicity reflects propazine's toxicity, and to the extent that prolactin levels can serve as a marker for effects on neuroendocrine control, this endpoint (10 mg/kg/day) is protective for potential neuroendocrine effects that may occur from acute exposures to propazine.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variability).

Acute RfD = 10 mg/kg/day/100 = 0.10 mg/kg/day

4.4.2 Acute Reference Dose (aRfD) - General Population

An endpoint attributable to a single exposure was not identified from the available database.

The remaining endpoints selected and described in this section are for atrazine, and are being applied to the propazine risk assessments in lieu of propazine-specific endpoints.

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Six-month LH surge study - RAT§ *none; special study*

MRID No.: 44152102

Executive Summary: In a study to evaluate the effect of long-term atrazine exposure on the proestrus afternoon luteinizing hormone [LH] surge (MRID 44152102) atrazine, 97.1% a.i., was administered to 360 female Sprague Dawley rats in the diet. Dose levels were 0 (negative control), 25, 50, and 400 ppm (0, 1.80, 3.65, 29.44 mg/kg/day) for 26 weeks (approximately six months).

Body weight, body weight gain and food consumption were significantly ($p \leq 0.05$) decreased in the high-dose animals compared to controls (body weight decreased 8.5% at the end of the study and food consumption decreased 3.75% for the entire study). The percentage of days in estrus were significantly increased ($p \leq 0.01$) during the 21-22 and 25-26 week time periods at the high dose. Percent days in estrus were also increased during the 21-22 and 25-26 week time periods at the mid-dose level, but the increase was only significant ($p \leq 0.05$) for the 21-22 week time period. The proestrus afternoon LH surge was severely attenuated at the high dose (LH levels were actually decreased compared to baseline at most sampling time points) and less so at the mid dose (maximum increase over baseline was 157% compared to maximum increase over baseline in controls of 273%). Pituitary weight were increase at the high dose (absolute weight increased 22% and weight relative to body weight was increased 28%). Pituitary weights at the other two doses were not affected. There was a slight increase at the high dose of animals displaying enlarged pituitaries (0% in controls compared to 3.4% at 29.44 mg/kg/day) and thickened

mammary glands (0% in controls compared to 6.7% at 29.44 mg/kg/day). There were no other gross necropsy findings in the high dose that could be attributed to compound exposure and there were no compound-related gross pathology findings at the mid or low dose. Selected tissues were saved for histopathology but those results have yet to be reported.

There were no compound related effects in mortality or clinical signs. The proestrus afternoon prolactin surge was not affected by compound exposure at any dose. The low dose had no effects on the estrous cycle, LH or prolactin surges.

The LOAEL is 3.65 mg/kg/day, based on estrous cycle alterations and LH surge attenuation as biomarkers of atrazine's ability to alter hypothalamic-pituitary function. The NOAEL is 1.8 mg/kg/day.

Dose and Endpoint for Establishing cRfD: **NOAEL = 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.**

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variations)

Comments about Study/Endpoint/Uncertainty Factor: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although a similar 6-month study is not available on propazine, the atrazine study is used as bridging data and based on common mechanism of toxicity. The atrazine study is considered protective of propazine's endocrine-related effects. The attenuation of the LH surge is considered to be an indicator of atrazine's neuroendocrine mode of action or its potential to alter hypothalamic-pituitary function. This six-month study is considered adequate for use in selecting a chronic endpoint without an additional safety factor being added to account for study duration of less than 12 months. This is based on the fact that examination of estrous cycle data from other studies indicates that beyond 6 months of exposure, the differences in estrous cycle deterioration between treated animals and controls no longer widens as the control animals begin the normal reproductive aging process.

These biomarkers of atrazine's neuroendocrine mode of action (i.e., LH surge attenuation and estrous cycle disruption) are considered to be applicable to the general population including infants and children given that they result from atrazine's CNS mode of action. HIARC noted that this dose is the lowest NOAEL available in the toxicology database on atrazine and therefore would be protective of other adverse effects, including those occurring in males, infants, and children. Therefore, a separate endpoint is not needed for this population (i.e., males, infants, and children). This endpoint is lower than all endpoints from studies using long-term dosing in the propazine database, and is considered protective of long-term effects of propazine.

Chronic RfD = 1.8 mg/kg/day / 100 = 0.018 mg/kg/day

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Short-Term (1-30 days)

Study Selected: pubertal [screening] study - male RAT § none

MRID No.: none. Stoker, T.E., Laws, S.C., Guidici, D. and Cooper, R.L. (2000) The effect of atrazine on puberty in male Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol. Sci.* Nov. 58: 50-59.

Executive Summary: Since atrazine, a chlorotriazine herbicide, has been shown previously to alter the secretion of luteinizing hormone (LH) and prolactin through a direct effect on the CNS, we hypothesized that exposure to atrazine in the EDSTAC male pubertal protocol (juvenile to peripubertal) would alter the development of the male rat reproductive system. We dosed intact male Wistar rats from postnatal day (PND) 23 to 53 and examined several reproductive endpoints. Atrazine (0, 6.25, 12.5, 25, 50, 100, 150 or 200 mg/kg) was administered by gavage and an additional pair-fed group was added to compare the effects of any decreased food consumption in the high dose group. Preputial separation was significantly delayed in the 12.5, 50, 100, 150 and 200 mg/kg atrazine dose groups. Preputial separation was also delayed in the pair-fed group, although significantly less than in the high dose atrazine group. The males were killed on PND 53 or 54 and pituitary, thyroid, testes, epididymides, seminal vesicles, ventral and lateral prostates were removed. Atrazine (50 to 200 mg/kg) treatment resulted in a significant reduction in ventral prostate weights, as did the pair-fed group. Testes weights were unaffected by atrazine treatment. Seminal vesicle and epididymal weights were decreased in the high dose atrazine group and the control pair-fed group. However, the difference in epididymal weights was no longer significantly different when body weight was entered as a covariable. Intratesticular testosterone was significantly decreased in the high dose atrazine group on PND 45, but apparent decreases in serum testosterone were not statistically significantly on PND 53, There was a trend for a decrease in luteinizing hormone as the dose of atrazine increased, however, dose group mean LH were not different from controls. Due to the variability of serum prolactin concentrations on PND 53, no significant difference was identified. Although prolactin is involved in the maintenance of LH receptors prior to puberty, we observed no difference in LH receptor number at PND 45 or 53. Serum estrone and estradiol showed dose-related increases that were significant only in the 200 mg/kg atrazine group. No differences were observed in thyroid stimulating hormone (TSH) and thyroxine (T4) between the atrazine groups and the control, however tri-iodothyronine (T3) was elevated in the high dose atrazine group. No differences in hormone levels were observed in the pair-fed animals. These results indicate that atrazine delays puberty in the male rat and its mode of action appears to be altering the secretion of steroids and subsequent effects on the development of the reproductive tract, which appear to be due to atrazine's effects on the CNS. Thus, atrazine tested positive in the pubertal male screen that EDSTAC is considering as an optional screen for endocrine disruptors.

Dose and Endpoint for Risk Assessment: **NOAEL = 6.25mg/kg/day), based on a delay in preputial separation at the LOAEL of 12.5 mg/kg/day.**

Comments about Study/Endpoint: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although a similar pubertal study is not available on propazine, the atrazine study is used as bridging data and based on a common mechanism of toxicity. This endpoint is lower than the endpoints in the propazine toxicity database from studies using short-term dosing, and is considered protective of propazine's short-term effects.

This study is appropriate for this scenario since it demonstrates an endpoint in the young animal that is consistent with atrazine's mode of toxicity. The endpoint, delayed puberty, is relevant to the population of concern (infants and children), and delayed puberty also was demonstrated to occur in the female. Following exposure during PND 22-41, delayed puberty was observed in the female at 50 mg/kg/day [NOAEL of 25 mg/kg/day]. A possible explanation for a higher NOAEL

in the female may be that the exposure duration in females [20 days] was shorter than in the males [31 days].

Intermediate-Term (1 - 6 Months)

Study Selected: Six-Month LH Surge Study - RAT § none
MRID No.: 44152102

Executive Summary: see under Chronic RfD.

Dose and Endpoint for Risk Assessment: NOAEL = 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.

Comments about Study/Endpoint: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although a similar 6-month study is not available on propazine, the atrazine study is used as bridging data and based on common mechanism of toxicity. This endpoint is lower than the endpoints in the propazine toxicity database from studies using intermediate-term dosing, and is considered protective of propazine's intermediate-term effects.

The endpoints, estrous cycle alterations and LH surge attenuation, are considered indicative of atrazine's ability to disrupt hypothalamic-pituitary function, and its potential to lead to various health consequences including, but not limited to, reproductive disruption. Although the endpoint selected [estrous cycle alterations and LH surge attenuation] for intermediate-term exposure of infants, children, young adults, and adults is derived from a 6-month study in adult rats, the endpoint is a reasonable surrogate for atrazine CNS-hypothalamic disruption in children. These biomarkers of atrazine's neuroendocrine mode of action (i.e., LH surge attenuation and estrous cycle disruption) are considered to be applicable to the general population including infants and children given that they result from atrazine's CNS mode of action. It should be pointed out that the population of concern includes teenage children, and some functional portions of the CNS, such as the hypothalamic controls of reproductive cycling, are not mature until the second decade [Developmental Toxicology, 2nd ed., edited by c. A. Kimmel and J. Buelke-Sam, Raven Press, Ltd. NY (1994)]. Additionally, since this dose is the lowest NOAEL available in the atrazine toxicology database, it would be protective of other adverse effects, including those occurring in males, infants, and children. Therefore, given the uncertainty of atrazine's potential effect during development *via* the mode of toxicity of atrazine, the use of the NOAEL from the 6-month study is considered protective of the population of concern [infants and children].

4.4.5 Dermal Absorption

Study selected**:** Human Dermal Absorption Guideline **#:** 85-3

MRID No.: 44152144

Executive Summary: The study selected is the same study which was used to derive the dermal absorption factor for atrazine. In this study, 10 human volunteers were exposed to a single topical dose of [triazine ring-U-^{14}C] atrazine (94.3-96.3% a.i., 98.0-98.4% radiochemical purity) at 6.7 (4 volunteers) or 79 ìg/cm^2 (6 volunteers) for 24 hours; equivalent to 0.1667 and 1.9751 mg of [14C]

atrazine for the low and high doses, respectively. After 24 hours, the atrazine was removed and determination of percent absorbed occurred was determined 168 hours (7 days) after the commencement of exposure. The maximum percent absorbed in this study was 5.6% of the dose in the lower dose group. Because the maximum percent absorbed is being used and because an ample amount of time (168 hours) was allowed for absorption to occur, 6% is deemed to be a protective estimate of dermal exposure.

Comments about Study: The dermal absorption factor derived from the human study using atrazine (MRID 44152114) is applied to propazine.

Dermal absorption Factor: 6% (Rounded off)

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

Short- and Intermediate-Term Dermal Endpoints:
Short-Term (1-30 days) Exposure

Study Selected: pubertal [screening] study - male RAT § none

MRID No.: none. Stoker, T.E., Laws, S.C., Guidici, D. and Cooper, R.L. (2000) The effect of atrazine on puberty in male Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol. Sci.* Nov. 58: 50-59.

Executive Summary: see under Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **NOAEL 6.25 mg/kg/day, based on a delay in preputial separation at the LOAEL of 12.5 mg/kg/day.**

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. This study is appropriate for this scenario since it demonstrates an endpoint that is consistent with atrazine's mode of toxicity and is protective of this exposure duration. Since an oral dose is selected, 6% dermal absorption factor should be used for route-to-route extrapolation. Although a dermal rat study was available, endocrine-related effects were not measured in this study, and there are concerns for potential developmental neuroendocrine effects.

Intermediate-Term (1 - 6 Months)

Study Selected: Six-Month LH Surge Study - RAT § *none*

MRID No.: 44152102

Executive Summary: see under Chronic RfD.

Dose and Endpoint for Risk Assessment: NOAEL 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. The endpoints, estrous cycle alterations and LH surge attenuation, are considered indicative of atrazine's ability to disrupt hypothalamic-pituitary function, and its potential to lead to various health consequences including, but not limited to, reproductive disruption. See comments under Incidental Oral Exposure (1-6 Months). Since an oral dose is selected, 6% dermal absorption factor should be used for route-to-route extrapolation.

Long-Term Dermal Endpoints:

Study Selected: Six-Month LH Surge Study - RAT §none

MRID No.: 44152102

Executive Summary: see under Chronic RfD.

Dose and Endpoint for Risk Assessment: NOAEL = 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. The attenuation of the LH surge is considered to be an indicator of atrazine's neuroendocrine mode of action or its potential to alter hypothalamic-pituitary function. This six-month study is considered adequate for use in selecting a chronic endpoint without an additional safety factor being added to account for study duration of less than 12 months. This is based on the fact that examination of estrous cycle data from other studies indicates that beyond 6 months of exposure, the differences in estrous cycle deterioration between treated animals and controls no longer widens as the control animals begin the normal reproductive aging process. Since an oral dose is selected, 6% dermal absorption factor should be used for route-to-route extrapolation.

4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)

Short-Term Inhalation Endpoint:

Study Selected: pubertal [screening] study - RAT§ none

MRID No.: none. Stoker, T.E., Laws, S.C., Guidici, D. and Cooper, R.L. (2000) The effect of atrazine on puberty in male Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol. Sci.* Nov. 58: 50-59.

Executive Summary: see under Short-Term Dermal.

Dose/Endpoint for Risk Assessment: NOAEL 6.25 mg/kg/day, based on a delay in preputial separation at the LOAEL of 12.5 mg/kg/day.

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. This study is appropriate for this scenario since it

demonstrates an endpoint in the young animal that is consistent with atrazine's mode of toxicity. The endpoint, delayed puberty, is relevant to the population of concern.

Intermediate-Term Inhalation Endpoint:

Study Selected: Six-Month LH Surge Study - RAT § none

MRID No.: 44152102

Executive Summary: see under Chronic RfD

Dose/Endpoint for Risk Assessment: NOAEL = 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. The endpoints, estrous cycle alterations and LH surge attenuation, are considered indicative of atrazine's ability to disrupt hypothalamic-pituitary function, and its potential to lead to various health consequences including, but not limited to, reproductive disruption. See comments under Incidental Oral Exposure (1-6 Months).

Long-Term Inhalation Endpoint:

Study Selected: Six-Month LH Surge Study - RAT § none

MRID No.: 44152102

Executive Summary: see under Chronic RfD

Dose/Endpoint for Risk Assessment: NOAEL = 1.8 mg/kg/day, based on estrous cycle alterations and LH surge attenuation at the LOAEL of 3.65 mg/kg/day.

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. The attenuation of the LH surge is considered to be an indicator of atrazine's neuroendocrine mode of action or its potential to alter hypothalamic-pituitary function. This six-month study is considered adequate for use in selecting a chronic endpoint without an additional safety factor being added to account for study duration of less than 12 months. This is based on the fact that examination of estrous cycle data from other studies indicates that beyond 6 months of exposure, the differences in estrous cycle deterioration between treated animals and controls no longer widens as the control animals begin the normal reproductive aging process.

4.4.8 Margins of Exposure

The Margins of Exposure (MOEs) that do not exceed HED's level of concern for **occupational** exposure risk assessments are as follows:

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (non-dietary) Exposure			
Oral	300	300	N/A
Dermal	300	300	300
Inhalation	300	300	300

For occupational exposure, short-term and intermediate-term inhalation exposure risk assessments, a MOE of 100 is required. The MOE is based on 10x for intraspecies variation, and 10x for interspecies extrapolation. For residential exposures, an MOE is required, and is based on 10x for intraspecies variation, 10x for interspecies extrapolation, and 3X special hazard-based FQPA factor.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows. The oral, dermal and inhalation routes of exposure can be combined to assess aggregate risks because of the selection of a common toxicity endpoint (i.e., endocrine toxicity) for short-term, intermediate-term, and long-term exposures via the oral, dermal and inhalation routes of exposure.

4.4.10 Classification of Carcinogenic Potential

In 1989, the HED Cancer Peer Review Committee (CPRC) classified propazine as a **Group C Carcinogen (possible human carcinogen)** with a linear low-dose approach (Q_1*) for human risk characterization.

In 1997, the HED Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of atrazine and discussed mode of action data submitted by the Registrant in regards to the ability of atrazine to produce mammary tumors in Sprague-Dawley rats.

Following discussion of the conclusions reached at the November 1, 2000 CARC meeting on atrazine and consideration of the comments and recommendations provided by the Scientific Advisory Panel, the December 13, 2000 CARC reaffirmed the classification of atrazine as "Not Likely To Be Carcinogenic To Humans" based on the overall weight of evidence that:

1. The mode of carcinogenic activity in the female SD rat is supported by the data.

2. The mode of carcinogenic activity in the female SD rat essentially involves an acceleration of the reproductive aging process.

3. The mode of action for the carcinogenicity of atrazine is unlikely to be expressed in humans; no human conditions can be established that support a potential for atrazine to lead to carcinogenicity in humans.

4. Other modes of action are not supported by the available data and, in particular, mutagenic and estrogenic activity do not appear to significantly contribute to atrazine's carcinogenic potential.

5. Although a few epidemiological studies suggest a possible association between atrazine (or triazine) exposure and NHL and ovarian cancer, these cancers do not appear to be plausible based on atrazine's mode of action. Therefore, the human studies by themselves do not make a strong case for an association.

Since propazine is associated with the same cancers in rodents as atrazine, and shares a common mechanism of action, it has been reclassified by the CARC (December 2005) as "Not Likely To Be Carcinogenic To Humans" (See memo: TXR No. 0053936, J. Kidwell, 12/8/05).

Table 4.4 Summary of Toxicological Doses and Endpoints for Propazine			
Exposure Scenario	**Dose used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49)	Developmental NOAEL = 10 mg/kg/day UF = 100 **Acute RfD = 0.1 mg/kg/day**	1X for Hazard-based concerns. aPAD = aRfD/FQPA SF **aPAD = 0.1 mg/kg/day*** 3X for Exposure -based concerns when monitoring data used. No monitoring data were used in this assessment.	**Development study in rats w/ propazine** LOAEL = 100 mg/kg/day based on decreased ossification
Acute Dietary (general population)	NA	NA	No toxic effect attributable to a single dose was identified for the general population
Chronic RfD (all populations)	NOAEL = 1.8 mg/kg/day UF = 100 **Chronic RfD = 0.018 mg/kg/day**	3X for residual Hazard-based. cPAD = cRfD/FQPA SF **cPAD = 0.006 mg/kg/day** 3X for Exposure-based uncertainties when monitoring data used. No monitoring data were used in this assessment.	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Incidental Oral Short-Term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Incidental Oral Intermediate-Term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal short-term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (MOE) occupational)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Dermal intermediate-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression

Table 4.4 Summary of Toxicological Doses and Endpoints for Propazine			
Exposure Scenario	**Dose used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal long-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Inhalation short-term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (MOE) occupational)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Inhalation intermediate-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Inhalation long-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal absorption = 6% (human data for atrazine)			
Cancer (oral, dermal, inhalation)	"Not Likely to be Carcinogenic to Humans" as per common mode of toxicity with atrazine. (See memo: TXR No. 0053936, J. Kidwell, 12/8/05)		

UF = uncertainty factor, FQPA SF = Special 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, MOE = margin of exposure, LOC = level of concern

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

The propazine team recommends the propazine assessment should reflect the following FQPA safety factors: the acute dietary assessment (3X) for residual "exposure-based" concerns when drinking water exposure assessments are based on monitoring data; chronic dietary assessment (3X) for residual "hazard-concerns, and (3X) for exposure-based" concerns when drinking water exposure assessments are based on monitoring data; and, residential assessments (3X) for residual "hazard-based" concerns. The hazard-based portion of the FQPA safety factor is applied because of residual uncertainty regarding the effects of the neuroendocrine mechanism of action on the developing child.

Since no drinking water monitoring data were used in this assessment, and conservative models were used to estimate drinking water exposures, an exposure-based FQPA safety factor of 1X has

been applied to the acute and chronic dietary assessments. The 3X hazard-based safety factor has been applied under FQPA to the chronic dietary assessment, only, per recommendation of the Hazard Identification Assessment Review Committee (HIARC). [Memorandum dated: 4/5/2002, TXR No. 0050592, Atrazine/DACT: Fourth Report of the Hazard Identification Assessment Review Committee from L. Taylor to J. Rowland.] Propazine does not have residential uses and no residential risk assessments have been conducted. The total uncertainty factors applied to these assessments are summarized below.

Summary of Uncertainty Factors for Propazine						
	Traditional Inter- and Intra-species (UFs)	**LOAEL to NOAEL (UF_L)**	**Subchronic to Chronic (UF_S)**	**Incomplete Database (UF_{DB})**	**Special FQPA Safety Factor (Hazard-based)**	**Default FQPA Safety Factor (Exposure-based)**
Magnitude of Factor	100X	1X	1X	1X	**3X**	**1X**
Rationale for the Factor	Typical UFs applied by Agency in the absence of pharmacokinetic and human data	No LOAEL to NOAEL extrapolations performed.	No subchronic to Chronic extrapolations performed	All required studies have been submitted	**Residual Concerns for Atrazine mode of action on the development of the young**	**Residual Concerns for exposure via drinking water based on infrequency of monitoring. Should not be applied to drinking water exposure assessments based on models.**
Endpoints to which the Factor is Applied	**All risk assessments**	Not Applicable	Not Applicable	Not Applicable	**Chronic RfD only. Should not be applied to the Acute RfD.** **No residential uses, no residential risk assessments.**	**Acute and Chronic RfDs when drinking water assessments are based on monitoring data, only.** **Since models used, no factor applied.**

Since propazine and atrazine share a common mode of toxicity, the rationale for the FQPA safety factors applied to propazine is based on decisions made for atrazine as follows:

On April 5, 2002 the HIARC Committee met and determined the "hazard-based" portion of the FQPA Safety Factor after considering the effects observed in the atrazine database. The HIARC identified the following residual "hazard-based" concerns:

"Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young

resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur compared to reproductive/developmental effects[1]."

Since all possible outcomes associated with atrazine, and by analogy propazine, exposures at all critical periods of development in the young have not been studies, residual uncertainties at to the effects of atrazine and propazine on the young remain.

"Considering the existing data used for toxicity endpoint selection, the HIARC used the following rationale to conclude that an additional Special FQPA Safety Factor of 3X would be adequate to account for these hazard-based residual uncertainties:

The toxicology endpoints selected for risk assessment are all consistent with Atrazine's mode of toxicity using the most sensitive endpoint with the lowest NOAEL (1.8 mg/kg/day). When comparing the effects observed in adults to those observed in the young, the HIARC considered the results of the pubertal assay. It is noted that delayed puberty was observed in both male and female offspring exposed to Atrazine during the pubertal period (30 days for the males and 20 days for the females) and that clear NOAELs were established for this endpoint in both sexes (6.25 mg/kg/day in males; 12.5 mg/kg/day in females). If the lowest offspring NOAEL from this study is protected by a factor of 3X, the extrapolated NOAEL is 2 mg/kg/day. Comparing this value to the adult NOAEL of 1.8 mg/kg/day from the 6-month LH Surge study (used to establish the Chronic RfD and for the intermediate and chronic oral, dermal, and inhalation exposure scenarios) indicates that the young are not likely to be an order of magnitude more sensitive than the adult. Therefore, the HIARC concluded that a half-log reduction in the default Special FQPA Safety Factor is considered to be sufficiently protective of the concerns for this CNS mode of action in the young.

HIARC also recommended that the additional Special FQPA Safety Factor of 3X would **not** be required for Acute dietary exposures (aRfD) because the open literature data demonstrate that while the neuroendocrine effects caused by Atrazine's mode of action could result from a single dose, this would only occur at very high doses (200-300 mg/kg which is significantly higher than the 10 mg/kg level used to establish the Acute RfD). " Although the FQPA Committee chose to apply the 3X safety factor to the acute dietary assessment, the propazine team agrees with the previous HIARC recommendation not to apply the factor to the acute dietary assessment, and did not apply the 3X safety factor to the acute dietary assessment for the reasons stated above and in the HIARC report.

The FQPA Committee met on April 8, 2002 to consider the recommendations of the HIARC with respect to any hazard-based residual concerns for atrazine, and to consider any residual "exposure-based" concerns. The FQPA Committee concluded that, as to dietary risk, residual concerns were identified with regard to the drinking water exposure assessment for atrazine based

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[1]SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization. "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...."

on inadequate monitoring data. Limitations in the extent, frequency, and the lack of monitoring data on the degradates raised uncertainties regarding the level of exposure to atrazine and its metabolites. Monitoring data, although available, were not abundant in the areas of high propazine use and high run off potential, such as the coastal areas of Texas. Furthermore, the quality of the available monitoring data are not sufficiently reliable and at times could not be adequately or reasonably assessed. Therefore, EFED recommends the use of modeling data for use in the human health risk assessment. The FQPA Committee concluded that an additional Special FQPA Safety Factor of 3X for "exposure-based" concerns is adequate for assessing drinking water exposures to atrazine based on monitoring data. The team has determined that a Special FQPA Safety Factor of 3X for "exposure-based" concerns should be applied to drinking water exposure assessments based on monitoring data for propazine, as well. However, the team has also determined that the additional Special FQPA Safety Factor of 3X for "exposure-based" concerns should **not** be applied to drinking water exposure assessments based on conservative models, i.e., PRZM/EXAMS. The team considers the model estimates of exposure to be conservative and protective. Since the propazine risk assessment relies entirely on conservative models to estimate drinking water exposures, an additional FQPA safety factor for exposure-based concerns was not applied to the risk assessments.

The FQPA Committee further concluded that an additional Special FQPA Safety Factor of 3X for "hazard-based" concerns is adequate for assessing residential exposures to atrazine. The Committee believed there were no residual "exposure-based" concerns for residential exposure assessments because the assessments were based on HED Standard Operating Procedures using default values and assumptions that would be protective of infants and children, and drinking water exposures (described above) would have little or no impact on the residential exposure scenarios. The concerns for the effect of the neuroendocrine mode of action on the development of the young remained and the Committee concluded that there are reliable data to address these concerns through use of an additional Special FQPA Safety Factor of 3X.

Given that propazine has no residential uses, a residential risk assessment has not been conducted. However, if residential uses existed or are proposed in the future: 1) the team recommends that the conservative methodologies used to estimate residential exposures will not underestimate exposure, and application of an Exposure-based FQPA safety factor is not warranted, and 2) the propazine team recommends for application of the 3X "hazard-based" FQPA Safety Factor to the residential exposure assessments.

4.6 Endocrine disruption

There is evidence that propazine is associated with neuroendocrine disruption. Direct measurements of serum hormones such as luteinizing hormone, as well as, changes in estrus cycling, indicate neuroendocrine disruption.

EPA is required under the 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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis 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).

5.0 Public Health Data

There were almost no reports of ill effects from exposure to Propazine in the available data bases.

5.1 Incident Reports

The following data bases have been consulted for the poisoning incident data on the active ingredient Propazine (Review of Propazine Incident Reports DP Barcode D308532, M. Hawkins, 8/22/05):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or documentation risk mitigation measures may be suggested.

There were no reports related to propazine found in the Incident Data System.

2) Poison Control Centers - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

Only one report was located in Poison Control Center records from 1993 through 2003. In 1993, a 12 year-old female was exposed as a result of unintentional misuse. She was not seen in a health care facility, but minor medical outcome was determined as a result of skin irritation.

3) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

No reports of Propazine poisoning were reported in California from 1982 through 2003.

4) National Pesticide Information Center (NPIC) - NPIC is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, Propazine was not reported to be involved in human incidents.

5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) performs standardized surveillance in seven states from 1998 through 2002. States included in this reporting system are Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas, and Washington. Reporting is very uneven from state to state because of the varying cooperation from different sources of reporting (e.g., workers compensation, Poison Control Centers, emergency departments and hospitals, enforcement investigations, private physicians, etc.). Therefore, these reports should not be characterized as estimating the total magnitude of poisoning. The focus is on occupationally-related cases not residential or other non-occupational exposures. However, the information collected on each case is standardized and categorized according the certainty of the information collected and the severity of the case.

Out of 5,899 reported cases from 1998-2003, none involved Propazine.

No scientific literature was found concerning human poisoning or other adverse effects from exposure to Propazine

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

A conservative Tier 1 acute dietary (food + water) assessment was performed using DEEM-FCID™ for females 13-49 yrs only since no toxic effect attributable to a single dose was identified for the general US population. The dietary exposure and risk assessment includes propazine and its 2 chlorinated metabolites (for sorghum only). Reassessed tolerance level residues for sorghum grain (0.15 ppm) and syrup (0.15 ppm), and 100% crop-treated values were used. A predicted market share value for propazine use on grain sorghum of 29% based on projections of market share by the Biological and Economic Analysis Division (BEAD) was available but not used in the assessment since there is no exposure to grain sorghum commodities reported in the diet. The assumption of 100% crop-treated is conservative and protective and overestimates the actual market share should propazine be registered for use on sorghum. Although field trial data were available, and residues in sorghum grain were <0.05 ppm, tolerance level residues were used for sorghum commodities because this is a new use. The combination of tolerance level residues and 100% crop-treated makes this dietary assessment very conservative for food. Results are shown below for the acute dietary assessments. Drinking water exposures are the driver in the dietary assessment accounting for 100% of the exposures. Exposures through food (sorghum grain and syrup) are zero. The acute assessment includes a maximum estimated drinking water concentration (for parent propazine only) from EFED's PRZM-EXAMS model (77 ppb).

Risk estimates for females 13-49 at the 95th percentile of exposure (Tier 1) are below HED's level of concern. The major contributor to the risk was water (contribution to the risk was 100%) and zero contribution from sorghum (0%). Results are shown in the Table below.

Results of the Acute Assessment for Propazine and its Chloro-Metabolites

Population Subgroup	Exposure at 95% (mg/kg/day)	Exposure at 95% (%aPAD)	Exposure at 99% (mg/kg/day)	Exposure at 99% (%aPAD)	Exposure at 99.9% (mg/kg/day)	Exposure at 99.9% (%aPAD)
Females 13-49	0.003748	3.75	0.006032	6.03	0.010697	10.7

A conservative chronic dietary (food + water) assessment was performed using DEEM-FCID™. The dietary exposure and risk assessment includes propazine and its 2 chlorinated metabolites (for sorghum only). Reassessed tolerance level residues for sorghum grain (0.15 ppm) and syrup (0.15 ppm), and 100% crop-treated values were used. There are 2 chronic assessments: one includes the 90th percentile 90-day average concentration (56 ppb, parent only) for propazine in drinking water from an Oklahoma scenario for sorghum using an 80% percent cropped area (PCA), and the other includes the 90th percentile annual average concentration (25 ppb, parent only) of propazine in drinking water from the same scenario. The 90-day average concentration was included as the triazines have been typically detected in surface water in pulses lasting several weeks to months after application. The 90-day average concentration represents the exposure duration resulting in the highest exposures to triazines in drinking water.

As can be seen in the tables below, the chronic assessment using a 90-day average water concentration value results in a %cPAD that does not exceed HED's level of concern for infants (65%, highest exposed population subgroup). The major contributor to the risk was water (100%). There was no contribution from grain sorghum to the dietary exposure. All other populations under the chronic assessment show risk estimates that are below HED's level of concern. Results are shown below.

Results of the Chronic Assessment for Propazine and its Chloro-Metabolites using a 90-Day Average Drinking Water Concentration.

Population Subgroup	Exposure mg/kg/day	Exposure %cPAD
General Population	0.00118	20
All infants	0.00387	**65**
Children 1-2 years	0.001753	29
Children 3-5 years	0.001641	27
Children 6-12 years	0.001132	19
Youth 13-19 years	0.000853	14
Females 13-49 years	0.001097	18
Adults 20-49 years	0.001102	18
Adults 50+	0.001159	20

Results of the Chronic Assessment for Propazine and its Chloro-Metabolites using an Annual Mean Drinking Water Concentration.

Population Subgroup	Exposure mg/kg/day	Exposure %cPAD
General Population	0.000527	9
All infants	0.001728	29

Population Subgroup	Exposure mg/kg/day	Exposure %cPAD
Children 1-2 years	0.000782	13
Children 3-5 years	0.000733	12
Children 6-12 years	0.000505	8
Youth 13-19 years	0.000381	6
Females 13-49 years	0.00049	8
Adults 20-49 years	0.000492	8
Adults 50+	0.000518	9

6.1.1 Residue Profile

Following a single preemergence broadcast application of a representative FlC formulation of propazine at 1.47-2.43 lb ai/A (1.2-2.0x the proposed single application rate), the results of the sorghum field trials indicate the following: In **sorghum forage** harvested at a PHI range of 69-117 days, residues of propazine and G-30033 were each less than the LOQ (<0.05 ppm) in/on 26 treated samples. Residues of G-28273 ranged 0.050-0.087 ppm in/on four treated forage samples but were <0.05 ppm in/on 22 treated samples. In **sorghum grain and stover** harvested at a PHI range of 86-152 days, residues of propazine, G-30033, and G-28273 were each <0.05 ppm in/on 26 treated samples. These data support reassessed tolerances for the combined residues of propazine and its two chlorometabolites (G-30033 and G-28273) in/on sorghum, grain, stover at 0.15 ppm, sorghum, grain, forage at 0.20 ppm, and sorghum, grain, grain at 0.15 ppm. Residue data on the aspirated grain fractions of sorghum are not required since the proposed use of propazine on grain sorghum is for preemergence or preplant application. No PDP data exist for propazine in sorghum as this is a proposed new use.

6.2 Drinking Water Exposure Pathway

Drinking water concentrations were estimated for propazine only and included in the DEEM runs. EFED estimates that the chlorinated degradates of propazine account for less than 5% of the parent compound in soil dissipation studies and recommends they not be included in the assessment as their contribution to drinking water exposure is expected to be insignificant. The fate parameters used in PRZM-EXAMS modeling are conservative and have been estimated at the 90th percentile. Percent cropped area (PCA) has been refined for this assessment since the sorghum production area where propazine may be needed is within the states of Colorado, New Mexico, Kansas, Oklahoma, and Texas, and further refinement was possible using the regional PCA values: 67% for Texas , 80% for Kansas and Oklahoma, 7 -11% for Colorado, and 28% for New Mexico. The table below reflects the surface water drinking water estimated concentrations (DWECs) predicted by PRZM-EXAMS and adjusted with the regional PCAs. Note that the DWEC values for Colorado, Oklahoma, and New Mexico were based on the values estimated from the TX sorghum scenario.

Sorghum 1.2 lb ai/A; 1 aerial app/yr	90th percent Peak	96 hr	21-day	60-day	90-day	Annual Mean	Yearly Average
Surface Water - Texas (0.67 Regional PCA adj)	65	64	59	52	47	21	10
Surface Water - Kansas (0.80 Regional PCA adj)	35	35	33	29	27	13	9
Surface Water - Oklahoma (0.80 Regional PCA adj)	**77**	76	70	62	**56**	**25**	12
Surface Water - Colorado (0.11 Regional PCA adj)	11	11	10	9	8	3	2
Surface Water - New Mexico (0.28 Regional PCA adj)	27	27	24	22	20	9	4

The groundwater model SCI-GROW2 estimates likely groundwater concentrations if the pesticide is used at the maximum allowable rate (or in the case of propazine, the maximum rate that results in the highest contamination level) in areas where groundwater is vulnerable to contamination. Characteristics of such vulnerable areas include high rainfall, rapidly permeable soil, and a shallow aquifer. In most cases, a large majority of the use area will have groundwater that is less vulnerable to contamination than the areas used to derive the SCI-GROW2 estimate.

Using one aerial application of 1.2 lb ai/A of propazine on sorghum, the lowest lowest Koc of 65 mL/g and the average aerobic metabolism half-life of 197 days, SCI-GROW2 estimates a ground water EDWC of 6.9 ug/L. This value can be used for both acute and chronic (i.e., peak and mean) in determining potential risk to human health from drinking water from ground water sources contaminated with propazine.

6.3 Residential (Non-Occupational) Exposure/ Risk Pathway

There are no current or proposed residential uses of propazine.

6.3.2 Recreational Uses

There are no recereational uses of propazine.

6.3.3 Other (Spray Drift, etc.)

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 the ground application method employed for propazine. 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. On a chemical by chemical basis, 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 with specific products with significant risks associated with drift.

7.0 Aggregate risk Assessments and Risk Characterization

Propazine has agricultural uses that result in exposures to humans through their diet and drinking water; it has no registered residential uses. As a result, aggregate assessments combine exposures through the food and drinking water pathways.

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: the oral, dermal and inhalation routes of exposure can be combined to assess aggregate risks because of the selection of a common toxicity endpoint (i.e., endocrine toxicity) for short-term, intermediate-term, and long-term exposures.

7.1 Acute Aggregate

See the results for the acute dietary assessment above in Section 6.1.

7.2 Short-term Aggregate Risk

Since no residential uses exist for propazine, no short-term aggregate risk assessment was conducted.

7.3 Intermediate-term and Chronic Aggregate Risk

See the results for the chronic dietary assessment above in Section 6.1.

7.4 Cancer Risk

A cancer risk assessment for propazine has not been conducted based on its pending reclassification as “Not Likely to be Carcinogenic to Humans”. The pending reclassification is based on the common mechanism of toxicity shared by atrazine, propazine, and simazine and their common degradates and the lack of relevance to humans of the mammary tumors seen in Sprague-Dawley rats treated with atrazine, propazine, and simazine.

8.0 Cumulative Risk Characterization/Assessment

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 evaluated atrazine, simazine, and propazine for a mechanism of toxicity common to all three compounds and their degradates. Although propazine has been grouped with other chlorinated triazine compounds as having a common mechanism of toxicity, HED has not perform a cumulative risk assessment as part of this risk assessment for simazine yet. Once the aggregate, single chemical assessments are completed for atrazine, simazine, and propazine, HED can begin the cumulative risk assessment for these compounds and their common chlorinated degradates. For purposes of this tolerance reassessment review, EPA has provided an aggregate risk assessment for propazine and its chlorinated metabolites, only.

9.0 Occupational Exposure/ Risk Pathway

The occupational exposures and risks associated with the use of propazine were not assessed in this document as it supports a TRED.

9.1 Occupational Handler

9.2 Short-and Intermediate-term Postapplication Risk

10.0 Data Needs and Label Requirements

10.1 Toxicology

None

10.2Residue Chemistry

HED has examined the residue chemistry database for propazine and identified the residue chemistry deficiencies listed below before the use of propazine on grain sorghum can be reinstated.

- For consistency of the proposed use pattern with the submitted field trial data, the following label amendments are required for sorghum: (i) a maximum of one preemergence application per growing season; (ii) a maximum seasonal rate of 1.2 lb ai/A; (iii) a preharvest interval of 70 days for sorghum forage; and (iv) a preharvest interval of 90 days for sorghum grain and stover.

- A plant enforcement method is required. HED is recommending that the data-collection method (CHW 6641-106, Method 1, Rev. 1) be subjected to an independent laboratory validation as per GLN 860.1340. If the ILV is successful, the method will be further validated by Agency chemists at ACL/BEAD.

- There are no multiresidue methods recovery data for the chlorometabolites G-30033 and G-28273, and these data are required. To fulfill this requirement, the petitioner is required to follow the directions for the protocols found in PAM Vol. I, Appendix II under paragraph (d)(1) of OPPTS GLN 860.1360, starting with the decision tree for multiresidue methods testing and the accompanying guidance found in the suggestions for producing quality data.

- The results of an ongoing storage stability study need to be submitted upon completion to support the storage conditions and intervals of samples collected from the sorghum field trials and limited field rotational crop trials.

- The following label restrictions should be added for rotational crops:

  "Do not rotate to leafy vegetables. Do not rotate to root crops or cereals (small grains) at less than a 120-day plant back interval."

  In addition, the label needs to specify that rotation to all other crops should be restricted to a 12-month PBI.

  If shorter or different PBIs are desired by the registrant, then extensive field rotational trial data, as described under OPPTS 860.1900, to determine appropriate tolerances for inadvertent residues of propazine and its chlorometabolites should be submitted.

- Analytical standards for propazine are currently available at the National Pesticide Standards Repository. However, standards for the chlorometabolites G-30033 and G-28273 are not available and are required.

- The tolerances established under 40 CFR §180.243 are currently defined for residues of propazine *per se*. Griffin Corporation has filed a petition, PP#7F4837, to amend 40 CFR §180.243, by establishing tolerances for residues of propazine and its two chlorometabolites: 2-amino-4-chloro, 6-isopropylamino-s-triazine (G-30033) and 2,4-diamino-6-chloro-s-triazine (G-28273) in/on sorghum, grain, stover at 0.15 ppm, in sorghum, grain, forage at 0.20 ppm, and in sorghum, grain, grain at 0.15 ppm. The results of a sorghum metabolism study indicate that the proposed tolerance expression for plants is appropriate. Therefore, HED is recommending the revision of the residue definition under 40 CFR §180.243 to specify tolerances for the combined residues of propazine and the chlorometabolites G-30033 and G-28273. Also, HED recommends that the designation "(N)" be deleted from the 40 CFR for all tolerance level entries.

- Tolerances for propazine residues of concern in meat, milk, poultry, and eggs are not required for the purpose of this petition only. The results of the reviewed ruminant and poultry metabolism studies suggest a Category 3 situation with regard to the need for animal commodity tolerances as per 40 CFR §180.6. There is no expectation of finite residues of propazine and its chlorometabolites in animal commodities as a result of the proposed use on grain sorghum. Thus, animal

feeding studies are not needed, and tolerances need not be established for meat, milk, poultry, and eggs.

- The established tolerance for sweet sorghum should be revoked unless propazine use on sweet sorghum is proposed and supporting residue data are submitted.

10.3 Occupational and Residential Exposure

Not applicable.

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

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

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
			-
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	submitted/in review
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5380	Mutagenicity—Spermatogonial Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	-	-
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	-
870.6200b	90 Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes

2.0 NON-CRITICAL TOXICOLOGY STUDIES

Combined Chronic Toxicity/Oncogenicity - Mice

Executive Summary: In a combined carcinogenicity toxicity study (MRID 0044335), Randomized groups of 60/sex/dose CD-1 mice were fed in the diet at doses of 0, 3, 1000, or 3000 ppm (**0, 0.45, 150, or 450 mg/kg/day**) for two years with technical propazine.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption or gross pathology. Hematology, urinalysis, clinical chemistries, and organ weights were not determined. At 3000 ppm, an increased incidence of myocardial degeneration was observed in the female mice (17/59 vs 4/60 in controls). At the doses tested, there was not a treatment-related increase in tumor incidence.

The NOAEL is 1000 ppm (150 mg/kg/day) and the LOAEL is 3000 ppm (450 mg/kg/day) based on myocardial degeneration in females.

The dosing in this study was considered to have been adequate.

This Carcinogenicity study is classified as acceptable/guideline.

Combined Chronic/Oncogenicity - Rat

Executive Summary: In a combined carcinogenicity toxicity study (MRID 00041408), propazine (% purity not specified) was administered to 60 sex/dose Sprague-Dawley rats in diet at dose levels of 0, 3, 100, or 1000 ppm (0, 0.1, 5.2, or 51 mg/kg/day males; 0, 0.2, 6.4, or 68 mg/kg/day females) for 2 years. An additional 10/sex were added to control and high-dose groups for interim sacrifice at 12 months (5/sex) and after a 4 week recovery period (5/sex).

Hematology, clinical chemistry, and urinalyses were conducted on 10/sex from control and high-dose groups at 3, 6, 12, 18, and 24 months. All animals were necropsied, organ weights were taken at 12 and 24 months, and a total of 65/sex from control and high dose groups were examined microscopically at both necropsies.

At termination, mean body weight for the high-dose group was decreased in comparison to controls (-13.1% males and -11.4% females). Body weights for low- and mid-dose groups of both sexes were decreased approximately 4-6% in comparison to controls. Food consumption was comparable between groups.

The NOAEL for systemic toxicity is 100 ppm (5.2 mg/kg/day males and 6.4 mg/kg/day females) and the LOAEL is 1000 ppm (51 mg/kg/day males and 68 mg/kg/day females) based upon decreased body weight.

This Carcinogenicity study is classified as acceptable/guideline.

21-Day Dermal Toxicity - Rat

EXECUTIVE SUMMARY: In a 21-day subchronic dermal toxicity study, propazine TECHNICAL (98.0%, Lot # 309027C) was dermally applied to 5 rats/sex/dose at dose levels of 0, 10, 100 or 1000 mg/kg/day.

There was a slight decrease in body weight gain in males (38.2%) in the 1000 mg/kg/day group. There was a slight decrease in body weight in females (5.2%) in the 1000 mg/kg/day group. There was no effect on clinical signs of toxicity, mortality, dermal irritation, food consumption, hematology, clinical chemistry, organ weights or pathology. **The LOEL is 1000 mg/kg/day based on decreased body weight gain. The NOEL is 100 mg/kg/day.**

The 21-day dermal study is classified **ACCEPTABLE** and satisfies the guideline requirements for a 21-day dermal toxicity study (82-2) in rats.

***In vivo* Mammalian Spermatogonial Chromosome Aberration Test-mouse**

EXECUTIVE SUMMARY:In a spermatogonial chromosome aberration test (MRID 46171701), 6 male Crl:CD-1®(ICR)BR mice/dose were treated via gavage with a single dose of propazine, (96.9 % a.i., lot # SG90502205) at doses of 0, 500, 1000, or 2000 mg/kg. Spermatogonial cells were harvested 24 hours post-treatment. The vehicle was 0.5% aqueous carboxymethyl cellulose (CMC).

Propazine was tested up to the limit dose, 2000 mg/kg. There were no clinical signs of toxicity or mortality in any of the treated animals. Cytotoxicity was not observed in spermatogonia cells at any dose level. The mitotic index was slightly decreased in the high dose group and slightly increased in the low and mid dose groups, relative to controls. There was no increase in chromosomal aberrations in any treated group when compared to controls. The vehicle and positive control values were appropriate. Historical control data were not provided for chromosome aberrations in mouse spermatogonial cells, but were provided for mouse bone marrow cells. **There is no evidence for a biologically or statistically significant increase over the vehicle control values in the number of cells with chromosome aberrations following treatment with propazine**.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for an *In vivo* Mammalian Spermatogonial Chromosome Aberration test (OPPTS 870.5380; OECD 483).

3.0 TOLERANCE REASSESSMENT

The tolerances established under 40 CFR §180.243 are currently defined for residues of propazine *per se*. Griffin Corporation has filed a petition, PP#7F4837, to amend 40 CFR §180.243, by establishing tolerances for residues of propazine and its two chlorometabolites: 2-amino-4-chloro, 6-isopropylamino-s-triazine (G-30033) and 2,4-diamino-6-chloro-s-triazine (G-28273) in/on sorghum stover, forage, and grain at 0.25 ppm. The results of a sorghum metabolism study indicate that the proposed tolerance expression for plants is appropriate. Therefore, HED is recommending the revision of the residue definition under 40 CFR §180.243 to specify tolerances for the combined residues of propazine and the chlorometabolites G-30033 and G-28273.

Tolerances for propazine residues of concern in meat, milk, poultry, and eggs are not required for the purpose of this petition only. The results of the reviewed ruminant and poultry metabolism studies suggest a Category 3 situation with regard to the need for animal commodity tolerances as per 40 CFR §180.6. There is no expectation of finite residues of propazine and its chlorometabolites in animal commodities as a result of the proposed use on sorghum. Thus, animal feeding studies are not needed, and tolerances need not be established for meat, milk, poultry, and eggs.

For the combined residues of propazine and the chlorometabolites G-30033 and G-28273, HED recommends tolerance levels of 0.20 ppm for sorghum, grain, forage, 0.15 ppm for sorghum, grain, grain, and 0.15 ppm for sorghum, grain, stover. The reassessed tolerances are supported by adequate data pending submission of supporting storage stability data and label revision. Following a single preemergence broadcast application of a representative FlC formulation of propazine at 1.47-2.43 lb ai/A (1.2-2.0x the proposed single application rate), the results of the sorghum field trials indicate the following: In **sorghum forage** harvested at a PHI range of 69-117 days, residues of propazine and G-30033 were each less than the LOQ (<0.05 ppm) in/on 26 treated samples. Residues of G-28273 ranged 0.050-0.087 ppm in/on four treated forage samples but were <0.05 ppm in/on 22 treated samples. In **sorghum grain and stover** harvested at a PHI range of 86-152 days, residues of propazine, G-30033, and G-28273 were each <0.05 ppm in/on 26 treated samples.

HED recommends that the designation "(N)" be deleted from the 40 CFR for all tolerance level entries. A summary of propazine tolerance reassessment is presented in Table 6.

Table 6. Tolerance Reassessment Summary for Propazine.			
Commodity	Current Tolerance Listed in 40 CFR §180.243 (ppm)	Reassessed Tolerance (ppm)	Comments [*Correct Commodity Definition*]
Sorghum, forage	0.25 (N)	0.20	Sorghum, grain, forage
Sorghum, grain	0.25 (N)	0.15	Sorghum, grain, grain
Sorghum, grain, stover	0.25 (N)	0.15	Sorghum, grain, stover
Sorghum, sweet	0.25 (N)	Revoke	No registered uses on sweet sorghum.