UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: July 10, 2018

SUBJECT: **Propazine.** Draft Human Health Risk Assessment for Registration Review.

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As part of Registration Review, the Pesticide Re-Evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary (food and drinking water), residential, aggregate, and occupational exposure assessments to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's draft human health risk assessment (DRA) for propazine to support Registration Review.

The most recent human health risk assessment for the chlorotriazine herbicides (atrazine, simazine, and propazine) was completed in 2006 (J. Morales *et a.l.*, D317976, 03/28/2006). A scoping document for Registration Review was completed in 2013 (W. Donovan, D407489, 06/04/2013). The following risk assessment updates have been included in the current risk assessment:

- The toxicity points of departure and uncertainty factors for the neuroendocrine effects have been updated using a rat and human physiologically-based pharmacokinetic (PBPK) model;
- The drinking water assessment has been updated;
- A non-occupational spray drift exposure assessment was completed; and
- An occupational exposure assessment for the registered uses was completed reflecting recent updates to the points of departure, and policy changes for body weight, unit exposure, and area/amount treated assumptions.

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1.0 Executive Summary

Atrazine, propazine, and simazine are selective triazine herbicides that are referred to collectively as the "chlorotriazine herbicides." These chlorotriazine herbicides, along with their three common chlorinated metabolites, desethyl-s-atrazine (DEA), desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT), have been determined by the Agency to share a common neuroendocrine mechanism of toxicity and constitute the triazine common mechanism group (CMG). This document serves as the draft human health risk assessment (DRA) to support the Registration Review for propazine. Atrazine, simazine, and the cumulative risk assessment (CRA) for all of the chlorotriazine herbicides are addressed in separate documents.

Use Profile

Propazine is a systemic herbicide that is usually applied to the soil, and is absorbed through leaves and roots. Propazine acts by inhibiting photosynthesis within the targeted plant. It is used as a selective herbicide to control most annual grasses and broadleaf weeds before the weeds emerge or after removal of weed growth. It is registered for use on sorghum fields prior to planting and before emergence, and on greenhouse grown-ornamentals. Propazine is formulated into one liquid end-use product (EPA Reg. No. 42750-148) containing 43% active ingredient (ai). The registered product is a restricted use pesticide (RUP). The maximum single application rate for sorghum is 1.2 lb ai/A and the maximum single application rate for greenhouse ornamentals is 1.5 lb ai/A. Propazine may be applied via ground, aerial (sorghum only), or handheld equipment; application through irrigation systems is prohibited. The registered label requires occupational handlers to wear baseline attire (long sleeved shirt, long pants, shoes, and socks), chemical resistant gloves, and protective eyewear. A chemical-resistant apron must also be worn when mixing/loading, cleaning up spills, cleaning equipment, or when otherwise exposed to the concentrate. Mixer/loaders supporting aerial applications must use a closed system along with the personal protective equipment (PPE) required for mixer/loaders. Flaggers supporting aerial applications must use an enclosed cab. The restricted entry interval (REI) is 24 hours.

Hazard Characterization

Propazine has a similar structure, and shares a common mechanism of neuroendocrine toxicity with atrazine, as well as simazine and their chlorotriazine metabolites. Because of the similar structures and metabolites among these three pesticides, they are also assumed to be of equal potency for neuroendocrine effects. Therefore, the more robust toxicological database for atrazine has been used to characterize neuroendocrine toxicity, and for endpoint selection, for all of these compounds. The neuroendocrine endpoint chosen for these chemicals is attenuation of the LH (luteinizing hormone) surge after 4 days of exposure, an effect which also protects for other downstream adverse endocrine-related toxicological effects (*e.g.,* estrous cyclicity disruption and delays in puberty onset). *In vivo* pharmacokinetic studies indicate that plasma concentrations of triazine equivalents achieve steady state after approximately 4 days of exposure in the rat. In addition, data from multiple laboratories demonstrate that attenuation of LH is fairly constant with durations ≥ 4 days. While much of the hazard characterization of this risk assessment discusses the neuroendocrine effects of atrazine, these discussions apply equally to propazine and its metabolites.

The current physiologically-based pharmacokinetic (PBPK) model for the chlorotriazines (atrazine, simazine and propazine) was derived from modifications of a previous oral PBPK model developed specifically for atrazine and its chlorinated metabolites (DEA, DIA, DACT). Plasma concentration of total chlorotriazines (TCT) was selected as the dose metric for cross-species extrapolation of the effect of the chlorotriazines on the LH surge. The revised PBPK model allowed for risk assessment to be based on an internal dose metric, which is more closely related to tissue responses, rather than on an external intake dose traditionally used when a PBPK model is not available.

Based on the structural similarity of propazine to atrazine, and the shared common chlorinated metabolites, the atrazine PBPK model was extrapolated to propazine by utilizing specific parameter values for propazine. A PBPK model has been utilized to estimate human equivalent doses and toxicological points of departure (PODs) for repeated dose exposures to propazine. These PODs are applicable to exposures of four days (or longer) since that is the time to elicit a decrease of the LH surge in rats. PODs for propazine for relevant lifestages (infants, children, youths, and adults) were derived for the standard routes of exposure (oral, dermal, and inhalation) (excluding acute dietary for propazine and its chlorinated metabolites and chronic dietary for hydroxypropazine and its hydroxy metabolites as discussed below). The model was used to derive scenario-specific PODs for residential and occupational exposures. To derive dermal PODs, a shower was incorporated into the modeling as a way to "turn off" or end daily exposure times. For residential, non-occupational, and occupational scenario-specific PODs, showers were assumed to occur 24 hours after initial exposure to account for any residues left on the skin following exposure. The dermal component of the model also included an hourly flux rate to determine the rate of absorption through the skin.

Because the PBPK model quantitatively considers differences in pharmacokinetic, but not pharmacodynamic parameters between laboratory animals and humans, the default interspecies uncertainty factor is reduced to 3X. Chemical-specific propazine toxicity data were used to characterize other toxic effects of the chemical, including developmental effects (decreased ossification) which comprise the endpoint for the acute dietary assessment. The Food Quality Protection Act (FQPA) Safety Factor has been reduced to 1X for all risk assessment scenarios since the toxicological database for the chlorotriazines and hydroxyatrazine is considered complete, there are no residual uncertainties in the exposure databases, the selected PODs are based on the most sensitive effect (LH surge attenuation) for non-acute assessments. The total uncertainty factor for 4-day risk assessment is 30X (3X interspecies factor, 10X intraspecies factor, and 1X FQPA when applicable). The total uncertainty factor for acute risk assessment is 100X (10X interspecies factor, 10X intraspecies factor, and 1X FQPA).

In addition to the chlorotriazine metabolites, simazine also has an analogous series of metabolites, known as the hydroxy metabolites, in which the chlorine is replaced by a hydroxy moiety. While the hydroxy metabolites are all considered to be of equal toxicity, these compounds exhibit different toxicological properties than the chlorinated metabolites, and risk estimates are therefore quantified separately using an endpoint and POD based on hydroxyatrazine. The risk assessment endpoint is histopathological lesions in the kidney observed in a rat chronic toxicity study. No acute effects were observed. As with the chlorotriazines, much of the discussion in the hazard characterization portions of this risk

assessment discuss the kidney effects of hydroxyatrazine because the hydroxyatrazine database is more extensive; however, these discussions apply equally to hydroxypropazine and its hydroxy metabolites. Dermal and inhalation exposures are not expected for hydroxypropazine. There are no residual uncertainties in the hazard or exposure databases for the hydroxy compounds, so the FQPA safety factor is reduced to 1X. The total uncertainty factor for chronic risk assessment is 100X (10X interspecies factor, 10X intraspecies factor, and 1X FQPA).

Exposure Profile

The residues of toxicological concern for neuroendocrine risk assessment are parent compound propazine and its two chlorinated metabolites, DEA and DACT. Propazine and its chlorinated metabolites are assumed to have equivalent toxicity. The residues of concern for risk assessment for kidney effects are propazine's metabolite hydroxypropazine, along with the associated hydroxylated metabolites, DEHA, and ammeline. These hydroxylated residues of concern are assumed to have equal toxicity. Dietary exposure to propazine and its chlorinated and hydroxylated metabolites may occur from ingestion of residues in foods and in drinking water. Dietary exposure durations may be acute (one day) or chronic. However, for the chlorotriazine herbicides, only acute and 4-day exposure durations for dietary exposures are applicable; risk assessment considering a 4-day exposure duration and time-to-effect will be protective for longer duration exposures which will have lower average residues. For acute assessment of propazine and its chlorinated metabolites, the toxicological endpoint is delayed ossification in fetuses and is only applicable to females of reproductive age (13-49 years old). For the 4-day assessment for propazine and its chlorinated metabolites, the endpoint is attenuation of LH surge (the most sensitive endpoint) and is applicable to all lifestages. The duration appropriate for assessing dietary risks for the hydroxypropazine and its hydroxylated metabolites (which have a different toxicological profile than the chlorotriazines) is chronic. The chronic endpoint (kidney effects) is applicable to all lifestages.

Non-dietary exposure to parent compound propazine may occur from occupational and non-occupational exposure sources; exposure to the chlorinated and hydroxylated metabolites are not expected to occur. Based on the currently registered uses of propazine, the durations of exposure are expected to be both short- and intermediate-term for occupational handler and post-application workers. Exposures from non-occupational spray drift from application to sorghum are expected to be short-term only. Residential exposures are not expected because there are no registered or proposed residential uses of propazine. For the chlorotriazine herbicides, only the 4-day exposure duration is assessed since it will be protective for longer durations of exposure.

Food Exposure and Risk

The residue chemistry database is complete for the established uses of propazine. The residue definition for tolerance enforcement includes the parent propazine and its chlorinated metabolites, while that for risk assessment also includes the corresponding hydroxy metabolites. Because they have different toxicity endpoints, hydroxy metabolites are assessed separately from propazine and the chlorinated metabolites.

Propazine is registered for use on grain sorghum. However, the 2003-2010 U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) reports no human consumption for sorghum grain, the only food

commodity from grain sorghum in the Dietary Exposure Evaluation Model with Food Commodity Intake Database (DEEM-FCID). Field trial studies have demonstrated that residues of propazine and its regulated metabolites are less than the limit of quantitation (LOQ) of the analytical method in sorghum grain. Considering the less than LOQ residues in sorghum combined with minimal expected consumption, human exposure to propazine residues from the sorghum use may be considered negligible.

With insignificant exposure to propazine in food expected from the current uses, the total dietary exposure to propazine is through drinking water. A drinking water level of comparison (DWLOC) approach is used to calculate the amount of exposure available in the total 'risk cup' for drinking water. Typically, this approach would involve accounting for any exposures from food and/or residential use as well; since there are no anticipated food or residential exposures to propazine, the entire 'risk cup' is available for drinking water exposures. The DWLOCs for propazine were compared to the estimated concentrations in drinking water (EDWCs). EDWCs were derived using a total toxic residue (TTR) approach and include all chlorotriazine residues of concern that may occur in drinking water when considering all triazine uses, referred to as TCT (total chlorotriazines). This approach was also used for the hydroxytriazine residues of concern, referred to as THT (total hydroxytriazines). Separate ground water (monitoring data) and surface water (modeling) concentrations were provided. The DWLOC approach facilitates determining aggregate risk estimates when there are multiple EDWCs and is also the approach being used for the atrazine, simazine, and triazine cumulative risk assessments.

For propazine, the acute DWLOC for females 13-49 years old is greater than the acute EDWCs for TCTs in surface water or ground water; the acute toxicological endpoint is only applicable to females of reproductive age. The 4-day DWLOCs for infants, children, youth, and adults, are greater than the EDWCs for TCTs in surface water or ground water. There are no acute or 4-day dietary risks of concern for propazine.

For hydroxypropazine, the chronic DWLOCs for infants, children, youth, and adults, are greater than the EDWCs for THTs in surface water or ground water. There are no chronic dietary risks of concern for hydroxypropazine.

Residential Exposure and Risk Assessment
There are currently no registered residential uses of propazine.

Aggregate Exposure and Risk Assessment
There are no residential uses of propazine and exposures from food are not expected. Exposures are only expected from drinking water and there are no risks estimates of concern for this pathway. There are no aggregate risks of concern for propazine.

Non-Occupational Spray Drift Exposure and Risk Assessment
A quantitative non-occupational spray drift assessment was conducted for propazine use on sorghum (1.2 lb ai/A); spray drift is not expected from the registered use on greenhouse ornamentals. Although there are no chemical-specific turf transferable residue (TTR) data for propazine, TTR data are available for atrazine and simazine. Simazine and atrazine TTR data are suitable surrogates for propazine because all three chemicals are members of the *s*-triazine

family, share a common mechanism of toxicity, share similar physicochemical properties, and their uses as an herbicide are very similar. The simazine TTR data provided the highest/most protective Day 0 residue estimates; therefore, the propazine non-occupational spray drift assessment incorporated simazine transferrable residues. A 4-day average residue was used to estimate risk from contact with treated turf because the POD is based on decreased LH surge; and available toxicity data indicate that the decrease occurs after a 4-day exposure. The residue estimate was then adjusted for the maximum registered single application rate of propazine on sorghum. Using these assumptions, the adult dermal and children's (1 to < 2 years old) dermal and incidental oral risk estimates from indirect exposure to propazine were not of concern at the field edge assuming screening-level nozzle types and droplet sizes (MOEs > the level of concern (LOC) of 30).

Occupational Handler Exposure
Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of propazine. The occupational handler exposure and risk estimates indicate that some of the combined dermal and inhalation risk estimates are of concern (MOE > 30) with baseline attire + label specified PPE (chemical resistant gloves). Mixing/loading/applying liquids via backpack spray equipment to greenhouse ornamentals is not of concern with the addition of a double layer of clothing. Mixing/loading/applying liquids with a mechanically pressurized handgun to greenhouse ornamentals remains of concern when assuming label-specified PPE, a double layer of clothing, and a PF10 respirator. Dermal exposures are the highest contributors to the combined dermal + inhalation risk estimates.

Occupational Post-Application Exposure
Occupational post-application dermal exposure and risk estimates were assessed for registered uses of propazine (sorghum and greenhouse-grown ornamentals). Although there are no chemical-specific dislodgeable foliar residue (DFR) data available for propazine, DFR data are available on field corn treated with liquid and dry flowable formulations of atrazine. Using atrazine-specific DFR data, the occupational post-application MOEs are not of concern for the registered uses of propazine on the day of application.

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

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment (see Section 3.5).

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix E provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of

EPA's Rule for the Protection of Human Subjects of Research (40CFR Part 26) have been satisfied.

2.0 Risk Assessment Summary & Conclusions

There are no dietary or non-occupational risk estimates of concern for the registered uses of propazine. There are some occupational handler combined dermal and inhalation risk estimates of concern with baseline attire and label-specified PPE (chemical resistant gloves). There are no post-application risk estimates of concern.

2.1 Data Deficiencies

There are no multiresidue method testing results (OCSPP 860.1360) for the regulated chloro metabolites of propazine: G-30033 and G-28273 (DEA and DACT; see Figure 3.1.1.). These data should be submitted.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Suitable analytical enforcement methods are available for propazine and its two regulated chloro metabolites: G-30033, and G-28273 (DEA and DACT; see Figure 3.1.1.). Corning Hazelton analytical method CHW 6641-106 (Method 1, Rev. 1) determines residues of propazine and G-30033 by gas chromatography/mass-selective detector (GC/MSD), while residues of G-28273 are determined by GC/nitrogen-phosphorus detector (NPD). The limit of quantitation (LOQ) for each analyte in all sorghum matrices is 0.05 ppm. Additionally, Method GRM052.01A, a liquid chromatography with tandem mass spectroscopy (LC-MS/MS) method with a validated LOQ of 0.01 ppm for residues of simazine, G-28279 (DIA), and G-28273 (DACT) in plant matrices, is also available for tolerance enforcement. No enforcement methods for livestock commodities are needed for propazine.

According to the Food and Drug Administration's (FDA's) Pesticide Analytical Method (PAM) Volume I, Appendix II, propazine is completely recovered using Section 302 (Protocol D), partially recovered using Section 303 (Protocol E), and not recovered using Section 304 (Protocol F). Similarly, multiresidue methods (MRM) based on the Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method as used by the USDA Pesticide Data Program (PDP), provide results for the parent triazine compound (atrazine, propazine, and simazine), but not the corresponding chloro metabolites. There are no MRM recovery data for G-30033 or G-28273, and these data should be submitted.

Analytical standards for residues of concern for propazine are presently up to date and available at the EPA National Pesticide Repository, as indicated in the table below (electronic communication with Gregory Verdin on 11/8/2017). The registrant should replenish supplies of standards prior to expiration.

Analytical Standard	CAS#	Expiration Date
Atrazine	1912-24-9	8/28/24

Analytical Standard	CAS#	Expiration Date
Propazine	139-40-2	8/31/21
Simazine	122-34-9	5/31/21
G-30033 [DEA]	6190-65-4	11/30/20
G-28279 [DIA]	1007-28-9	6/30/18
G-28273 [DACT]	3397-62-4	12/31/18

2.2.2 Recommended & Established Tolerances

Tolerances are established under 40 CFR §180.243 for residues of propazine in/on sorghum commodities. HED recommends that the residue definition for the tolerance expression for propazine be modified in accordance with current policy on tolerance definitions, to read:

> *"Tolerances are established for residues of the herbicide propazine, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of propazine, 6-chloro-N,N'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine, and its metabolites 6-chloro-2-N-(1-methylethyl)-1,3,5-triazine-2,4-diamine, and 6-chloro-1,3,5-triazine-2,4-diamine, calculated as the stoichiometric equivalent of propazine, in or on the commodity."*

Table 2.2.2. Tolerance Summary for Propazine.

Commodity	Established Tolerance (ppm)	Recommended Tolerance (ppm)
Sorghum, grain, forage	0.25	0.20
Sorghum, grain, grain	0.25	0.15
Sorghum, grain, stover	0.25	0.15

The recommended tolerances are lower than the established tolerances and are based on LOQ considerations. There were no detects in sorghum grain or stover; therefore, the recommended tolerance is 0.15 ppm (LOQ = 0.05 ppm; 0.05+0.05+0.05=0.15 ppm). There were no detects in trials with sorghum forage for propazine or G-30033, but a maximum level of 0.078 ppm was found for DACT, so the tolerance is recommended to be set at 0.20 ppm.

2.2.3 International Harmonization

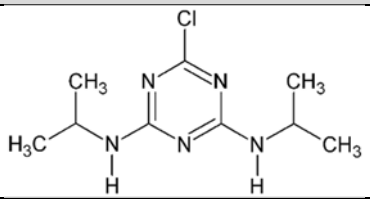
No Codex or Canada Pest Management Regulatory Agency (PMRA) maximum residue levels (MRLs) have been established for propazine. There are no harmonization issues at this time.

2.3 Label Recommendations

- HED notes that there are occupational handler scenarios for registered uses that have non-cancer risk estimates of concern where potential mitigation may impact label language.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Propazine Nomenclature.	
Chemical structure	
Common name	Propazine
Company experimental name	G-30028
IUPAC name	6-chloro-N^2,N^4-di-isopropyl-1,3,5-triazine-2,4-diamine
CAS name	6-chloro-*N*,*N*'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine
CAS registry number	139-40-2

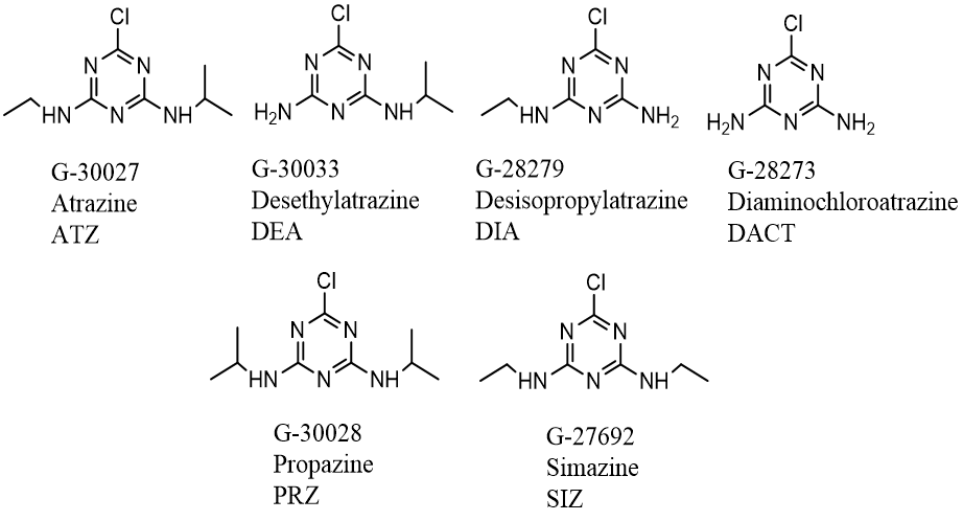


Figure 3.1.1. Chemical Structures for the Total Chlorinated Triazines (TCTs).

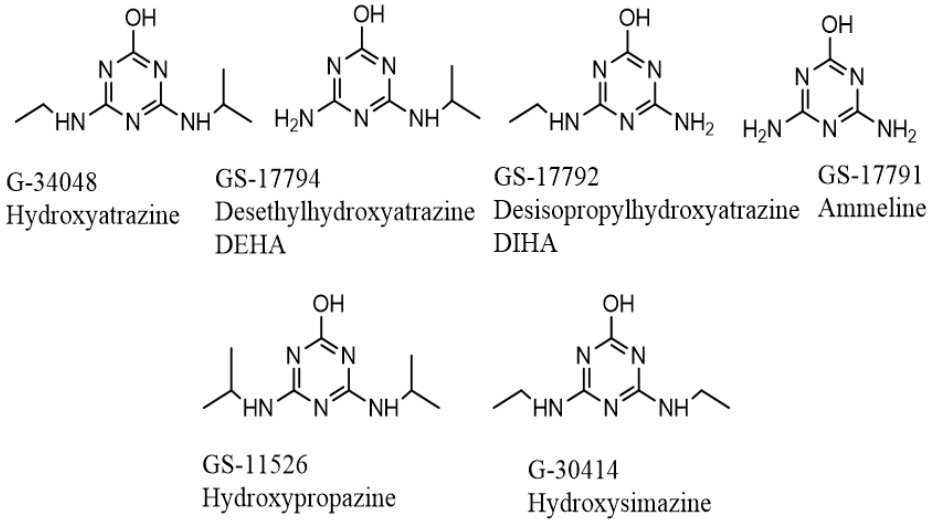


Figure 3.1.2. Chemical Structures for the Total Hydroxy Triazines (THTs).

3.2 Physical/Chemical Characteristics

The chlorotriazine herbicides, atrazine, propazine, and simazine, have low volatility and are somewhat lipophilic. Similar environmental degradation pathways are operative for the chlorotriazine herbicides. These chemicals are considered moderately persistent and mobile in most soils, showing relatively slow breakdown by hydrolysis, photolysis, or biodegradation. Environmental fate data indicate that the hydroxytriazines, while persistent, are less mobile than the chlorotriazines.

The physical and chemical properties of propazine are provided in Appendix B.

3.3 Pesticide Use Pattern

The registered uses of propazine are summarized in Table 3.3.

Table 3.3. Summary of the Registered Uses of Propazine.

Application Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Application Rate	Max. No. Applications per Season or Growing Cycle	Max. Seasonal Application Rate	PHI (days)	Use Directions and Limitations[1]
Sorghum						
Pre-emergence, Early Post-Emergence Aerial, Ground	Liquid 4 lb ai/gal [42750-148]	1.2 qts/A (1.2 lb ai/A)	1	1.2 lb ai/A	70 (forage) 90 (grain or stover)	RUP product. Apply in 10 gals/A by ground and 3 gals/A by air. Application through irrigation is prohibited.
Containerized Greenhouse Ornamentals						
Pre-emergence, Early post-emergence Ground, Handheld	Liquid 4 lb ai/gal [42750-148]	2.25 Tablespoons/1000 ft^2 (1.5 lb ai/A) Or 0.15 lb ai/gal[1]	1	0.15 lb ai/gal	NS	RUP product. Apply through flood or drench nozzles only.

1. ROTATIONAL CROP RESTRICTIONS
   - Do not rotate to leafy vegetables.
   - Do not rotate to root crops or cereals (small grains) at less than a 120-day plantback interval.
   - Do not rotate to any crop other than sorghum except:
     - Texas Gulf Coast and Texas Blacklands, cotton, soybeans or corn may be planted 12 months after treatment. Do not plant other crops for 18 months after treatment.
     - In West Texas, cotton or corn may be planted 12 months after a broadcast application of 1.2 quarts.
     - In all other sorghum growing regions, corn may be planted 12 months after treatment. Do not plant other crops for 18 months after treatment.
     - If replanting is necessary, sorghum may be replanted in soil treated with this product, however, an additional application is prohibited.
2. Rate specified as 2.25 TBS per 1000 ft^2. 2.25 TBS = 0.008789 gal. Assumes spray dilution of 10 gals/A for ground applications as specified on page 8 of the registered label. Application rate in lb ai/gal calculated as follows: 0.008789 gal/1000 ft^2 × 4 lb ai/gal product × 1 A/10 gal × 43560 ft^2/A = 0.15 lb ai/gal.

3.4 Anticipated Exposure Pathways

Humans may be exposed to propazine and its chlorinated and hydroxylated metabolites in drinking water, since propazine application may result in these residues reaching surface and ground water sources of drinking water. There are no residential uses of propazine; however, adults and children may be exposed to spray drift/volatilization from occupational applications.

Occupational exposures are expected from the application of propazine and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all of the existing uses of propazine.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

This section provides summary information and weight of evidence findings integrating multiple lines of evidence from experimental toxicology and epidemiology with respect to the atrazine risk assessment. Propazine is considered to be equivalent in neuroendocrine toxicity to the chlorotriazines atrazine and simazine, as well as their shared chlorinated metabolites (see Section 4.1). 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, atrazine data are used as bridging data for propazine because propazine, simazine and atrazine share a common mechanism of toxicity for neuroendocrine effects. Separate risk assessments for atrazine and simazine have been developed.

The risks associated with exposure to the hydroxylated metabolites of propazine are also presented in this risk assessment. The toxic effects attributed to the hydroxy-metabolites of atrazine, simazine, and propazine are different from their chlorinated analogs, and are therefore not included in the common mechanism grouping of the chlorinated triazines (see Section 4.5.2). The endpoint for all hydroxytriazines is kidney histopathology observed in a chronic rat study for hydroxyatrazine.

This section also describes the data related to the FQPA Safety Factor, and the use of a PBPK model for deriving PODs and the reduction of the standard inter-species extrapolation uncertainty factor (reduced from 10X to 3X).

4.1 History of Toxicological & Epidemiologic Analysis & Peer Review

Atrazine, propazine, and simazine are selective triazine herbicides that are referred to collectively as the "chlorotriazine herbicides". These chlorotriazine herbicides, along with their three major chlorinated metabolites, DEA, DIA, and DACT, have been determined by the Agency to share a common neuroendocrine mode of action (MOA) which results in both reproductive and developmental alterations ("The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity"; http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2005-0481-0011).

The human health risk assessment for atrazine is complex and has a long history of data development, regulatory evaluation, and Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Science Advisory Panel (SAP or "Panel") review. Atrazine was first presented to the SAP for evaluation of rat mammary gland tumor response in 1998 (FIFRA SAP, 1998). At that time, the SAP noted that a "hormonal influence" might be an important consideration in the development of these mammary gland tumors. Subsequent to this meeting, substantial research was conducted on atrazine's hormonal or neuroendocrine mode of action. The Agency returned to the SAP in 2000 (FIFRA SAP, 2000) for comment on atrazine's MOA leading to mammary gland tumors and, reproductive and developmental effects in rats, as well as the human relevance of these findings. The SAP agreed with the Agency on atrazine's neuroendocrine mode of action. The SAP stated that the "Panel concluded that it is unlikely that the mechanism by which atrazine induces mammary tumors in female Sprague-Dawley (SD) rats could be operational in man. Nevertheless, it is not unreasonable to expect that atrazine might cause adverse effects on hypothalamic-pituitary function in man if exposures were high enough (p. 14, FIFRA SAP, 2000)." At the 2000 SAP, the panel further advised the Agency to evaluate the cancer epidemiology in more depth as more information became available, particularly for prostate cancer and Non-Hodgkin lymphoma. In 2003, the Agency presented its evaluation on prostate cancer. At that meeting, the FIFRA SAP concurred with EPA's conclusion that an increase in Prostate-Specific Antigen (PSA) screening could explain the observed increase in prostate cancer incidence in the workers

In recent years, numerous governmental and academic research groups have published experimental toxicology and epidemiologic studies evaluating the toxicity profile and/or MOA of atrazine. These new studies have considered a variety of adverse outcomes such as reproductive toxicity in males and females, adverse birth outcomes, hormone disruption, neurotoxicity, immunotoxicity, respiratory health, effects on the mammary gland, and carcinogenicity. To consider the extent to which these new studies may influence the Agency's human health risk characterization for atrazine, OPP in collaboration with the Office of Research and Development (ORD) has evaluated the new research on atrazine and its chloro-s-triazine metabolites (DEA, DIA, and DACT). To ensure that the best science possible is used to inform the atrazine human health risk assessment, and to ensure transparency in regulatory decision making, EPA sought advice from the FIFRA SAP on a variety of challenging scientific issues.

Between 2009 and 2011, the Agency held five meetings of the FIFRA SAP on topics related to non-cancer and cancer effects of atrazine and its chlorinated metabolites of concern (https://www.epa.gov/sap/fifra-scientific-advisory-panel-historical-meetings). A summary of the charge and outcomes of each SAP meeting is provided below:

- **2009:** The first SAP meeting held in November of 2009 announced the Agency's approach to this re-evaluation and set forth an ambitious schedule for a series of SAP meetings to discuss various topics related to the potential impact of atrazine exposure on human health.
- **2010:**
    - **February 2010:** The Agency solicited the SAP's advice on a draft framework for implementing the use of epidemiology and incident data into human health risk assessment. The Agency's analysis included an evaluation of several ecological and retrospective cohort epidemiology studies for atrazine. OPP, in collaboration with EPA ORD and Office of Water (OW), solicited comment on the strengths and weaknesses of these types of epidemiology studies, and sought advice on the appropriate use of such studies in the atrazine human health risk assessment (Public Docket EPA-HQ-OPP-2009-0851).
    - **April and September 2010:** The SAP reviewed the Agency's evaluations of the extensive atrazine database (100s of studies) encompassing mechanistic, *in vitro, in vivo,* toxicology, and pharmacokinetic studies as well as epidemiology studies concerning the non-cancer health effects of atrazine (Public Docket ID EPA-HQ-OPP-2010-0125 and EPA-HQ-OPP-2010-0481, respectively). Among the non-cancer effects considered during these meetings, the Agency evaluated studies on the potential impact of atrazine exposure on sexual maturation, development of prostatitis, pregnancy maintenance as well as the immune, nervous, and reproductive systems. Although effects were noted in all these systems, the dose levels at which they occur were higher than the doses eliciting attenuation of the luteinizing hormone (LH) surge. In all, the Agency concluded, and the SAP concurred, that attenuation of the LH surge continues to be the most sensitive effect (*i.e.,* occurs at the lowest dose) identified to date in the atrazine database and that the new experimental toxicology studies did not alter or contradict the major key events in the neuroendocrine MOA leading to mammary gland tumors in the rat or the conclusion that the MOA leading to mammary gland tumors in the rat is not relevant to humans.
    - **2011:** The fifth SAP meeting held in July 2011 continued the Agency's evaluation of non-cancer effects as well as the cancer epidemiology data published since 2003 (Public Docket ID EPA-HQ-OPP-2011-0399). The Agency concluded that the epidemiology evidence is not strong enough to warrant a change to its current cancer classification for atrazine. The SAP panel members reiterated their recommendation to the Agency to continue to follow the published cancer epidemiology literature regarding ovarian, thyroid, and possibly lymphohematopoietic cancers, specifically. The SAP stated that although studies of these anatomical cancer endpoints are inconclusive at this time, Panel members believed the data were suggestive of a possible association and warrant close evaluation in future assessments.

4.2 Toxicology Studies Available for Analysis

As indicated above, the database for propazine is not as robust as atrazine. However, atrazine data can be used to bridge data for propazine because they share a common mechanism of toxicity based on neuroendocrine effects. The toxicology database on atrazine is extensive and consists of 100s of studies on a wide range of issues, and there is a high degree of confidence in the scientific quality of the toxicity studies conducted with atrazine (EPA-HQ-OPP-2010-0125; EPA-HQ-OPP-2010-0481; EPA-HQ-OPP-2011-0399). Toxicity studies required under the Subdivision F Guidelines have been submitted and found acceptable by the Agency. Special studies examining the toxicology, MOA, and pharmacokinetics of atrazine have been performed by the registrant in addition to the required guideline studies. Additionally, EPA's National Health and Environmental Effects Research Laboratory (NHEERL) has performed studies investigating atrazine's neuroendocrine mode of action and related reproductive and developmental effects, in addition to numerous experimental laboratory studies conducted in academic labs and published in the peer reviewed literature. Furthermore, the database includes epidemiology studies on a variety of cancer and non-cancer outcomes. The atrazine database, including both experimental toxicity and epidemiology studies, has been the subject of several reviews by the EPA SAP. EPA's reviews of the previous literature are provided in the appendices of the 2010 and 2011 issue papers presented to the SAPs. Information from the issue papers supports this risk assessment. As part of the revised human health risk assessment, EPA has reviewed and updated experimental toxicology literature since the 2011 SAP. The experimental toxicology literature search was conducted in PubMed for the time period between May 2011 and January 2017 (J. Liccione, D444631, 02/01/2018). EPA has also updated the epidemiology literature search regarding atrazine, simazine, and propazine and potential cancer and non-cancer health effects. On January 11, 2017, a literature search was run in PubMed, Web of Science, and ScienceDirect to identify peer reviewed published literature on the human health effects associated with exposure to atrazine, simazine, and/or propazine as part of a systematic literature review of these chemicals (A. Aldridge, D447696, 07/09/2018, and A. Aldridge, D447697, 07/09/2018). Over 90 publications from 1990 – 2017 were identified for inclusion in the epidemiology literature review. The atrazine risk assessment (K. Rickard *et al.,* D418316, 07/10/2018) highlights the 11 epidemiology studies identified in the literature that reported a statistically significant estimate of effect for atrazine, that emanated from a prospective cohort and/or were otherwise of a moderate or high quality study design[1] or were often cited in the epidemiology literature, and that were unavailable at the time of the 2009-2011 SAPs (Appendix B of K. Rickard *et al.,* D418316, 07/10/2018).

The most significant development in the hazard evaluation of atrazine since the 2011 SAP is the development of a PBPK model. This model is based on an earlier model developed by McMullin *et al.,* (2007a) in rats. The McMullin model has since undergone several revisions and refinements by the researchers at the Hamner Institutes and Syngenta (Campbell 2011; Campbell 2014; Hinderliter 2015; Campbell 2015) to include new metabolism rate constants scaled from *in vitro* experiments using rat and human hepatocytes. In addition, the McMullin model described

[1] Quality of study design and methods per US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

oral uptake using an empirical function, which cannot be extrapolated from rats to humans, and thus, additional model code for simulating oral uptake and absorption was developed to replace the original model descriptions. The PBPK model provides simulations of plasma time-course of atrazine and chlorinated metabolites in the rat, monkey and human after oral exposure, and allows for the calculation of internal doses. Both inhalation and dermal route were added to the human model. Although there were no human time-concentration data to evaluate model predictions from these two routes, the inhalation route was modeled using the most conservative assumption that all inhaled doses enter directly into the plasma compartment. For the dermal route, the dermal absorption rate was obtained from an *in vivo* human study, providing confidence in dermal simulations. The model, including all three exposure routes, has undergone review twice by the Pacific Northwest National Laboratory (PNNL) to verify model equations accurately reflect the conceptual descriptions of the model, and computational implementation is accurate. PNNL also conducted an independent evaluation of the model's predictive ability by comparing model predictions with available rat and human time course data. In addition, the Agency also established an external peer review group to conduct a similar review of the model. For this review, an expert panel was selected to independently evaluate the model and answer charge questions relating to model representation, model coding, model evaluation, model documentation, and the estimation of human points of departure. A more detailed description of the PBPK model, as well as the review process for the model, is provided in Section 4.6.2.4 of this document.

While the PBPK model was developed for atrazine, based on structural similarity, the model can also be used for propazine with the addition of propazine-specific pharmacokinetic and chemical parameters. While discussion of the model focuses on atrazine, the information is pertinent to propazine as well.

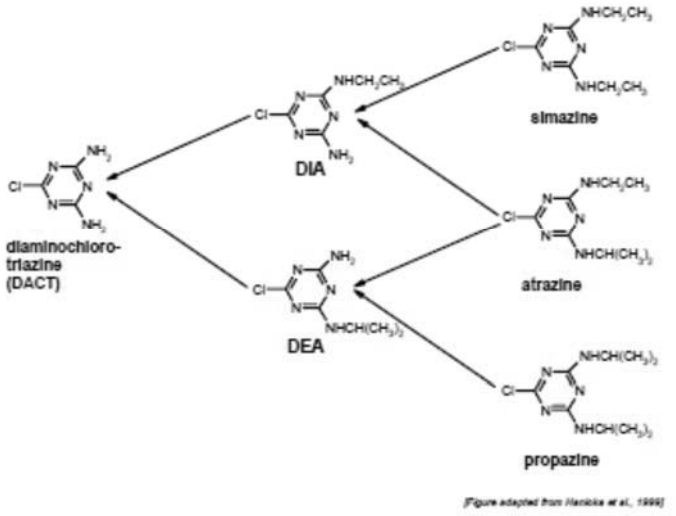
4.3 Absorption, Distribution, Metabolism, & Elimination (ADME)

Characterization of the pharmacokinetics and internal dosimetry of atrazine and its metabolites represents a critical step for elucidating the link between exposure and attenuation of the pre-ovulatory LH-surge for the application of a MOA approach to risk assessment. Atrazine is quickly metabolized via the oral route to its dealkylated chlorinated metabolites DEA, DIA, and DACT as illustrated in Figure 4.3. DACT is the major metabolite (MRID 44713802; McMullin, 2003). DEA, DIA, and DACT are considered to have similar potency as atrazine with respect to potential for neuroendocrine activity based on results of multiple studies (Minnema, 2001; Laws *et al* 2002: Stoker *et al.,* 2002; Petterson *et al.,* 1991).

The chlorinated triazines and their chlorinated metabolites may also undergo glutathione conjugation followed by transformation to mercapturic acid derivatives. The primary routes of excretion have been identified to be urinary and fecal (MRID 44713802; Timchalk, 1990). The 2002 common mechanism grouping science policy document (USEPA, 2002)[2] provides a review of the available metabolism studies for atrazine, propazine, and simazine. All three pesticides share similar pharmacokinetic profiles. In oral rat studies, all three are readily absorbed by the oral route supporting the assumption of 100% oral absorption used in the PBPK model.

[2] USEPA. 2002. The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity. U.S. EPA Office of Pesticide Programs Health Effects Division, March 2002

Figure 4.3: Atrazine and its chlorinated metabolites Extracted from USEPA (2002)



A recent pharmacokinetic study (MRID 49482201) of atrazine after single oral or intravenous doses to adult female monkeys was conducted to support the PBPK model development. In this study, atrazine was rapidly and completely absorbed (T_{max} = 1 hour), metabolized to DEA and DIA, and cleared from plasma with a $T_{1/2}$ of 4.0 hours. DEA and DIA appeared rapidly in plasma with similar pharmacokinetic profiles as atrazine. DACT took slightly longer to reach maximum plasma concentration (T_{max} = 1.8 hours) and cleared with a longer half-life ($T_{1/2}$ = 10.3 hours). Internal dose metrics [(C_{max} and area under the curve (AUCs)] for the chlorotriazines scaled linearly with administered dose indicating that absorption and metabolic processes were not saturated over the 20-fold dose range investigated. Ninety percent of the chlorotriazines identified were found in urine and 10% in feces.

A single-dose human oral pharmacokinetic study (MRIDs 43598603 & 43598604)[3] in six male human volunteers (dosed with 0.01 mg/kg bw atrazine via gelatin capsules) demonstrated that atrazine and DIA were detected in whole blood at levels below the limit of quantitation. In contrast, DEA appeared at a rapid rate reaching a peak within 2 hours and declined rapidly with a half-life of 2.8 hours. The rate of appearance of DACT in blood peaked at 5 hours and was eliminated with a half-life of 17.8 hour. Urinary monitoring of DACT was considered to be the best indicator of human atrazine exposure. The average half-life of urinary excretion of DACT was 11.5 hours. The time course blood data in this human study were used to compare with simulations using the PBPK model. The concordance between the observed data and model

[3] In 2011, OPP conducted a human research ethics review of both MRIDs 43598603 and 43598604 and found that there is no barrier in law or regulation to EPA reliance on these studies in EPA actions taken under FIFRA or Section 408 of FFDCA.

predictions increases the confidence in the model's capability to simulate internal dosimetry from human exposures.

4.4 Dermal Absorption

Dermal absorption data for atrazine can be translated to propazine because of their structural similarity and similar physicochemical properties. The atrazine dermal absorption data represent the best available data for estimating dermal absorption for all three chlorotriazine herbicides.

In a human dermal absorption study (MRID 44152114)[4], in which 10 volunteers were exposed to a single topical dose of ^{14}C-atrazine at 6.7 or 79 µg/cm^2 for 24 hours (equivalent to 0.1667 and 1.9751 mg of [^{14}C] atrazine, respectively), the majority (91.1-95.5%) of the dose remained unabsorbed. After 168 hours, only 5.6% of the dose was absorbed and excreted in the urine and feces of the low-dose group and only 1.2% in the high-dose group. The renal excretion half-life was 19.6-29 hours for the low-dose group and 25.9-31 hours for the high-dose group. In both dose groups, peak urinary elimination occurred at 24-48 hours and peak fecal elimination occurred at 48-72 hours. Based on the results of this study, a dermal absorption factor (DAF) was estimated at 6%.

In the rat dermal absorption study (MRID 43314302), the maximum absorption of atrazine was approximately 30% following a single application of 0.01 mg/cm^2 ^{14}C-atrazine for up to 24 hours. The maximum percentage of atrazine absorbed in the rat study after a 10 hour (representative of a typical workday) exposure was 21.6% (rounded up to 22%). The maximum percent absorbed after any duration of exposure in the human dermal penetration study described above was 5.6% (rounded up to 6%). 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 penetration in the human and used as the DAF for assessment of dermal exposures.

4.5 Toxicological Effects

For most pesticides, there is little information on the MOA/adverse outcome pathway (AOP), and even fewer pesticides have epidemiology studies that can be used in the risk assessment process. As such, the Agency makes assumptions about the relevance of animal findings to humans, and quantitative animal to human extrapolation. In the case of atrazine, the wealth of data across many scientific disciplines allows for a highly refined assessment for atrazine using MOA understanding, human relevance of animal studies informed qualitatively by epidemiology studies, refined analysis of critical durations of exposure, and a PBPK model to extrapolate internal dosimetry from animals to humans. The following sections will describe the critical data/studies that form the basis for the atrazine hazard assessment, and by translation, the propazine hazard assessment. A more comprehensive description of the totality of the data may be found in the issue papers presented by the Agency during the 2009-2011 SAP review process (http://www.regulations.gov Public Dockets: EPA-HQ-OPP-2009-0851, EPA-HQ-OPP-2010-0125, EPA-HQ-OPP-2010-0481, and EPA-HQ-OPP-2011-0399).

[4]Hui et al. (1996). In vivo Percutaneous Absorption of Atrazine in Man (MRID 44152114). This intentional exposure human study underwent an ethics review in 2006, at which time it was confirmed that it meets all requirements under EPA's Human Studies Rule at 40 CFR part 26 for EPA reliance on the study.

4.5.1 Mode of Action (MOA)

In describing and analyzing a MOA for any chemical, the Agency applies the MOA/AOP frameworks for organizing and analyzing the available data (U.S. EPA, 1999, 2005; Boobis *et al., 2*008; Sonich-Mullin *et al.,* 2001; Meek *et al.,* 2014; Seed *et al.,* 2005, Ankley *et al.,* 2010). MOA/AOPs provide important concepts and organizing tools for risk assessment. The MOA and weight of the evidence (WOE) frameworks rely heavily on the Bradford-Hill Criteria[5], which are often used in epidemiology for establishing causality. Recently, OPP proposed extending this MOA framework and related Human Relevance Framework to the integration of epidemiology and experimental toxicology data into a WOE analysis (USEPA, 2016). MOAs/AOPs describe a set of measurable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events. An AOP further defines the initial step in the process as the molecular initiating event (MIE; Ankley, *et al.,* 2010).

4.5.1.1 A Well-Established MOA: Reproductive Senescence & Mammary Tumors in Rats

Initially postulated to elucidate the physiological events and endocrine changes leading to mammary tumor formation in the SD rats, the operative MOA for atrazine involves a series of key events that ultimately lead to early reproductive senescence in SD rats resulting in mammary gland tumor development. The key events described in the 2003 atrazine Interim Reregistration Eligibility Decision (IRED) are:

- Hypothalamic effects resulting in changes in catecholamine function and regulation of the pulsatile release of gonadotropin releasing hormone (GnRH).
- Attenuation of the LH surge and disruption of ovarian cycles
- Cessation of ovulation with the ensuing persistent release of estrogen
- Increased prolactin release by the pituitary as a secondary consequence resulting from the elevated estrogen levels
- Prolactin and estrogen-induced proliferative processes in the mammary gland leading to tumorigenesis.

In 2003, the Agency concluded, and the SAP concurred that this MOA for the development of mammary tumors is not operative in humans as the reproductive senescence process in humans is related to ovarian atresia[6] rather than persistent estrous as in the rat. Nonetheless, it is not unreasonable to assume that the same endocrine perturbations that induce mammary tumors in rats may play a role in at least some developmental effects (not associated with reproductive aging) that may be relevant to hypothalamic-pituitary function in humans. As such, the Agency used an early key event (i.e., attenuation of the pre-ovulatory LH surge) from atrazine's toxicity pathway as the basis for setting the PODs for the intermediate and chronic assessments. Similarly, the effect of atrazine on the neuroendocrine control of rat reproduction was considered a key step in the atrazine-induced delay in pubertal development

[5] Hill, Austin Bradford. "The environment and disease: association or causation?." Proceedings of the Royal society of Medicine 58.5 (1965): 295.

[6] Degeneration of ovarian follicles that do no ovulate during the menstrual cycle

in both sexes (Stoker *et al.,* 2000; Laws *et al.,* 2000) and the disruption of prostate function in the male offspring when the dam is exposed immediately following birth. The perturbation of the LH surge is the cornerstone of the cascade of events leading to the adverse reproductive outcomes (e.g., disruption of ovarian cycling and sexual maturation) attributed to atrazine exposure. For example, sexual maturation is the culmination of a complex cascade of sex developmental effects that ultimately leads to the attainment of reproductive capacity. Activation of the hypothalamic-pituitary-gonadal axis (HPG) resulting in the pulsatile secretion of GnRH and LH is critical to puberty onset. For instance, decreased LH during puberty would lead to insufficient stimulation of the gonads, with reduction of the circulating hormone levels needed for development of sex accessory tissues in males and females. Moreover, researchers have found that disruption of GnRH release and the ensuing dampening of the LH surge can lead to delays in vaginal opening (VO) and preputial separation (PPS).

The current evaluation of the post-2003 data supports the neuroendocrine MOA/AOP and key events originally identified in the 2003 IRED. In addition, new research has become available that extends our understanding of the neuroendocrine events that occur following atrazine exposure and that are germane to our understanding of the processes responsible for the adverse outcomes identified in different rodent models. Thus, this risk assessment will briefly discuss atrazine's established neuroendocrine MOA and then, how this MOA informs our understanding of the reproductive and developmental effects observed after atrazine exposure.

4.5.1.2 LH Changes as a Sentinel Effects for Adverse Health Outcomes

Perturbation of the neuroendocrine system – in particular the HPG axis – manifested as the attenuation of both the GnRH pulsatile secretion and the LH surge is the hallmark of atrazine toxicity. The Agency considers the atrazine-induced disruption of the LH surge, in rats, as the key event of the cascade of changes leading to the adverse reproductive outcomes following atrazine exposure. Relevant to this MOA, a number of studies have characterized the cellular and neuroendocrine changes responsible for how atrazine interferes with the regulation of LH secretion. The preponderance of evidence provides support for the hypothesis that atrazine modifies the hypothalamic (GnRH) control of pituitary function (Kalra and Kalra, 1983; Fox and Smith, 1985; Bergendahl *et al.,* 1996; Veldhuis *et al.,* 2008; Cooper *et al.*, 2007, 2010; Foradori *et al.*, 2009) which in turn has an impact on the LH surge. It is important to note that the modulation of GnRH/LH during the peripubertal period is not limited to rodents, but is seen across several species including primates (Terasawa *et al.,* 1984).

Testing the hypothesis that atrazine-induced changes in the regulation of LH ultimately alter gonadal function in rodents, several studies reported adverse effects on reproductive development and adult function including delayed puberty in both sexes (Stoker *et al.*, 2000; Laws *et al.*, 2000), disruption of regular ovarian cycles in the adult female (Cooper *et al*., 1996, 2000), and reduced testicular hormone secretion in the male (Stoker *et al*., 2000; Trentacoste *et al*., 2001; Rosenberg *et al*., 2007) after atrazine exposure. Atrazine has also been demonstrated to cause pregnancy loss – manifested as litter resorptions – in F344 rats when administered during the LH-dependent period of pregnancy, but not when administered afterwards (Narotsky et al., 2001). Pregnancy maintenance is dependent upon progesterone from the corpora lutea (CL). After the first week of gestation, the CL becomes dependent on LH during GD 7 through

10. The findings of Narotsky et al. (2001) support the hypothesis of an LH-mediated mechanism of pregnancy loss. It should be noted that litter resorptions occurred at doses that were 5-fold higher than the dose used as the POD for the acute dietary risk assessment and approximately 25-fold higher than the POD used for all other assessments. Of these potential adverse outcomes, the two that appear to be the most sensitive (*i.e.* occurred at the lowest dose levels) and/or occurred after the shortest duration of exposure are the disruption of the ovarian cycles and the delays in puberty onset (Figure 4.5.1.2). Although other effects ranging from immune suppression to mitochondrial and insulin dysfunction have been reported in the peer reviewed literature, these effects occur at doses well above the no observed adverse effect levels (NOAELs)/lowest observed adverse effect levels (LOAELs) for LH surge attenuation.

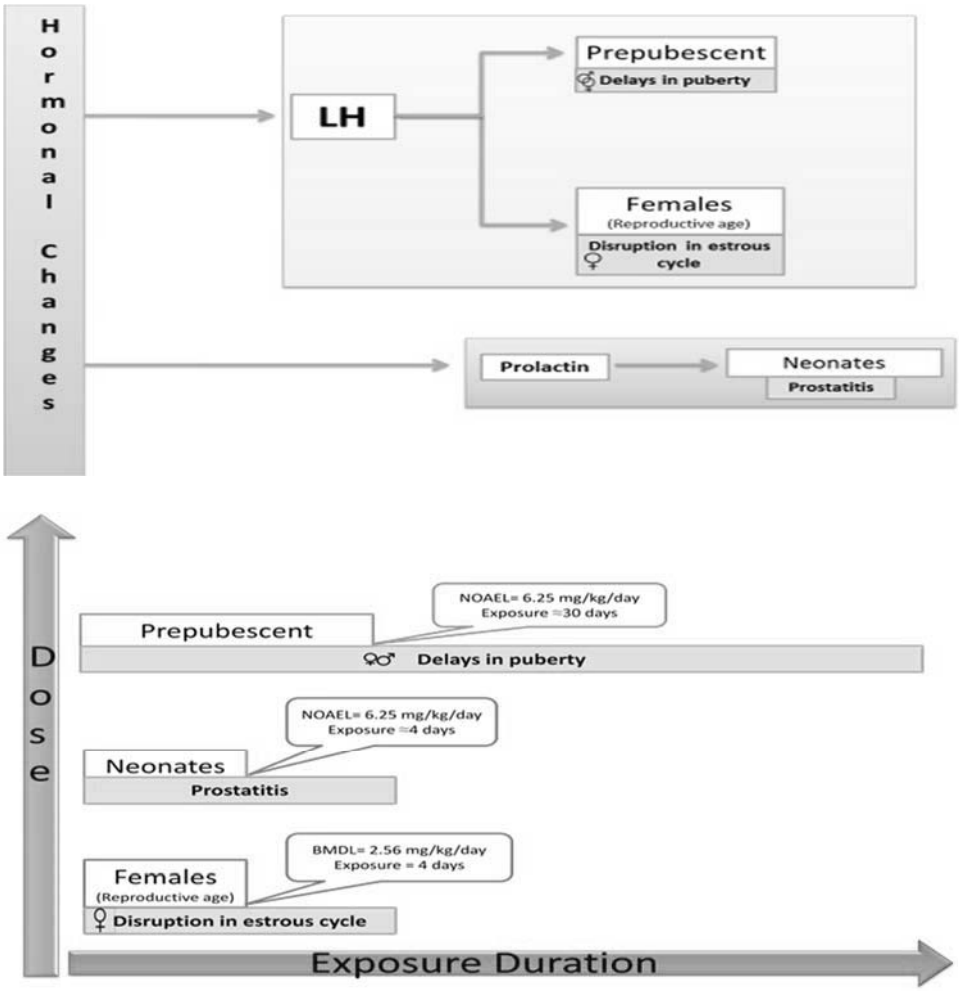


Figure 4.5.1.2. LH Suppression and Adverse Outcomes Observed in Rats

Atrazine-induced changes in the hormonal milieu lead to a cascade of effects on reproductive function in male and female rats. The decrease in LH is a precursor event to reproductive effects both on a quantitative (i.e., occurs at lower doses) and temporal basis (occurs after 4 days of exposure). An atrazine related suppression of suckling-induced prolactin release in the lactating dams, is another hormonal change leading to an adverse effect (prostatitis) in the rat animal model.

LH Surge Attenuation and Estrous Cyclicity

The most sensitive apical endpoint (effect) associated with LH surge attenuation is disruption of the estrous cycle. Potential effects of atrazine on LH surge attenuation and estrous cyclicity have been evaluated over a wide dose range (1.56-300 mg/kg/day) by several researchers (Cooper *et al.,* 1996, 2000, 2007, 2010; Minnema *et al.,* 2001, 2002; McMullin *et al.*, 2004; Morseth *et al.,* 1996; Foradori *et al.,* 2009; Laws *et al.,* 2000; Shibayama *et al.,* 2009; and Coder *et al.,* 2010). Of these studies, the research conducted in 1996 by Morseth and coworkers and in 2010 by Cooper *et al.,* identified the lowest dose levels capable of inducing a biologically and statistically significant attenuation of the LH surge. The Cooper *et al.,* (2010) dataset provided the most robust LH data in terms of dose selection (number of dose levels - particularly low dose range - spacing between dose levels) and variability of the data. The study design addressed the low-dose region of the dose-response curve and exhibited less data variability (i.e., smaller standard deviations). In the Cooper *et al.,* (2010) study, rats were exposed to atrazine for 4-days at doses ranging from 1.56 to 75 mg/kg/day to determine the NOAEL for LH surge attenuation. It is noteworthy that virtually identical NOAELs/LOAELs were identified by Morseth *et al.*, (1.8/3.65 mg/kg/day) and Cooper *et al.* (1.56/3.12 mg/kg/day) despite having strikingly different durations of exposure (Morseth study – 6 months; Cooper study – 4 days). Interestingly, 3.65 mg/kg/day is the lowest dose level identified to date eliciting a disruption in estrous cyclicity after a 6-month exposure. Therefore, the Agency has concluded that basing the POD for the atrazine risk assessment on LH surge attenuation would be protective of effects on estrous cyclicity.

In an attempt to correlate atrazine-induced changes in ovarian function to fertility impairments, Shibayama and colleagues (Shibayama *et al.,* 2009) conducted a study exposing rats to atrazine for 2 or 4 weeks at doses ranging from 3-300 mg/kg/day. Irregular estrous cycles (typically longer cycles) due primarily to a lengthened diestrus were seen only after exposure to 300 mg/kg/day. This effect was accompanied by decreased numbers of corpora lutea, follicular atresia, uterine atrophy, as well as decreased ovarian and uterine weights. Noticeably, the duration of atrazine exposure (2 *vs.* 4 weeks) had no effect on the nature, severity, or dose level causing the estrous cycle disruption or the histopathology changes. Even more notable is the observation that atrazine exposures at levels between 3 and 100 mg/kg/day for a period of time encompassing 2 weeks prior to mating up to gestation day (GD) 7 (a total exposure duration of ≥ 3 weeks) did not result in any signs of impaired fertility and none of the signs typically associated with impaired fertility (*e.g.,* number of implantation, corpora lutea, pre- or post-implantation loss) were affected. Given that estrous cyclicity can be disrupted at dose levels 30-100x lower, these findings indicate that disruption of the estrous cycle does not necessarily result in fertility impairments.

The HPG Axis across Lifestages

LH and the HPG Axis during Prenatal and Postnatal Periods

In addition to the critical role that HPG axis has in reproduction, there is evidence that it is also functional during fetal and neonatal life (de Zegher et al.1992). The HPG axis is active in the fetus during mid-gestation, but is diminished towards term due to negative feedback from placental hormones (Kuiri-Hanninen et al. 2014). At birth, however, the axis is reactivated leading to increased gonadotrophin levels (LH and FSH) in both males and females. This reactivation period has been termed mini-puberty (Kuiri-Hanninen et al. 2014; Abreu and Kaiser 2016; Copeland and Chernausek, 2016). Gonadotropin concentrations gradually decrease towards age 6 months, with the exception of FSH concentration in females, which remains elevated until age 3 - 4 years. In males, testosterone concentration increases to a peak at age 1 - 3 months, then declines thereafter. In females, estradiol levels are elevated during mini-puberty. HPG axis activity during the pre- and postnatal period has been implicated in male genitalia development. In females, HPG activation during early life leads to increased concentrations of gonadotropins resulting in ovarian follicle maturation and an increase in estradiol. It has been postulated that this minipuberty serves to "prime" the system for its pituitary LH and follicle stimulating hormone (FSH) response to GnRH later in life (Abreu & Kaiser, 2016).

Although LH is typically associated with the onset of puberty, in male infants, pulsatile LH secretion has been demonstrated as early as the first day of life (De Zegher et al. 1992; Bergendahl et al. 1996). This pulsatile LH secretion is supported by the finding of pulsatile GnRH release demonstrated in human fetal hypothalamic explants *in vitro* (Bergendahl et al. 1996). The pulse frequency of immunoreactive LH release in male infants is approximately one pulse every 60-90 minutes, a frequency similar to that in adult men. At 6-12 weeks of age, male infants exhibit increased pulsatile LH secretion with pulse amplitudes similar to those observed in healthy adults. This increased pulsatile LH secretion is accompanied by increased production of testosterone indicating the biological responsiveness of neonatal Leydig cells of the testes to LH release (Bergendahl et al. 1996). Besides increases in LH and testosterone, there is also an increase in secretion of inhibin B, a marker of Sertoli cell function (Andersson et al. 1997). In infant boys, serum levels of inhibin B peak at 3 months of age and exceed levels in adult men (Andersson et al. 1997). Stimulation of inhibin B secretion by LH has been demonstrated in primary prepubertal mixed testicular cell cultures (Berensztein et al. 2000), a finding in line with the observation of a positive correlation between increased LH and inhibin B levels at the onset of puberty (Andersson et al. 1997).

Taken together, evidence indicates that the HPG axis is functional during infancy, a period that is considered to be an important developmental event related to subsequent reproductive function in males and females (Copeland et al. 2016). Disruption of the HPG axis activation during mini-puberty may, therefore have consequences later in life.

LH Attenuation and Delays in Puberty Onset

In addition to the disruption in ovarian cyclicity, atrazine exposure has also been implicated in delays in sexual maturation in both males and females following both perinatal and peripubertal exposure. Pubertal development is directly related to the progressive increases in the neurosecretory activity of GnRH neurons. As such, researchers have found that disruption of GnRH release and the ensuing dampening of the LH surge can lead to delays in VO and PPS.

Activation of the HPG axis, resulting in the pulsatile secretion of GnRH that triggers a precisely regulated hormonal cascade of gonadotropins [LH and follicle stimulating hormone (FSH)] and ovarian steroids, is critical to puberty onset. In female rats, sheep, monkeys, and humans (Grumbach, 2002), detailed analyses of peripubertal LH secretory patterns have been conducted to provide surrogate measures of GnRH release throughout pubertal maturation. These studies have revealed that the initial stages of pubertal maturation are mediated by an acceleration of GnRH pulse generator activity (GnRH pulse frequency), an increase in the amplitude of GnRH pulses, or both of these alterations in GnRH neurosecretion. The work of Sisk *et al.*, (2001) in the rat is consistent with the hypothesis that maturation of the female rodent's reproductive axis is dependent upon a pubertal increase in GnRH pulse generator activity and a progressive increase in the ability of the hypothalamus to generate surge-like releases of GnRH.

Female sexual maturation is the culmination of a complex cascade of cellular events at the HPG levels that ultimately lead to the attainment of reproductive capacity. Disruption of GnRH and LH release can lead to delays in pubertal development. A number of studies have been conducted to evaluate the impact of atrazine and/or its metabolites on pubertal development and estrous cyclicity in female rats (Laws *et al*., 2000, 2003; Ashby *et al*., 2002; Davis *et al*., 2011; Rayner *et al*., 2004). Collectively, these studies have shown that atrazine delays the onset of puberty, as measured by a delay in the age of VO and first estrus (Safranski *et al*., 1993) at doses ranging from 30-100 mg/kg/day depending on the lifestage of exposure.

Gestational exposure to high doses of atrazine (100 mg/kg/day) during late gestation (GD 14-21) have been shown to delay sexual maturation of female offspring, however, exposures to lower doses (≤ 20 mg/kg/day) do not affect the age of pubertal onset. A study by Davis *et al*., (2011) evaluated the effects of prenatal exposure to atrazine on pubertal and postnatal reproductive indices in the female (Sprague Dawley) rat. Exposures from gestational day (GD) 14-21 at doses ranging from 1-20 mg/kg/day did not elicit a delay in VO or the timing of the first estrus. However, at 100 mg/kg/day atrazine exposure led to a significant decrease in pup weight (seen at birth, but resolved by post-natal day (PND) 21) and most importantly a delay in VO. These results are consistent with the observations by Rayner and coworkers (2004) that atrazine exposure at 100 mg/kg/day during GD15-19 led to a delay in VO without affecting estrous cyclicity once sexual maturation was reached. As was the case after *in utero* exposure (*i.e.* gestational), peripubertal exposure to atrazine and/or DACT for 19-23 days delayed pubertal development in female rats at doses ≥ 34 mg/kg/day (Laws *et al.,* 2000, Ashby *et al.*, 2002, Laws *et al.*, 2003). While delays in female puberty onset – as determined by the time of VO – occur at doses ≥ 10 times higher than the doses resulting in disruption of the LH surge, it is important to note that the duration of exposure sufficient to cause delays in VO ranges between 5 (prenatal exposure) and 23 days (peripubertal exposure). **Thus, using the Point of Departure (POD) for the LH surge attenuation as the basis for the risk assessment is protective of this effect.**

Over the last decades, a number of studies demonstrated that atrazine also delays male puberty following both peripubertal and perinatal exposure (Stoker *et al.*, 2000; Friedmann, 2002; Trentacoste *et al.,* 2001; Rayner *et al.*, 2006 and Rosenberg *et al.,* 2008; Pogrimic *et al.*, 2009). These studies support the hypothesis that impaired reproductive development is the result of an apparent delay in the maturation of the GnRH pulse generating mechanism and lower LH

concentrations leading to insufficient stimulation of the gonads during the period that puberty would normally occur. The low testosterone concentrations result in delayed maturation of the androgen dependent sex accessory tissues. A reduction in testosterone levels following atrazine exposure has been reported in a number of studies in mammals, as well as other species, revealing a consistency in the effects of atrazine on androgens. It is well known that the development of the size of the penis and cornification of the epithelium of the prepuce and preputial separation in immature rats are regulated by androgens (Marshall, 1966). A decrease in testosterone secretion during the juvenile period can delay PPS (Lyons *et al.*, 1942) and reduce the size of the androgen-dependent tissues, such as the ventral prostate and seminal vesicles.

In the male rat, atrazine exposure resulted in delays in the onset of puberty, as determined by assessment of PPS. In a study with peripubertal males that were exposed to atrazine at doses ranging from 6.25 to 200 mg/kg/day (Stoker *et al.,* 2000) PPS was delayed (after a 20-day exposure)at doses ≥12.5 mg/kg/day while exposure a dose of 6.25 mg/kg/day was found to have no effect on the day of PPS. Subsequent to this study, the authors conducted another study evaluating the effects of chlorinated atrazine metabolites on puberty (Stoker *et al.,* 2002). In this latter study, exposure to DACT, atrazine's major metabolite, at a dose equivalent to the atrazine equimolar dose (AED) of 6.25 mg/kg/day identified a clear NOAEL for PPS. Given the rapid metabolism of atrazine into its chlorinated metabolites, it is not unexpected that both atrazine and DACT have identical NOAELs for delays in PPS. In addition to delays in PPS, decreases in ventral prostate and seminal vesicle weights as well as decreases in serum and intratesticular testosterone levels have also been reported following atrazine exposure. This has corresponded to the work of others showing that serum testosterone is decreased in SD rats when dosed during a similar period of time (PND 22 to 47) (Trentacoste *et al.*, 2001; Friedmann, 2002). It should be noted, however, that the effects occur at doses ≥ 6-fold higher than the NOAEL for LH surge attenuation currently used for risk assessment purposes.

Prostatitis

Though not directly related to alterations in the LH surge, prostatitis is another reproductive tract effect related to atrazine exposure. In rodents, non-bacterial prostate inflammation is typically noted in older males (e.g. greater than one year of age) and can be induced with elevated prolactin concentrations (hyperprolactinemia) (Tangbanluekal and Robinette. 1994). In 1999, Stoker *et al.* reported an increase in prostatitis in the male offspring of mothers exposed orally to atrazine from PND 1 to 4. This effect is the result of the atrazine related suppression of suckling-induced prolactin release in the lactating dams. An increase in the incidence of prostatitis was observed in the 120-day old male offspring of dams treated with atrazine (≥ 12.5 mg/kg/day) from postnatal day 1-4. An increase in the incidence of prostatitis was also reported by Rayner *et al.,* (2007) in which dams were exposed to 100 mg/kg/day atrazine during GD 15-19. The dose level eliciting the increase in the incidence in prostatitis in the offspring is ≥6-fold higher than the NOAEL for LH surge attenuation used as the basis for the Agency's risk assessment.

In order to understand the significance of this observation, it is necessary to understand the development of the tuberoinfundibular dopaminergic (TIDA) neurons located within the hypothalamus and their role in regulating prolactin secretion in the adult. Prolactin plays a

crucial role in the neonatal brain for normal TIDA neuron development. In the adult offspring, the impaired TIDA regulation is reflected by elevated prolactin levels (hyperprolactinemia) (Shyr *et al*., 1986, Stoker *et al*., 1999; 2000). It is this elevated level of circulating prolactin in the adult males that has been linked to an increased incidence of prostatitis. Thus, an increased incidence of prostatitis in the offspring of dams exposed to atrazine during the critical time for TIDA neurons activation (first postnatal week) may be attributed to elevated blood prolactin concentrations due to impaired TIDA neuronal maturation (Stoker *et al*., 1999). In summary, the data indicate that atrazine induces prostatitis at doses ≥ 12.5 mg/kg/day and that – in rats – early postnatal exposure is a critical window of susceptibility to this effect.

Other effects

In addition to the neuroendocrine effects associated with atrazine exposure, other adverse outcomes have been reported in the literature including carcinogenesis, neurotoxicity, immunotoxicity, and developmental toxicity. *In utero* exposure to atrazine at doses 70-100 mg/kg leads to delays in ossification in both rats and rabbits. Regarding carcinogenesis, the Agency has concluded and the SAP concurred that mammary tumorigenesis seen in rats is not relevant to humans. This conclusion is consistent with the conclusion reached by the World Health Organization's (WHO's) Joint Meeting of Pesticide Residues (JMPR) in 2007. Consequently, atrazine has been classified as "Not Likely to be Carcinogenic to Humans." For other potential adverse outcomes reported in the peer reviewed literature, the effects occurred at dose levels approximately one order of magnitude or higher than the NOAEL/LOAEL for LH surge attenuation.

Summary

The neuroendocrine MOA of atrazine leads to a perturbation of the hormonal milieu in laboratory animals. This perturbation – in turn – leads to a series of adverse outcomes at different lifestages as observed in rats. Quantitatively, the most sensitive POD is the lower 95% confidence limit on the benchmark dose associated with 1SD change ($BMDL_{1SD}$) of 2.42 mg/kg/day (Section 4.6.2.3.1) corresponding to a change in the mean LH surge attenuation equal to one standard deviation from the control mean observed after female rats of reproductive age are exposed to atrazine for 4 days. The Agency is using the BMDL value for LH surge attenuation after a 4-day exposure as a precursor event to protect for other adverse outcomes including estrous cyclicity disruption, and delays in sexual maturation occurring at higher doses in laboratory animals.

In the case of atrazine, it has been noted that in addition to dose, duration of exposure is an important parameter that must be considered in evaluating the relationship between dose and attenuation of the LH surge. Currently available data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats. This is also the length of the estrous cycle in rats and the exposure duration needed for atrazine to reach time to effect. Even shorter atrazine exposures can result in LH changes, albeit at high doses (100 mg/kg/day). Other effects of concern, such as delays in puberty onset and decrease in suckling-induced prolactin release and eventually prostatitis in young rats, identified in the animal toxicity database, occur at higher doses but have a different temporal profile compared to the LH surge attenuation. For instance,

atrazine-induced delays in puberty onset have been reported in both peripubertal male and female rats after exposures to atrazine (≥12.5 mg/kg/day) for approximately 20-30 days. Similarly, prostatitis can be seen in the male offspring of rats exposed to 12.5 mg/kg/day of atrazine for 3 days shortly after birth. Although drawing a direct temporal correlation between the effects seen in the rat animal model and potential human health outcomes is not feasible at this time, it is prudent to consider the possibility of a critical temporal window of ≈ 4 days that may be sufficient to induce alterations in the hormonal environment leading to adverse effects. The temporal and dose profile of toxicity/effects after atrazine exposure is shown in Table 4.5.1.2. Concentrating on the most sensitive effects (*i.e.,* occurring at the lowest doses) observed at different lifestages, a pattern of endpoint sensitivity emerges. **Taking into consideration the totality of the data, LH surge attenuation continues to be the most sensitive effect in the atrazine database.**

Table 4.5.1.2. Summary of Primary Toxicological Oral Studies of Atrazine Exposure after Gestational, Perinatal, and Peripubertal Exposure.			
Author (YR)	**Exposure**	**NOAEL/LOAEL (mg/kg/day)**	**Effect**
Cooper (2007)	4days adult cycling ♀	NA/25	↓ GnRH release
Cooper (2000)	1-day adult cycling ♀	NA/300 mg/kg	↓ LH surge, estrous cyclicity disruption
	3-day adult cycling ♀	NA/50	↓ LH surge
Cooper 2000 & 2010	4- day adult cycling ♀	1.56/3.12*	↓ LH surge
Morseth (1996)	26 week	1.8/3.65	↓ LH surge, estrous cyclicity disruption
Cooper (1996)	21 days	NA/75	estrous cyclicity disruption
Stoker *et al.*, 2000	PND 23 to 53	6.25/12.5	Delayed PPS
Trentacoste *et al.*, 2001	PND 22 to 47	50 lowest dose/100	Delayed PPS
Stoker *et al.*, 2001	PND 23 to 53	25/50	Decreased VP and SV
Trentacoste *et al.*, 2001	PND 22 to 47	50 lowest dose/100	Decreased VP and SV
Stoker *et al.*, 2001	PND 23 to 53	150/200	Decreased intra-testicular T on PND 45
Trentacoste *et al.*, 2001	PND 22 to 47	ND/50	Decreased T on PND 47
Friedmann, 2002	PND 22 to 47	ND/50	Decreased test. and serum T on PND 47
Pogrimic *et al.*, 2009	PND 23 to 50	50/200	Decreased T/DHT on PND 50
Laws *et al.*, 2009 (2010)	15 minutes - ♂ rats	5./50 mg/kg	↑ACTH. CORT, progesterone
Fraites *et al.*, 2009	15 minutes – cycling ♀	N.A./75 mg/kg atrazine 60.2 mg/kg DIA	↑ACTH. CORT, progesterone
Pruett *et al.*, 2009	1 hour – adult ♀ mice	N.A./200 mg/kg atrazine	N.A./200 mg/kg atrazine
Pruett *et al.*, 2003	6 hours– adult ♀ mice	N.A./100 mg/kg atrazine	N.A./100 mg/kg atrazine
Fraites *et al.*, 2009	4 days – cycling ♀	N.A./12.5 mg/kg/day atrazine or 10 mg/kg/day DIA	↑ACTH. CORT, progesterone
McMullin (2004)	5 days – OVXD ♀	NA/30	↓ LH surge
Foradori (2009)	4 days – adult ♀	NA/50	↓ LH surge
		50/100	↓ GnRH immunoreactive cells
Zorrilla (2010)	*Ex vivo*	1/10 µM	↓ GnRH release
Narotsky et al., 2001	GD 6-10	25/50	Pregnancy loss (full-litter resorption)
Laws (2000)	PND 22-41	25/50	Delayed VO
	PND 42-149	50/100	Disrupted cyclicity
Shibayama (2009)	2 or 4 weeks – start treating 5 wk old ♀	30/300	Disrupted cyclicity, ↓ ovarian and uterine weights, ovarian, uterine histopath

Table 4.5.1.2. Summary of Primary Toxicological Oral Studies of Atrazine Exposure after Gestational, Perinatal, and Peripubertal Exposure.			
	2 weeks pre-mating to GD 7	300/NA	No effect in fertility
Rosenberg (2008)	GD14-parturition	10/50	Delayed PPS
Rayner 2007	GD 15-19	NA/100	Delayed PPS, prostatitis
Stoker 1999	PND1-4	6.25/12.5	Prostatitis
	PND 6-9	NA/25	Non-stat sig prostatitis
Coder 2010	GD 0 to 5 days post-VO	FO: 25/50 F1: 25/50	F0: Non-stat sig. ↓ LH, ↓ food consumption F1 pre-weaning: ↓ pup weight, pup survival F1 post-weaning: ↓ body weight, body weight gain, food consumption, 1.4-day delay in VO, ↓ LH
	GD 0 – PND 133	FO: 25/50 F1: 25/50	F0: Non-stat sig. ↓ LH, ↓ food consumption F1 post-weaning: ↓ body weight, body weight gain, food consumption, 1.4-day delay in VO, ↓ LH

*After BMD analysis the BMDL/BMD @ 1 standard deviation = 2.42/4.92 mg/kg/day

4.5.2 Hydroxypropazine

For this assessment, it is assumed that hydroxypropazine has a toxicity profile identical to hydroxyatrazine. Therefore, the risk assessment for hydroxypropazine relies on toxicity data available on hydroxyatrazine (see K. Rickard *et al.,* D418316, 07/10/2018). Unlike the chlorotriazines and their chlorinated metabolites, hydroxypropazine is the major metabolite in plants, but a minor metabolite in animals. Subchronic, chronic/carcinogenicity, and developmental toxicity studies are available for hydroxyatrazine. The data indicate that the kidney – **not the neuroendocrine system** – is the primary target organ for hydroxyatrazine associated toxicity. Hydroxyatrazine appears to crystallize in the serum leading to the formation in the blood stream of hydroxyatrazine crystals. These crystals cause direct physical damage to the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorinated metabolites of atrazine.

There is no evidence for increased susceptibility of rat fetuses following *in utero* exposure to hydroxyatrazine in the prenatal developmental toxicity study in rats. In this study, there was a statistically significant decrease in fetal weights and an increase in incompletely ossified interparietals and hyoid bones seen in the presence of maternal toxicity. The developmental alterations seen in this study were seen only at the high dose (125 mg/kg/day) and a clear NOAEL (25 mg/kg/day) was identified. These conclusions are also pertinent to propazine.

As part of the atrazine evaluation process, the Agency evaluated its metabolism to identify the residues of concern for the dietary risk assessment. HED's Metabolism Assessment Review Committee (MARC) concluded that the residues of concern for dietary risk assessment are the parent compound (atrazine) and its chloro-metabolites, and hydroxyatrazine and its hydroxylated metabolites, assessed separately according to their endpoints (C. Eiden, D270177, 11/15/2000). These conclusions are also pertinent to propazine.

In a chronic toxicity/carcinogenicity study, (MRID 43532001), technical hydroxyatrazine (97.1% pure) was administered in the diet to groups of 70 or 80 male and 70 or 80 female Crl:CD (SD) BR strain rats at dose levels of 0 (control), 10, 25, 200 or 400 ppm (equivalent to 0, 0.388, 0.962, 7.75, or 17.4 mg/kg/day in males; and to 0, 0.475, 1.17, 9.53, or 22.3 mg/kg/day in females). There were no statistically significant increases in any tumor type at any dose level in either sex of rats. In particular, there was no increase in the incidence of mammary gland tumors in either males or females compared to control animals.

4.5.3 Epidemiology

The Agency recently conducted an updated epidemiology systematic literature review to investigate evidence on the human health effects associated with exposure to atrazine, simazine, and/or propazine. Ninety-three publications from 1990 – 2017 were identified for inclusion in the epidemiology literature review. Of these 93 publications, 90% reported an estimate of effect for atrazine and 14% reported an estimate of effect for simazine (not mutually exclusive). No epidemiology studies were found with propazine. However, since atrazine, simazine and propazine share a common mechanism of toxicity, refer to the risk assessments for atrazine (K. Rickard *et al.,* D418316, 07/10/2018) and simazine (K. Rickard *et al.,* D402163, D428603, 07/10/2018) for additional information.

4.5.4 Durations of Exposure, Critical Windows of Exposure, & Temporality of Effects

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an MOA/AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. The following text provides an evaluation of relevant information on exposure, pharmacokinetics, and pharmacodynamics which provides the basis for determining which exposure durations are appropriate for assessing human health risk to atrazine.

Exposure to any pesticide does not occur at the same level every day; instead, exposure varies significantly across time with seasonal applications and related events such as run-off. As such, chlorotriazine exposure can occur from acute events or from repeated exposure events. With respect to acute exposures, the Agency has identified effects in developmental studies (i.e., delayed ossification) which may, albeit at maternally toxic doses, result from an acute exposure. However, the delays in ossification are likely not the result of a single day exposure. The delayed ossification observed in the developmental toxicity study in rats provided a highly conservative endpoint.

With respect to repeated exposures, plasma concentration profiles of total radiolabeled triazine equivalents corresponding to different administered doses of radiolabeled atrazine achieve steady state after approximately 4 days of exposure in the rat such that continued dosing does not alter the internal dose (Thede, 1987). With respect to the pharmacodynamic response in the rat, data from multiple laboratories ranging in duration from four days up to six months of exposure show that attenuation of LH is fairly constant at a given dose such that NOAELs/LOAELs do not change with durations from four days to 6 months. In studies longer than 6 months of exposure, the differences in estrous cycle deterioration between atrazine treated animals and controls no longer widens (*i.e.,* less apparent response) as the control animals begin the normal reproductive aging process.

Although the estrous cycle in rats is 4 days long, in humans, the menstrual cycle lasts – on average – 28 days. Thus, the question arises whether a brief exposure (*e.g.,* a few days) in humans could lead to an attenuation of the LH surge. One can infer information about possible windows of susceptibility from what is known about human physiology and from the pharmaceutical literature. Evidence of chemically-induced decreases in GnRH or LH secretion is sparse in humans and non-human primates relative to rodents. The available evidence in humans comes primarily from the pharmaceutical arena. Nal-Glu, Cetrorelix®, and Ganirelix are three GnRH antagonists used to block the LH surge and ovulation in women prior to *in vitro* fertilization (IVF) procedures. In a series of experiments, regularly ovulating women received two 5 mg injections of Nal-Glu on days 8 and 11 of the follicular phase of the natural cycle (Frydman *et al.* 1992[7]). This treatment resulted in a block of the spontaneous LH surge. This work was further corroborated by Olivennes *et al.* (1994) who demonstrated that a single 3 mg

[7] Frydman, R., Cornel, C., de Ziegler D. *et al* . (1992) Spontaneous luteinizing hormone surges can be reliably prevented by the timely administration of donadotrophin releasing hormone antagonist (Nal0Glu) during the late follicular phase. *Human Reproduction* **7**(7):930-933

administration of the GnRH antagonist Cetrorelix® on day 8 of the follicular phase was sufficient to block the LH surge. Ganirelix exposure during the late follicular phase of the menstrual cycle has also been demonstrated to inhibit the LH surge and ovulation by competing with the endogenous GnRH for receptor binding (Fauser *et al.,* 2002[8]). One must consider these studies with caution with respect to atrazine human health risk since the potency and pharmacokinetics of these pharmaceuticals relative to atrazine is unknown. Moreover, data in rats have shown that one dose of atrazine (up to 200 mg/kg administered in the morning of the expected LH surge) is not sufficient to block the LH surge (Cooper *et al.,* 2000[9]). As such, given the current database of atrazine studies, the Agency does not believe that one or two exposures of atrazine is sufficient to block the LH surge in humans. However, these studies do help qualitatively inform a potential window of vulnerability to chemicals disrupting the HPG axis in women. Specifically, all of these pharmaceutical agents are administered during the late follicular phase of the menstrual cycle (days 8-12 of the follicular phase)[10]. Thus, one can infer that the follicular phase (lasting ≈12 days) and possibly the late follicular phase (days 8-12 of the follicular phase) of the menstrual cycle may be a possible window of susceptibility in humans.

For an exposure assessment of drinking water, averaging time is a key factor in determining the magnitude of the exposure. Specifically, with longer averaging times, low values (or even 0 values) reduce the peaks and smooth the "spikey" pattern of the exposure. Conversely, with shorter averaging times, peaks of exposure remain high—and thus provide a more conservative, *i.e*., health protective approach. In the 2002 human health risk assessment for atrazine, the POD for the intermediate and chronic exposure risk assessments was based on the attenuation of the LH surge reported by Morseth *et al.* (1996b) at doses ≥ 3.65 mg/kg/day (NOAEL/LOAEL = 1.8/3.65 mg/kg/day). In the 2002 assessment, the drinking water assessment was conducted using a 90-day duration of concern. The L Cooper *et al.* (2010) study suggests that a shorter averaging time is warranted.

For the 2010-2011 reviews by the SAP, the Agency proposed a range of durations from 4-28 days. The SAP commented in the December 2010 report that, "the imprecision in the Agency's proposed sampling frequency seems justified. This may be about as precise an estimate as can be obtained when starting with the experimental animal data and the exposure requirements for LH surge suppression as opposed to using outcomes that are more unequivocally adverse." Given the totality of information, although theoretically possible, a 4-day atrazine exposure resulting in LH suppression is likely a conservative assumption. The SAP concurred with OPP on this issue, "Without the relative rat vs. human effect kinetics, the conservative (science policy-based) approach would be to use the 4-day duration identified in the studies with rats." (FIFRA SAP, 2011). ***Based on the totality of evidence, for this human risk assessment, the durations of exposure are: acute/single day and 4-day repeated exposure.***

[8] Triggering of Final Oocyte Maturation with GnRH Agonist after Cotreatment with the GnRH Antagonist Ganirelix during Ovarian Hyperstimulation for *in Vitro* Fertilization. *J Clin Endocrinol Metab.* **87**(2):709-715

[9] Cooper, R.L., Stoker, T.E., Tyrey, L., Goldman, J.M., & McElroy, W.K. (2000). Atrazine disrupts the hypothalamic control of pituitary-ovarian function. Toxicol Sci., Feb; 53(2): 297-307

[10] In humans, the follicular phase lasts approximately 12 days, assuming a 28-day menstrual cycle

4.5.5 Dose-Response Assessment

4.5.5.1 Acute/Single Day Dietary Exposure

For the acute dietary endpoint for propazine (summarized in Table 4.6.2.2), a POD of 10 mg/kg/day for females 13-49 years of age was selected from a propazine developmental toxicity study (MRID 00150242). In this study, propazine was administered to Sprague-Dawley female rats (25/dose) by gastric intubation at dose levels of 0, 10, 100, or 500 mg/kg/day from days 6 through 15 of gestation. The NOAEL of 10 mg/kg/day was based on delayed ossification seen at 100 mg/kg/day (LOAEL).

The delayed ossification observed in the developmental toxicity study in rats provided a highly conservative endpoint. The delayed ossification occurred at the high dose and only in the presence of maternal toxicity, such that one cannot separate direct effects on the fetus from indirect effects from the dam's disrupted physiology due to the toxicity. Furthermore, ossification involves numerous processes that occur over time including, but not limited to, osteoclast differentiation, collagen matrix and calcium deposition. Consequently, the delays in ossification are likely to be the result of repeated rather than a single exposure. Combined, these factors lead to a conservative acute dietary assessment for females of reproductive age that is useful for screening purposes.

4.5.5.2 Acute/Single Day Uncertainty Factors

In the acute dietary assessments for propazine, the Agency is applying the typical 10-fold factors for inter- and intra-species extrapolation. Thus, the total uncertainty factors for acute dietary is 100X. The FQPA Safety Factor of 10X was reduced to 1X based on the lack of increased sensitivity for infants and children, as supported by the SAP, and discussed in Section 4.8. The SAP concluded that "there is sufficient information available to reach the conclusion that the issue of differential sensitivity has been adequately studied. This relatively extensive database, spanning all life stages from conception to adulthood indicates no unique susceptibility to atrazine in the developing organism." (SAP Report on July 2011 meeting, EPA-HQ-OPP-2011-0399-0080.pdf; pp. 52-54).

Table 4.6.2.2. Summary of Toxicological Doses and Endpoints for Propazine for Use in Acute Dietary Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL = 10 mg/kg/day	UF_A= 10X UF_H=10X FQPA SF= 1X	Acute RfD = 0.1 mg/kg/day	Developmental toxicity study in the rat with propazine MRID 00150242 LOAEL =100 mg/kg/day based on delayed ossification

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF =

uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose.

4.5.5.3 Four-Day Repeated Exposure (Oral, Dermal, Inhalation)

In the human health risk assessments that supported the 2005 propazine risk assessment (J. Morales, D323271, 12/13/2005) and the 2012 atrazine risk assessment (C. Eiden, D272009, D281917, D281936, 4/16/2002), the chronic RfD and intermediate-term oral, dermal, and inhalation exposures were based on the attenuation of the LH surge reported by Morseth *et al.* (1996b) (MRID 44152102) at atrazine doses ≥ 3.65 mg/kg/day (NOAEL/LOAEL = 1.8/3.65 mg/kg/day). The current atrazine risk assessment has been revised based on the Cooper et al. (2010) dataset which provided the most robust LH data in terms of dose selection (number of dose levels – particularly at the low dose range, spacing between dose levels, and variability of the data). The study design addressed the low-dose region of the dose-response curve and exhibited less data variability (i.e., smaller standard deviations). This study is also being used in the propazine risk assessment for 4-day repeated exposure (oral, dermal, and inhalation).

In light of the critical role that the HPG axis has in reproduction and evidence that it is also functional during fetal and neonatal life, the LH surge attenuation endpoint was applied to all populations. The attenuation of the LH surge provides a sentinel effect for numerous potential endocrine related downstream effects in both males and females across lifestages. This endpoint is protective of other such effects as it occurs at lower doses than downstream neuroendocrine effects and ≥10-fold lower than other endocrine hormone effects.

A detailed description of the Cooper *et al.* (2010) study, and its use in BMD modeling and PBPK modeling to assess the exposure from oral, dermal, and inhalation exposure is discussed below.

4.5.5.3.1 Critical Study: ORD NHEERL Study by Cooper *et al.*, (2010)

In the Cooper *et al.* (2010) study, regularly cycling female rats were exposed to atrazine starting on the day of vaginal estrous until the day after proestrous (4 consecutive days) at doses of 0, 1.56, 3.12, 6.25, 12.5, 25 or 75 mg/kg/day. The magnitude of the LH surge was dampened at doses ≥ 3.12 mg/kg/day. The Cooper *et al.* (2010) study uses the exact same study protocol as Cooper *et al.* (2007)[11]; the 2010 study was conducted to confirm the Cooper *et al.* 2007 study and identify a NOAEL for LH suppression. The summary report, raw data, statistical analysis, and BMD analysis of the 2010 study were provided to the SAP docket; the study was part of the September 2010 and July 2011 reviews by the FIFRA SAP. At both meetings, the Panel supported its use in deriving PODs for atrazine.

The Agency conducted a BMD analysis of the Cooper *et al.* (2010) study which was reviewed by the FIFRA SAP. EPA calculated both the BMD (central estimate) and the BMDL (the BMDL corresponds to the 95% lower bound on dose). As a matter of science policy, EPA uses the

[11] Cooper R.L., Laws S., Das P.C., Narotsky M.G., Goldman J.M., Tyrey E.L., Stoker T.E. (2007). Atrazine and reproductive function: mode and mechanism of action studies. Birth Defects Res B Dev Reprod Toxicol, Apr; 80(2): 98-112.

BMDL as the POD. In the case of continuous endpoints, like LH attenuation, the benchmark response (BMR) most often represents an X% change from background levels (or untreated controls). Typically, the BMR is selected on the basis of a combination of biological (MOA, quantitative link between key events, historical/concurrent controls) and statistical considerations (sample size, variability, etc.). However, in the absence of information concerning the level of response (or % change) associated with an adverse effect, the Agency's BMD guidance[12] suggests that the BMD and BMDL corresponding to a change in the mean response equal to one standard deviation from the control mean be used as the BMR. In the case of atrazine, the level of attenuation of the LH surge considered to be adverse is a function of several factors including, but not limited to, the life-stage and functional outcomes under consideration (*e.g.*, estrous cyclicity disruptions in rats). Moreover, the differences in reproductive cycles/aging between rodents and humans add an additional level of complexity to establishing a specific BMR value.

EPA's Benchmark Dose Software (BMDS) version 2.1.2 was used; among the continuous models evaluated, the exponential model provided the best fit. The BMD analysis yields: $BMDL_{1SD}$ = 2.42 mg/kg/day; BMD_{1SD} = 4.92 mg/kg/day (Figure 4.6.2.3). **This $BMDL_{1SD}$ = 2.42 mg/kg/day provides the animal POD used in extrapolating to humans.**

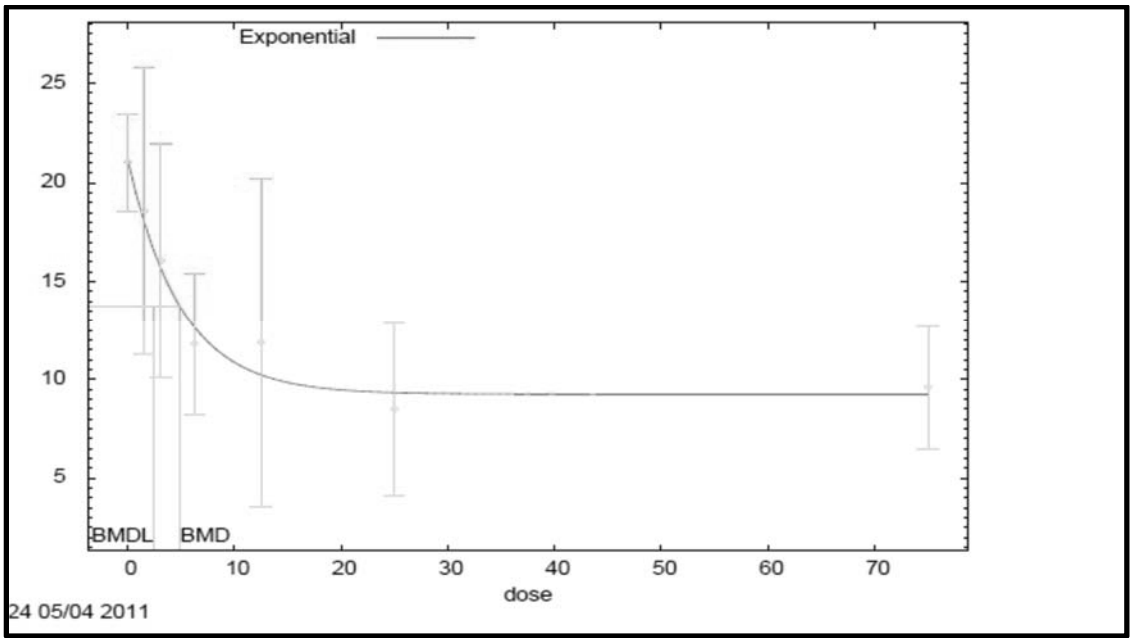


Figure 4.6.2.3. Plot of benchmark dose analysis from Cooper *et al* (2010) using the exponential model.

The current chlorotriazine risk assessment continues to rely on atrazine's established neuroendocrine MOA. Based on the robust data from reliable, well-designed and conducted studies, attenuation of the LH surge continues to be the most sensitive effect (i.e., occurs at the lowest dose) identified to date in the atrazine database. Perturbations of the LH signal – a disruption of the hormonal environment in the individual – serves as a sentinel effect used to

[12] U.S. Environmental Protection Agency. (2012). *"Benchmark Dose Technical Guidance Document" report, Risk Assessment Forum, Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/100/R-12/001*.

establish a POD for the risk assessment that would be health protective for the other effects noted in the database. These other effects occur at higher doses than the LH surge attenuation and include delays in puberty onset, disruption of estrous cycles, and reduced prolactin from milk early in life leading to prostatitis in young adult rats; they provide insight into the temporal relationship between atrazine exposure and adverse health outcomes.

4.6.2.3.2 Extrapolation from Laboratory Animal POD to Human Equivalent POD: Physiologically-Based Pharmacokinetic (PBPK) Model

The current PBPK model for the chlorotriazines (atrazine, simazine and propazine) was derived from modifications of a previous oral PBPK model developed specifically for atrazine and its chlorinated metabolites (DEA, DIA, DACT). The model was designed with data obtained from several studies: *in vitro* metabolism of atrazine in rat and human hepatocytes, time course of plasma concentrations in rodents and non-human primates, and time course of plasma and urine concentrations in human volunteers. The average plasma concentration of total chlorotriazines (TCT) was selected as the dose metric for cross-species extrapolation of the effect of the chlorotriazines on the LH surge.

The PBPK model allowed for risk assessment to be based on PODs derived from an internal dose metric. The model predictions from the rat PBPK model agreed well with measured plasma concentrations of the TCT after gavage dosing or dietary administration. The rat model was then scaled to humans, and the clearance of DEA, DIA and DACT from plasma into urine was calibrated against human data. The plasma concentrations of atrazine's chlorinated metabolites, predicted by the human PBPK model, agreed well with plasma and urinary concentrations measured in human volunteers following a single oral exposure. In addition, the model was revised to include life-stage calculations to estimate human internal dose metric at different ages from birth to adulthood. Based on the structural similarity of simazine and propazine to atrazine, and the shared common chlorinated metabolites, the atrazine PBPK model was extrapolated to these other two chlorotriazines by adopting parameter values for atrazine and propazine-specific parameters where applicable. The only differences between the three models are molecular weight for each chemical, and adjustments of the liver and gut metabolism rates for chloro metabolites of simazine and propazine. For simazine, the liver and gut metabolism rates for simazine to DEA were set to zero since DEA is not a metabolite of simazine. Similarly, the liver and gut metabolism rates from propazine to DIA were set to zero to reflect the lack of metabolism to this particular metabolite.

Another recent refinement to the atrazine PBPK model is the addition of dermal and inhalation routes. For the dermal route, the dermal absorption rate constant (6%/day) was obtained from an *in vivo* human dermal study on atrazine (see Section 4.4 – dermal absorption). Since the only model parameter that is specific to the dermal route is dermal absorption rate, the value for this parameter was obtained from an *in vivo* human study and provided confidence in dermal simulations. In the absence of a chemical-specific parameter on inhalation absorption, the model used an equilibrium equation to represent the mass balance transfer of atrazine between air and blood, with 100% of the inhaled dose absorbed into blood, which is the most conservative assumption. Both inhalation and dermal routes were also added to the simazine and propazine models. Since dermal absorption rates for simazine and propazine are not available in the literature, the absorption rate for atrazine was used for both simazine and propazine.

Details on the description and structure of the PBPK model, and its use in the derivation of human equivalent doses are presented below in section 4.6.2.4.

4.5.5.4 Introduction to the PBPK Model

As described in detail in the EPA's 2006 document entitled, "*Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment,"* PBPK modeling is a scientifically sound and robust approach to estimating the internal dose of a chemical at a target site, thus allowing a more accurate estimate of the toxicant dose causing an adverse toxic effect. PBPK modeling can also be used to evaluate and describe the uncertainty in risk assessments. PBPK models consist of a series of mathematical representations of biological tissues and physiological processes in the body that simulate the absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body. Examples of PBPK model applications in risk assessments include refinements in quantifying inter-species and intra-species extrapolation, route-to-route extrapolation, high-to-low dose extrapolation, estimation of response from varying exposure conditions, and interpretation of biomarker data. PBPK models can be used in conjunction with exposure assessment to improve the quantitative characterization of the dose-response relationship in the environmentally-relevant dose ranges, and consequently, the overall risk assessment.

A rat and a human version of the PBPK model for atrazine and its chloro metabolites, DIA, DEA, and DACT had been developed by Syngenta in collaboration with the Hamner Institute. This PBPK model has been used in this risk assessment to estimate the human equivalent doses from the rat 4-day neuroendocrine POD described above. Summary information, and for purposes of transparency, parameter values are provided in this document. Comparisons between model predictions and observed data in rats and humans can be found in Appendix A.3 and in Hinderliter (2015) and reports from PNNL (2015a, b). All model code, parameters, and associated reports can be found in the docket.

4.5.5.4.1 Description & Structure of the PBPK Model

The PBPK model for atrazine used here was based on an earlier model developed by McMullin *et al*. (2007a) in rats. The McMullin model has since undergone several revisions and refinements by the researchers at the Hamner Institutes and Syngenta (Campbell 2011; Campbell 2014; Hinderliter 2015; Campbell 2015) to include new metabolism rate constants scaled from *in vitro* experiments using rat and human hepatocytes. In addition, the McMullin model described oral uptake using an empirical function which cannot be extrapolated from rats to humans, and thus, a two-compartment sub-model was developed for simulating oral uptake and absorption of atrazine, as well as pre-systemic metabolism of atrazine to DEA and DIA. Atrazine, DEA, and DIA were 100% absorbed in this model. The revised model (which is referred to as "the 2015 PBPK model") expanded the original two-compartment (liver and rest of body) structure (McMullin *et al*., 2007a) to contain 10 tissue compartments, including mammary, fat, brain, hypothalamus, pituitary, testes/ovaries, adrenals, liver, and rapidly and poorly perfused tissues. All tissues were described as flow limited compartments. Metabolism of atrazine to DIA and DEA, as well as the subsequent metabolism of DIA and DEA to DACT, were described as saturable processes. The competitive inhibition of metabolism was retained from the McMullin

model (2007a) in which DIA and DEA inhibited atrazine metabolism, atrazine and DEA inhibited DIA metabolism, and atrazine and DIA inhibited DEA metabolism. A schematic of the atrazine PBPK model is presented in Figure 4.6.2.4.1 (extracted from Campbell *et al*., 2015).

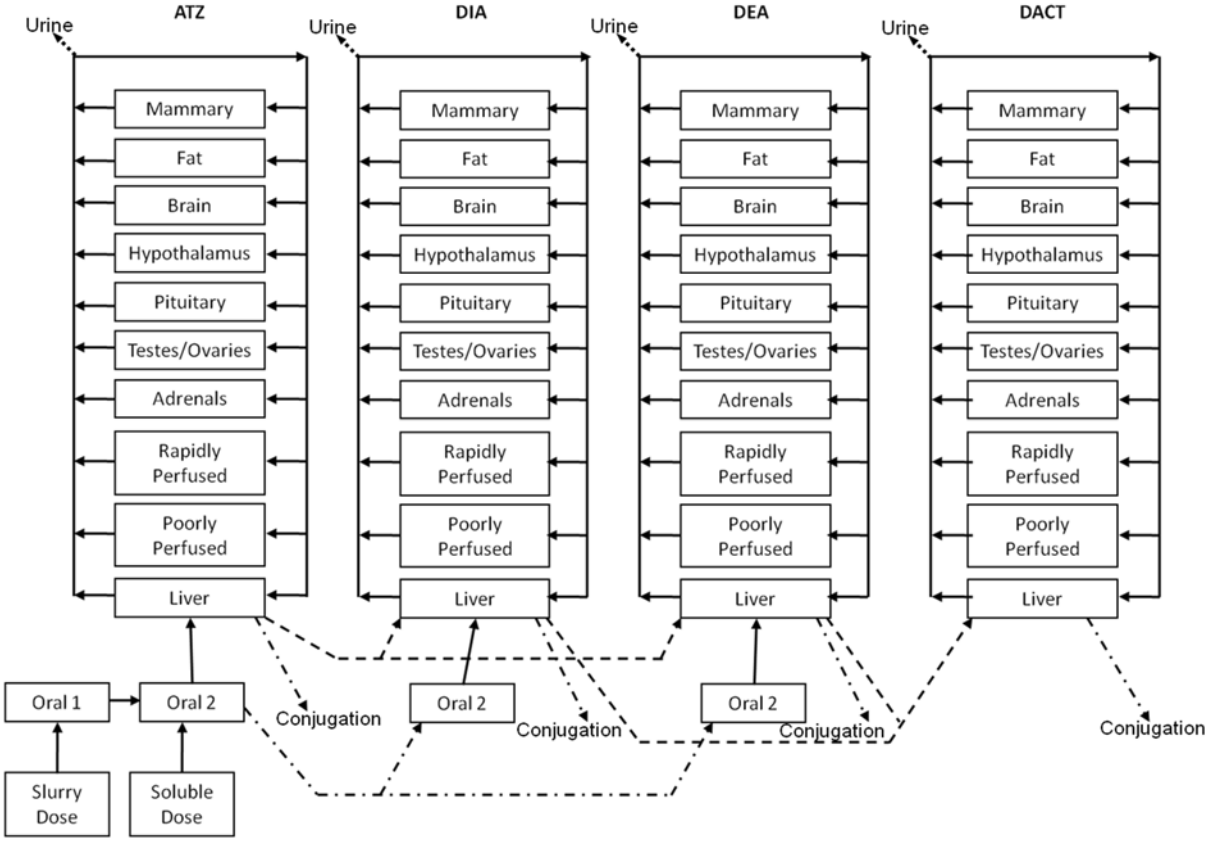


Figure 4.6.2.4.1. Schematic of the PBPK model for atrazine and triazine metabolites (dashed line represents metabolism in liver of atrazine to DIA and DEA and conversion of DIA and DEA to DACT)

In the 2015 PBPK model, most physiological parameters for rats and humans were obtained from Brown *et al*. (1997) and O'Flaherty *et al*. (1992). Human adrenal volume and blood flow, mammary volume, and testes/ovaries volume were obtained from the International Commission on Radiological Protection (ICRP) Pub 89 (2002). Tissue volumes and blood flows for monkeys were obtained from Davies and Morris (1993). For parameters that are unavailable for rats and monkeys, their values were taken from the human values adjusted for body weight. Values of physiological parameters are summarized in Table 4.6.2.4.1 (extracted from Campbell *et al*., 2016). Chemical-specific tissue to blood partition coefficients for liver and brain were measured (Tremblay *et al*., 2012), but no measured values were available for other tissues. It was found that the measured values for brain and liver were very similar (0.69 for liver and 0.73 for brain), and thus, a simplified approach to use the value of 0.7 for all tissue to blood partition coefficients was adopted by the Agency. No partition coefficients have been measured for any of the three metabolites, and thus, the value of 0.7 used for atrazine was also used for DIA, DEA, and DACT given the structural similarity between atrazine and these metabolites. Such an approach is a common practice in PBPK modeling, and the values for these blood to tissue partition

coefficients estimated using quantitative structure activity relationship (QSAR) algorithm in the ADMET Predictor/GastroPlus (Simulations Plus, Inc. Lancaster, CA) were within a two-fold change of 0.7. This simplified approach, which assumes tissue to blood partition coefficients for all tissues and all chemicals to be 0.7, still allows the model to reasonably predict the time course of total chlorotriazines (TCT) concentrations in plasma.

Table 4.6.2.4.1. Physiological Parameters for the Atrazine PBPK model.				
Physiological Parameters	**Symbol**	**Rat**	**Monkey**	**Human**
Fraction of Body Weight				
Liver	VLC	0.034	0.03	0.026
Brain	VBRC	0.006	0.018	0.02
Pituitary	VPITC	0.0000082	0.0000082	0.0000082
Hypothalamus	VHTLC	0.000015	0.000015	0.000015
Fat	VFC	0.07	0.199	0.21
Mammary	VMAC	0.01	0.00034	0.00034
Testes/Ovaries	VROC	0.00063	0.0007	0.0007
Adrenal	VADC	0.0002	0.00024	0.0002
Rapidly Perfused	VRPC	0.25-VLC-VBRC-VHTLC	0.25-VLC-VBRC-VHTLC	0.25-VLC-VBRC-VHTLC
Poorly Perfused	VSPC	0.93-Sum other tissue Fractions	0.93-Sum other tissue Fractions	0.93-Sum other tissue Fractions
Plasma	VBLC	0.074	0.0734	0.079
Cardiac output (L/hr/kg$^{0.74}$)	QCC	18.7	18.96	15.6
Fraction of QC				
Liver	QLC	0.174	0.2	0.25
Brain	QBRC	0.02	0.066	0.114
Pituitary	QPITC	0.000027	0.00003	0.000047
Hypothalamus	QHTLC	0.000048	0.000053	0.000083
Fat	QFC	0.07	0.018	0.05
Mammary	QMAC	0.002	0.0002	0.0016
Testes/Ovaries	QROC	0.0005	0.0012	0.0012
Adrenal	QADC	0.003	0.003	0.003
Poorly Perfused	QSPC	0.19	0.19	0.19
Rapidly Perfused	QRPC	1 - sum other tissue fractions	1 - sum other tissue fractions	1 - sum other tissue fractions

The values of parameters for saturable metabolism of atrazine, DIA and DEA in liver were scaled from an *in vitro* model. The elimination rates for atrazine, DIA, DEA and DACT, representing hepatic phase II conjugation and urinary/biliary excretion, were adjusted on the basis of the concentrations of atrazine and the chlorinated metabolites in plasma. Rate constants

for oral uptake/absorption of atrazine that were used for propazine, as well as metabolism in liver and excretion, are listed in Tables 4.6.2.4.2 and 4.6.2.4.3.

Table 4.6.2.4.2. Oral uptake and metabolic parameters for atrazine, DIA, DEA, and DACT.

Parameter	Symbol	Rat	Monkey	Human
Oral absorption				
Insoluble portion oral dose (mg/kg)	SOLORDOSE	2400	10000	10000
Absorption rate ATZ in Oral 2 (/hr*BW$^{0.25}$)	KAOR2ATRAC	0.09	0.09	0.09
Transfer Rate ATZ from Oral 1 to Oral 2 (/hr*BW$^{0.25}$)	KOR1_OR2ATRAC	0.181	0.181	0.181
Metabolism of ATZ to DIA in Oral 2 (/hr*BW$^{0.75}$)	KMETRTRA_ISO_OR2C	0.917	0.317	1.05
Absorption rate DIA in Oral 2 (/hr*BW$^{0.25}$)	KAOR2ISOC	0.8	0.8	0.8
Metabolism				
Elimination of ATZ (/hr*BW$^{0.25}$)	KELIMATRAC	41.0	41.0	41.0
Maximum velocity liver ATZ to DIA (µmol/hr/kg$^{0.75}$)	VMAXCATRA_ISO	202.5	202.5	188.2
Affinity constant for ATZ (µmol/L)	KMATRA	30.0	30.0	30.0
Elimination of DIA (/hr*BW$^{0.25}$)	KELIMISOC	48.4	48.4	48.4
Maximum velocity liver DIA (µmol/hr/kg$^{0.75}$)	VMAXCISO	13.5	13.5	25.1
Affinity constant for DIA (µmol/L)	KMISO	13.0	13.0	13.0
Elimination of DACT (/hr*BW$^{0.25}$)	KELIMDAC	1.19	1.19	1.19

Table 4.6.2.4.3. Parameters Used to Simulate the *in vitro* Intact Hepatocyte Metabolism of Atrazine and its Chlorinated Metabolites.

Parameter	Symbol	Syngenta		McMullin
		Rat	Human	Rat
Volume of hepatocyte suspension (mL)	VSUSP	0.25	0.25	10
Initial number of hepatocytes (10^6)	INITNOHEPAT	0.5	0.5	20
Atrazine				
Vmax (µmol/10^6 cells/min)	VMAXCATRA	0.0023	0.0015	0.0023
Affinity constant atrazine (µM)	KMATRA	30.0	30.0	30.0
Fraction atrazine metabolized to DIA	FRAC	0.35	0.2	0.35
DIA				
Vmax (µmol/10^6 cells/min)	VMAXCISO	0.00008	0.00004	0.00008
Affinity constant DIA (µM)	KMISO	13.0	13.0	13.0
DACT				
Clearance (mL/min)	KELDACT	0.001	0.001	0.001

To evaluate the model performance, the human PBPK model was used to simulate concentrations of DACT and DIA measured in whole blood and DACT, DIA, and DEA

measured in urine from a human study (MRIDs 43598603 & 43598604)[13], in which six male human volunteers were dosed with 0.01 mg/kg atrazine via gelatin capsules. The human PK study showed that atrazine and DIA were detected in whole blood at levels below quantitation, but DEA and DACT were measured in blood.

As described earlier, the liver metabolic rate constants for humans were estimated from *in vitro* results measured using human hepatocytes. The model predictions were in good agreement with the blood data. The model-predicted peak DEA concentration in plasma was lower than the measured value by a factor of 3; and the model-predicted peak DACT concentration in plasma was higher than the measured value by a factor of 2. Since available *in vivo* human data are limited, the concordance between species was conducted by scaling the PBPK model developed for rats to monkeys, and consequently, comparing monkey model simulations with monkey pharmacokinetic data (MRID 49482201). The monkey PBPK model provided good concordance with the time-course of plasma concentrations of atrazine, DIA, DEA, and DACT in monkeys exposed to atrazine in a single oral bolus of 2.5 mg/kg administered in 1% methylcellulose. The results of the human and monkey simulations show that the model can be used to extrapolate across species to reasonably predict time-course of plasma concentrations of atrazine and its chlorinated metabolites.

The human PBPK model parameterized for an average adult (based on physiological parameters in Table 4.6.2.4.1) was later modified to include description of growth from birth to adulthood. This life-stage model was modified based on previous work on chlorpyrifos (Smith *et al*., 2014). Body weights are described using an age-dependent Gompertz equation (Luecke *et al.,* 2007, Smith *et al.,* 2014). All tissue volumes were adjusted by body weight using a high order polynomial function[14] (Luecke *et al.,* 2007, Young *et al.,* 2009, Smith *et al.,* 2014[15]). Brain, liver, blood, and fat compartments all have age-dependent descriptions. The life-stage model can be run in two modes: static or dynamic. In static mode, age-specific parameters are held constant whereas in dynamic mode, the parameters change with the age of the simulated individual. For this human health risk assessment, the duration of exposure is 4-days; during infancy and childhood, growth and maturation occur on scales longer than 4 days. As such, the human equivalent PODs derived below were calculated in static mode.

[13] This intentional exposure human study underwent an ethics review in 2011, at which time it was confirmed that it meets all requirements under EPA's Human Studies Rule at 40 CFR part 26 for EPA reliance on the study.

[14] Volume Fraction = P0+P1*BW+P2*BW2+P3*BW3+P4*BW4+P5*BW5+P6*BW6

[15] Luecke, R. H., Pearce, B. A., Wosilait, W. D., Slikker, W., Jr., and Young, J. F. (2007). Postnatal growth considerations for PBPK modeling. *J. Toxicol. Environ. Health A* **70**, 1027-1037.
Smith, J. N., Hinderliter, P. M., Timchalk, C., Bartels, M. J., and Poet, T. S. (2014). A human life-stage physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos: Development and validation. *Regul. Toxicol. Pharmacol.* **69**, 580-597.
Young, J. F., Luecke, R. H., Pearce, B. A., Lee, T., Ahn, H., Baek, S., Moon, H., Dye, D. W., Davis, T. M., and Taylor, S. J. (2009). Human organ/tissue growth algorithms that include obese individuals and black/white population organ weight similarities from autopsy data. *J. Toxicol. Environ. Health A* **72**, 527-540.

In addition to body/tissue weight changes with age, two additional age-dependent features were added to the model. The first age-dependent feature was incorporating changes in glomerular filtration rate (GFR) from birth to 12 months (DeWoskin and Thompson, 2008). During this early life period, the infant GFR level is a fraction of the adult GFR level. Thus, in addition to scaling urinary clearance of DEA, DIA, and DACT from plasma allometrically (i.e., body weight$^{0.75}$), a GFR fraction was added to infants from birth to 12 months using a function that linearly interpolates between measured fractions (Appendix A.3). The second age-dependent feature was scaling the reaction of DEA, DIA and DACT with glutathione transferase (GSH) by body weight rather than scaled body weight (i.e., body weight$^{0.75}$). The chemical reaction with GSH is not the product of an enzymatic reaction (Jablonkai and Hatzios, 1993)[16], and thus, this reaction was not scaled allometrically in the model as other enzymatic reaction, such as CYP metabolism.

A local sensitivity analysis was conducted using the acslX sensitivity analysis routines to determine the sensitive model parameters of which the uncertainty is likely to affect the performance of the model. This sensitivity analysis was run under the following exposure scenario: a single daily oral dose to atrazine of 2.5 mg/kg/day exposed by individuals for 365 days. A total of six ages were examined using both the static (no growth) and the dynamic life-stage versions of the model, including 0.175, 0.45, 1.08, 10, 15.4, and 40 years of age. It was found that both versions of the model resulted in the same set of sensitive parameters. These parameters are liver:blood partition coefficient for DIA, liver:blood partition coefficient for DACT, max velocity of metabolism from DIA to DACT, urinary clearance of DACT, non-enzymatic clearance of DIA, and non-enzymatic clearance of DACT. While liver:blood partition coefficients for DIA and DACT were not measured directly, using the value measured for the parent was a reasonable approach. The max velocity of metabolism from DIA to DACT was extrapolated from *in vitro* measurement using human hepatocytes. Urinary clearance rate of DACT was estimated by fitting model predictions to human urinary data. Non-enzymatic clearance rates of DIA and DACT were estimated by fitting model predictions to rat data; these rates were then scaled allometrically to humans.

An independent external review of the model code and parameter values was performed by the Health Impacts and Exposure Science Group at the PNNL. The PNNL is one of the U.S. Department of Energy's ten national laboratories to support national needs in nuclear energy, environmental management, and national security. The PNNL has evaluated the model twice as part of the process to ensure its readiness for use in risk assessment. After the first review, PNNL identified multiple areas for improvement. In response to PNNL's comments, modelers at the Hamner Institutes and Syngenta have updated and refined the model. EPA and PNNL independently confirmed that PNNL's recommended changes were incorporated. During PNNL's second review on the model modification, additional areas for improvement have been identified. After the model update, PNNL concluded that "this atrazine model is coded appropriately and could support risk/safety assessment with the ability to extrapolate among species, administration routes, and life-stages." All model code, parameters, and PNNL reviews

[16] Jablonkai I. and Hatzios, K. (1993). In vitro conjugation of chloroacetanilide herbicides and atrazine with thiols and contribution of nonenzymatic conjugation to their glutathione-mediated metabolism in corn. J Agric Food Chem 41, 1736-1742.

for the PBPK model are provided in the public docket for the triazine risk assessment. The Agency also set up an external review panel via Versar to conduct a similar review. The comments from the five panel members were shared with Syngenta for additional refinement of the model.

4.5.5.4.2 Derivations of Human Equivalent Doses/Concentrations

The following discussion of human equivalent doses and concentrations considers the PBPK modeling parameters for all three chlorotriazine herbicides, even though all scenarios are not pertinent to all three.

In typical risk assessments, PODs are derived directly from laboratory animal studies and inter- and intra-species extrapolations are accomplished by use of default uncertainty factors (10X for inter-species and 10X for intra-species extrapolation). The 10X default uncertainty factor includes two components: PK (3.16X) and pharmacodynamic (3.16X). In the case of atrazine, PBPK modeling is being used as a data-derived approach for inter-species PK extrapolations to estimate PODs for all age groups (USEPA, 2014) based on the assumption that similar tissue response arises from equivalent tissue dose across species. The PBPK model for rats was first used to convert the rat POD (which was the oral $BMDL_{1SD}$ of 2.42 mg/kg/day from the Cooper *et al.* (2010) study) to a toxicologically relevant internal metric, which is the average TCT concentration in plasma. The rat PBPK model was run until steady-state had been achieved to get the average TCT concentration in plasma, which was 2.6 µmol/L. The human PBPK model was then applied to derive a human POD (an external dose in mg/kg/day) that could have resulted in the same TCT concentration in plasma.

Table 4.6.2.4.2.1. Body Weight Assumptions Incorporated into PBPK Model for Propazine.

Exposure Scenario	Exposure Pathway	Population & Body Weight (kg)				
		Infants (<1 year old)	Young Children (<1 - 2 years old)	Children (Residential:6-11 years old; Dietary: 6-12 years old)	Youths (Residential:11-16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
Dietary	Food and Drinking Water	4.8[1]	12.6[2]	37.1[2]	67.3[2]	72.9[2]
Non-Occupational Spray Drift	Oral		11[3]			
	Dermal					69[4]
Residential (Bystander/Volatilization Assessment)	Inhalation		11[3]			69[4]
Occupational	Dermal, Inhalation					69[4]

1 For infants from birth to < 1 year old, the Agency has selected the body weight for the youngest age group, birth to < 1 month old, 4.8 kg (Exposure Factors Handbook, Table 8-3, mean body weight for the birth to < 1 month age group).
2 NHANES/WWEIA
3 Exposure Factors Handbook, Table 8-3, mean body weight for the 1 to < 2 year old age group.
4 Exposure Factors Handbook, Table 8-5, mean body weight for females 13 to < 49 years old.
5 Exposure Factors Handbook, Table 8-3, mean body weight for the 6 to < 11 year old age group.

In order to derive the scenario specific PODs, assumptions were incorporated into the PBPK model on routes of exposure, surface area exposed, etc. Dietary exposure was assumed to be daily exposure for 21 days. All scenario-specific PODs were calculated as the average daily blood AUC for total chlorotriazines for the last 4 days even though the simulations were run for 21 days. Running the model for 21 days ensures that the predicted average TCT concentrations in plasma represented a steady-state condition (i.e., the value does not change when the total exposure time is longer than 21 days). For dietary food, the exposure assumption is single dose per day. For drinking water exposure, infants and young children (infants <1 year old, children between 1-2 year old, and children between 6-12 year old) were assumed to consume water 6 times a day, and a total consumption volume of 0.69 L/day. Youths and female adults were assumed to consume water 4 times a day, and a total consumption volume of 1.71 L/day.

The dermal component of the PBPK model included an hourly flux rate to determine the rate of absorption through the skin. Available information in the Exposure Factors Handbook[17] indicates that the median frequency for baths and showers was estimated to be 7 times per week (i.e., once per day) for children[18]. However, no additional information is available for children on the typical timing of showers or baths after outdoor activities. Survey information gathered from adult national respondents indicate that adults may shower more frequently than children after doing certain outdoor activities (i.e., gardening, yard work, playing sports, and home repair/digging, etc.); however, the available data do not provide certainty that a shower always occurs within one hour or within a few hours after exposure[19]. Therefore, the lack of specific activity diaries raises uncertainty in the typical timing between exposure and showering/bathing for both adults and children. To derive the dermal PODs in the PBPK model, showers were assumed to occur after one day (24 hours) because the typical timing of showers after exposures occur is uncertain. This assumption accounts for any potential continued absorption of residues remaining on unwashed skin. This approach is conservative because the PBPK model estimates exposures for a maximum of 24 hours before restarting exposures in the model the next day. Assuming a shower occurs 24 hours after initial exposure when deriving PODs for risk assessment is considered the most appropriate and realistic assumption; however, PODs were also derived assuming a shower occurs 8 hours after initial exposure. The PODs and corresponding risk estimates assuming a shower occurs 8 hours after initial exposure are provided in Appendix F.

All non-occupational and occupational PODs were simulated assuming 21 days of exposure.

For adults and children 1 to < 2 years old, non-occupational dermal PODs for spray drift were estimated assuming 50% of the skin's surface was exposed, and a daily shower occurred 24 hours after initial exposure. The incidental oral PODs for children 1 to < 2 years old was estimated assuming six events, 15 min apart, per day. For occupational handlers and post-application workers, the dermal PODs were estimated assuming a body weight of 69 kg (to

[17] Available at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

[18] Wang et al. 2000. Adult Proxy Responses to a Survey of Children's Dermal Soil Contact Activities. Journal of Exposure Analysis and Environmental Epidemiology. 10, 509-517. https://www.nature.com/articles/7500110.pdf?origin=ppub

[19] Garlock et al. 1999. Adult responses to a survey of soil contact-related behaviors. Journal of Exposure Analysis and Environmental Epidemiology. 2, 134-142. https://www.nature.com/articles/7500007.pdf?origin=ppub

represent a female aged 13-49), 100% of the skin's surface was exposed for 5 days/week, for 21 days, and that a shower occurred 24 hours after initial exposure. For occupational handlers, the inhalation PODs were estimated exposure for 8 hours/day, 5 days/week, for 21 days. Three breathing rates were simulated, 1 m^3/hr, 0.5 m^3/hr, and 1.74 m^3/hour to represent different occupational handler activities.

Table 4.6.2.4.2.2 Propazine PBPK Modeled External Doses (PODs) Corresponding to a $BMDL_{1SD}$ for LH Surge Attenuation

RA Type	Exposure Pathway (all triazines unless noted)	Infants (< 1 yr old)	Young Children (1 - 2 years old)	Children (Residential:6-11 years old; Dietary:6-12 years old)	Youths (Residential:11-16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
		Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)
Dietary	Drinking Water (conc, ppb)	18,899	45,789	105,570	67,967	80,637
	Food (mg/kg/day)	2.70	2.86	2.27	2.04	2.0
Non-Occupational (Spray Drift)	Dermal (mg/kg/day)		43.85			30.37
	Oral (mg/kg/day)		2.93			
Occupational	Dermal (mg/kg/day)					30.4
	Inhalation (mg/kg/day)[1]					1.8

1. Occupational handler breathing rates and results:
   a. 1 m^3/hr (16.7 L/min) = 15.8 mg/m^3 × 1 m^3/hr × 8 hr/day ÷ 69 kg = 1.8 mg/kg/day.
   b. 0.5 m^3/hr (8.9 L/min) = 31.6 mg/m^3 × 0.5 m^3/hr × 8 h/day ÷ 69 kg = 1.8 mg/kg/day.
   c. 1.74 m^3/hr (29 L/min) = 2.17 mg/m^3 × 1.74 m^3/hr × 8 hr/day ÷ 69 kg = 1.8 mg/kg/day.

4.5.5.4.3 Four-Day Repeated Exposure (Oral, Dermal, Inhalation) Uncertainty/Extrapolation Factors

In typical risk assessments, PODs are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by use of 10X factors. The Agency's 2014 Data-Derived Extrapolation Factors (DDEF) guidance allows for the separation of standard inter- and intra-species extrapolation factors into PK and PD components. In the case of atrazine, its chlorotriazine metabolites, and the other chlorotriazine herbicides, PBPK modeling is being used as a data-derived approach to estimate PODs for all age groups based on differences in PK across species.

Thus, PK differences between rats and humans are accounted for with human equivalent PODs which alleviates the need for the PK portion of the interspecies factor. Since the PBPK model does not address the pharmacodynamic component of intraspecies extrapolation, a factor of 3x was retained. Similarly, the PBPK model does not account for within-human variability; thus the 10x intra-species will be used. Therefore, for the 4-day repeated exposure scenarios, the total UF is 30X (3X for interspecies and 10x for intraspecies variability and 1X for FQPA when applicable).

4.5.6 Recommendation for Combining Routes of Exposures for Risk Assessment

The acute and chronic aggregate dietary assessments include exposures from food and water. For the 4-day aggregate assessment, it is appropriate to combine exposures from oral, dermal, and inhalation routes since the same endpoint was selected.

4.5.7 Cancer Classification and Risk Assessment Recommendation

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 epidemiological 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" (J. Kidwell, TXR# 0053936, 12/08/2005). Details on the carcinogenicity of atrazine are presented in the atrazine draft risk assessment (K. Rickard *et al.,* D418316, 07/10/2018).

4.6 Hydroxypropazine: Toxicity Endpoint and Point of Departure Selections and Uncertainty Factors

Although no toxicity data are available on hydroxypropazine, toxicity data for hydroxyatrazine can be bridged to the hydroxypropazine. For hydroxypropazine, only the chronic endpoint is applicable as it is the only relevant duration of exposure associated with a toxic effect. Exposure to hydroxypropazine is not expected through sources other than food and drinking water. Hydroxypropazine is a plant metabolite, and to a lesser extent a livestock metabolite; therefore, hydroxypropazine residues are not expected on the surfaces of plants limiting the potential for non-dietary exposures in residential and occupational settings. However, chronic dietary exposures to hydroxypropazine are considered (See Section 5).

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using all available dichotomous models for incidence data for various histopathological renal lesions in male and female rats from a combined chronic toxicity/oncogenicity study (MRID 43532001) on hydroxyatrazine in the rat. Criteria used to assess the best fit included statistical (goodness-of-fit) values, model criteria (Akaike Information Criteria; AIC), BMD/BMDL (Benchmark Dose/lower 95% confidence limit on the Benchmark Dose) ratios, visual inspection of fits, and comparison of male and female dose-response relationships. The BMR level of 10% extra risk for quantal incidence data was chosen as a biologically significant change. The female rat data provided the lowest BMD value - $BMDL_{10}$ of 6.76 mg/kg/day/ BMD_{10} of 7.92 mg/kg/day) based on renal lesions (fibrosis of the papillary interstitium). Additional details of the BMD analysis can be found in Appendix D.

Table 4.7. Summary of Toxicological Doses and Endpoints for Hydroxytriazines for Use in Acute and Chronic Dietary Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	A toxic effect attributable to a single dose was not seen in the toxicity database; therefore, an acute endpoint has not been identified and no risk is expected from this exposure scenario.
Chronic Dietary (All Populations)	$BMDL_{10}$ = 6.76 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.0676 mg/kg/day	Combined chronic toxicity/carcinogenicity in the rat; BMD_{10} = 7.92 mg/kg/day based on histopathological lesions of the kidney. MRID 43532001 (hydroxyatrazine study)

$BMDL_{10}$ = lower 95% confidence limit on the benchmark dose (benchmark response of 10%) BMD10 = benchmark dose associated with a benchmark response of 10%. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). RfD = Reference Dose. FQPA = Food Quality Protection Act (FQPA). SF = Safety Factor.

There are no residual uncertainties in the hazard or exposure databases for the hydroxy compounds, so the FQPA safety factor is reduced to 1X. The standard intra- and inter-species factors are applied; therefore, the total uncertainty factor is 100X.

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

The FQPA (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children**." As such, the FQPA requires that the Agency consider issues related to toxicity and exposure. Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

For the REDs and 2006 CRA, the Agency retained the FQPA 10X safety factor for uncertainties related to both available toxicology data and exposure information on drinking water. Specifically, the 2006 CRA states "there remains some degree of residual uncertainty as to the effects of triazines on the young……. In particular, exposures at all critical periods." These critical developmental periods were noted as gestation through puberty in both sexes, in particular, early in development (USEPA, 2002b[20]). With respect to the drinking water exposure, the 2006 CRA notes uncertainty worthy of retaining a portion of the FQPA SF where "monitoring data are used that are limited in temporal scope or frequency of sampling" but goes further to state that where "models [PRZM/EXAMS] have been used to estimate drinking water exposure, no additional FQPA Exposure-based Factor is warranted…...[the model] provides exposure estimates that are conservative and protective."

Since the REDs were finalized and the 2006 CRA was conducted, the available information on toxicology of various pre- and post-natal lifestages and on drinking water exposure has substantively changed. The drinking water assessment is described in Section 5.3. The exposure databases and modeling are sufficient to assure that residues in drinking water will not be underestimated. The exposure assessment for drinking water provides a conservative approach for estimating chlorotriazine concentrations in ground and surface source water for drinking water.

The atrazine hazard database consists of hundreds of studies including OECD/OPPTS guideline studies, literature studies, mechanistic studies, studies conducted by ORD scientists as well as epidemiology studies; included among these are many studies on pregnant, neonatal, developing, pre-pubertal, and adult animals. None of the available high-quality studies that meet the criteria[21] for use in risk assessment have demonstrated effects in rats exposed during gestation, lactation or the peri-pubertal periods at doses lower than those eliciting the LH surge attenuation in the Cooper study. In addition to LH, OPP has data on a variety of other hormones: estrogen, corticosterone, progesterone, testosterone, GnRH, Adrenocorticotropic hormone (ACTH). Changes in these hormones (other than LH) occur at doses at least 10-fold higher than the Cooper study. Issues related to lifestage sensitivity and drinking water monitoring were subject

[20] USEPA, 2002b, *ATRAZINE/DACT* - Reassessment Report of the FQPA Safety Factor Committee. April 8, 2002. TXR# 0050638

[21] U.S. EPA (2012). *Guidance for considering and using open literature toxicity studies to support human health risk assessment.* https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf

of three reviews by the SAP 2010-2011. Key summary information from the open scientific literature are provided below:

OECD/OPP Guideline Studies:

With respect to the OECD guideline studies submitted for registration, there was no increased quantitative or qualitative susceptibility in any of the guideline studies on atrazine in the rat, and there was no increased quantitative susceptibility in the rabbit study. Similarly, there was no evidence of increased susceptibility in the prenatal developmental toxicity study in rats with hydroxyatrazine. Although there was increased qualitative susceptibility in the atrazine rabbit study [increased resorptions (deaths) at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal], the observed effects occur at higher doses than the BMDL of 2.42 mg/kg/day used to assess risk. The BMDL of 2.42 mg/kg/day is protective of developmental effects in the rabbit.

Laboratory Animal Toxicity Data (nonguideline) on Pre- Natal Exposure:
With respect to toxicity outcomes following gestational exposure (i.e., pre-natal), Fraites *et al.* (2011) did not observe effects on male reproductive development or the androgen-dependent endpoints measured in the study after *in utero* exposure during gestation (GD 14-21) including (i) testosterone production at birth and on PND 59, (ii) rough and tumble play behavior, (iii) anogenital distance (AGD) and preputial separation (PPS), or (iv) androgen-dependent organ weights at doses as high as 100 mg/kg/day. This is consistent with the findings reported by Rayner *et al.,* (2007) who observed no change in the timing of male puberty, but did report a higher incidence in prostatitis at 100 mg/kg/day. In contrast, Rosenberg *et al.,* (2008) reported delays in PPS at 50 mg/kg/day. Another high dose effect reported after gestational exposure to atrazine is a delay in mammary gland development of female offspring (Rayner *et al.,* 2005, 2007). This effect, however, was not replicated by Davis *et al.,* (2011) at doses as high as 100 mg/kg/day when evaluated either using a subjective scoring approach (as described by Rayner and coworkers) or a morphometric analysis.

Laboratory Animal Toxicity Data on Post- Natal Exposure:
Two tissue dosimetry studies have been conducted by EPA laboratories to evaluate lactational transfer of atrazine and its metabolites to lactating pups (Stoker and Cooper, 2007; Stoker *et al.,* 2010; Kamel *et al.,* 2010). In general, these studies show a decrease in the concentration of atrazine and its metabolites as the chemicals move from the dam‘s mammary gland→ milk in the pup stomach → pup plasma and pup brain, such that the concentrations in the pup plasma and brain are approximately 10-fold (or more) lower than in the dam plasma. DACT is the major metabolite in milk collected from pup stomachs with only small amounts of atrazine, DIA, and DEA detected in the milk.

Several studies have evaluated the effects of atrazine in male and female pups during the peri-pubertal period. Overall, there is qualitative consistency among these studies as they show delays in the onset of puberty in both sexes, although the dose-response relationships differ somewhat among studies. Among these studies, Stoker *et al.,* (2001) provides the most sensitive NOAEL/LOAEL at 6.25/12.5 mg/kg/day atrazine; the NOAEL of 6.25 mg/kg/day is higher than the current repeat dosing BMDL of 2.42 mg/kg/day from Cooper *et al* (2010) used as the POD

for the risk assessment. With respect to hormone measurements, changes in testosterone have been shown at high doses (≥ 50 mg/kg). Given the inherent variability on testosterone levels during the peripubertal period, it is not unexpected that significant changes in testosterone were only reported after atrazine exposure at relatively high dose levels. It is also important to consider that although LH stimulates testosterone secretion from the Leydig cells, this modulation is the result of increased sensitivity of Leydig cells to the LH stimuli rather than an increase in circulating LH. As a result of this increased sensitivity, substantial decreases in LH are needed before changes in testosterone are observed.

Laboratory Animal Toxicity Data on Pre- & Post-Natal Exposure:
A study evaluating the impact of atrazine exposure across several lifestages has been submitted by Syngenta. The purpose of this study was to evaluate the effects of atrazine on sexual maturation, estrous cyclicity, and the LH surge in SD [Crl:CD(SD)] rats following atrazine doses of 0, 6.5, 25 or 50 mg/kg/day administered via gavage. Animals (all subsets) exposed to 50 mg/kg/day atrazine exhibited a 1.4-2.3 day delay in VO (mean = 1.6 day delay). Unlike the findings reported by several investigators (Foradori *et al.*, 2009; Cooper *et al.,* 2007; Morseth *et al.,* 1996, Davis *et al.,* 2011)), no LH surge attenuation was observed at any dose level. Given this study's inconsistency with the weight of evidence pertaining to LH surge attenuation, the agency continues to use the LH surge as the critical endpoint for the risk assessment.

Epidemiology Studies:
No epidemiology studies were found with propazine. However, since atrazine, simazine and propazine share a common mechanism of toxicity – refer to the risk assessments for atrazine (K. Rickard *et al.,* D418316, 07/10/2018) and simazine (K. Rickard *et al.,* D402163, D428603, 07/10/2018).

Conclusions by the FIFRA SAP:
As noted above, issues related to lifestage sensitivity and drinking water monitoring were subject of three reviews by the SAP 2010-2011.

The SAP "concluded that there is sufficient information available to reach the conclusion that the issue of differential sensitivity has been adequately studied. This relatively extensive database, spanning all life stages from conception to adulthood indicates no unique susceptibility to atrazine in the developing organism." (SAP Report on July 2011 meeting, EPA-HQ-OPP-2011-0399-0080.pdf; pp. 52-54).

Based on the currently available toxicity and exposure data, the triazine risk assessment team recommends that the FQPA Safety Factor be reduced to 1X. The details for reducing the FQPA Safety Factor to 1X are described below.

4.7.1 Completeness of the Toxicology Database

The toxicological database for the chlorotriazines and hydroxyatrazine is considered complete, acceptable, and adequate for assessing susceptibility of infants and children as required by FQPA. This conclusion is supported by the FIFRA SAP (2011) report that stated "there is sufficient information available to reach the conclusion that the issue of differential sensitivity

has been adequately studied. This extensive database, spanning all life stages from conception to adulthood indicates no unique susceptibility to atrazine in the developing organism." (SAP Report on July 2011 meeting, EPA-HQ-OPP-2011-0399-0080.pdf; pp. 52-54). In addition to the typical required guideline studies, the database contains numerous studies covering a wide array of disciplines including toxicokinetics, mechanistic, and epidemiology.

4.7.2 Evidence of Neurotoxicity

As mentioned previously, the chlorotriazines have an established neuroendocrine mode of action which involves disruption of the hypothalamic-pituitary-gonadal axis. Effects include perturbations in LH and GnRH, and alterations in neurotransmitters and neuropeptides. For hydroxyatrazine, there was no evidence of neurotoxicity including neuroendocrine effects in the available studies. The Hazard and Science Policy council (HASPOC) recommended on February 14, 2013 (K. Rury, TXR# 0056587, 04/16/2013) that acute and subchronic neurotoxicity studies be waived for atrazine, simazine, and propazine. The HASPOC noted that acute and subchronic neurotoxicity studies typically do not evaluate parameters related to the neuroendocrine system, particularly, the HPG axis, and that the acute and subchronic neurotoxicity studies are unlikely to provide more sensitive endpoints for use in risk assessment. LH attenuation continues to be the most sensitive endpoint identified in the database, and would be protective of potential health outcomes associated with the chlorotriazines.

4.7.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal[22]

The Agency has concluded that the available data do not identify a unique quantitative susceptibility in the developing organism. None of the available studies with atrazine evaluating rats exposed during gestation, lactation, or in the peri-pubertal periods have shown effects at doses lower than those eliciting the LH surge attenuation in adult female rats after 4 days of exposure. The SAP agreed with the Agency's conclusion that there is "no unique susceptibility in the developing organism. Additionally, the proposed POD, based upon attenuation of the LH surge, appears to be protective against adverse reproductive/developmental outcomes such as delays in onset of puberty, disruption of ovarian cyclicity and inhibition of suckling-induced prolactin release" (SAP Report on July 2011 meeting, EPA-HQ-OPP-2011-0399-0080.pdf; pp. 14).

Table 4.8.3. Atrazine: Comparison of LH Data from Adult Rats to Apical Endpoints from Developing Rats.

Life Stage	LH Hormone (NOAEL/LOAEL)	Apical Endpoint NOAEL/LOAEL
Pre-Natal (Fetus)		• 10/70 mg/kg/day; delays in ossification • 10/50 mg/kg/day; delayed PPS
Perinatal		• 6.25/12.5 mg/kg/day; increased prostatitis
Peripubertal		• 6.25/12.5 mg/kg/day; increased prostatitis, delayed PPS

[22] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

Table 4.8.3. Atrazine: Comparison of LH Data from Adult Rats to Apical Endpoints from Developing Rats.		
Life Stage	**LH Hormone (NOAEL/LOAEL)**	**Apical Endpoint NOAEL/LOAEL**
		• 25/50 mg/kg/day; delays in vaginal opening • 50/100 mg/kg/day; delays in vaginal opening, decreased testosterone
Adult	1.56/3.12 mg/kg/day † (4 day exposure)	• 1.8/3.65 mg/kg/day; disrupted cyclicity • 50/100 mg/kg/day; disrupted cyclicity
	1.8/3.65 mg/kg/day (26 week exposure)	

† After BMD analysis the BMDL/BMD @ 1 standard deviation = 2.42/4.92 mg/kg/day

4.7.4 Residual Uncertainty in the Exposure Database

The exposure databases and modeling are sufficient to determine the nature/magnitude of the residue in food and drinking water. The propazine residue chemistry database is robust. The exposure assessment for drinking water provides a conservative approach for estimating chlorotriazine and hydroxytriazine concentrations in ground and surface source water for drinking water, and thus is unlikely to underestimate exposure. The dietary exposure analyses are unlikely to underestimate exposure as they incorporated conservative assumptions. The non-occupational spray drift exposure assessment is based upon the 2012 Residential Standard Operating Procedures (SOPs). These assessments of exposure are not likely to underestimate the resulting estimates of risk from exposure to propazine.

4.8 Endocrine Disruptor Screening Program

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

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal

systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[23] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[24]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Plant and animal metabolism of propazine is well understood. In general, propazine is metabolized in plants through replacement of the chlorine atom with either a hydroxy group or by a glutathione. This leads to three families of metabolites: the chlorinated metabolites, the hydroxylated metabolites, and the glutathione-conjugated metabolites. Within each family, three additional metabolites can arise by removal of either one or both of the N-alkyl moieties. Other metabolites can also arise within the glutathione family of metabolites by metabolic changes to the glutathione moiety. All of the major modes of metabolism described above have been identified in plants and can be summarized as replacement of the chloroine atom with a hydroxy-group (hydrolytic dehalogenation), glutathione conjugation, and removal of either one or both of the N-alkyl groups (dealkylation). All routes leave the central triazine ring intact, and, since these modes exist in competition, all three families of metabolites (chloro-, hydroxy-, and glutathione conjugates) can exist in combination with each of the N-dealkylated forms. Metabolism by hydrolytic-dehalogenation dominates for residues absorbed through the roots while metabolism by glutathione conjugation dominates for absorbed through the foliage. Propazine's metabolism in animals is similar to plants. However, it is dominated by removal of either one or both of the N-alkyl groups (dealkylation), and subsequent glutathione conjugation. As in plants, all metabolic routes in the animal leave the central triazine ring intact.

5.1.2 Summary of Environmental Degradation

Similar environmental degradation pathways are operative for all chlorotriazine herbicides, atrazine, propazine, and simazine. These chemicals are considered moderately persistent and

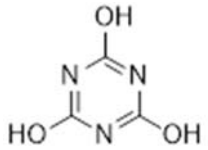
[23] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[24] https://www.epa.gov/endocrine-disruption

mobile in most soils, showing relatively slow breakdown by hydrolysis, photolysis, or biodegradation. In areas where soils are highly permeable, the water table is shallow, or where there is irrigation and/or high rainfall, the use of triazines use may result in ground or surface water contamination.

The chlorinated and hydroxylated metabolites observed in the plant and livestock metabolism studies are also the most abundant degradates found in drinking water. Environmental fate data indicate that the hydroxytriazines, while persistent, are less mobile than the chlorotriazines. Consistent with this observation, both monitoring and modeling data indicate that levels of the total chlorinated triazines (TCTs) are generally higher than those of the total hydroxylated triazines (THTs) (J. Hetrick and M. Biscoe, D428938, 10/28/2015).

5.1.3 Comparison of Metabolic Pathways

Environmental/aquatic degradation of the triazine herbicides is similar to degradation seen in plants, livestock, and rats, in that both dealkylated chlorinated and hydroxylated degradates are formed (Figures 3.1.1 and 3.1.2). Further degradation to cyanuric acid (see Figure 5.1.3) and other terminal breakdown products also occurs.



Cyanuric Acid

Figure 5.1.3 Chemical Structure for Cyanuric Acid

5.1.4 Residues of Concern Summary and Rationale

The nature of the residue in plants and livestock is adequately understood for propazine. Risks are quantified separately for propazine and hydroxypropazine residues, based on different toxicological endpoints. As a result, propazine parent plus its chlorinated and hydroxylated metabolites comprise the residues of concern for risk assessment. For tolerance enforcement, the residues of concern are propazine plus its chlorinated metabolites (C. Eiden, D270177, 11/15/2000; C. Eiden, D288715, 02/10/2003). This information is summarized in Table 5.1.4.

Table 5.1.4. Summary of Metabolites and Degradates to be Included in the Propazine Risk Assessment and Tolerance Expression.

Matrix	Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Propazine and its chlorinated[1] and hydroxylated[2] metabolites	Propazine and its chlorinated[1] metabolites
Livestock	Propazine and its chlorinated[1] and hydroxylated[2] metabolites	Propazine and its chlorinated[1] metabolites
Drinking Water	Propazine and its chlorinated[1] and hydroxylated[2] metabolites	NA

[1] desethyl-s-atrazine (DEA) and diaminochlorotriazine (DACT). See Figure 3.1.1.
[2] hydroxypropazine, desethylhydroxyatrazine (DEHA) and ammeline. See Figure 3.1.2. Risks are assessed separately for the hydroxy metabolites as they are associated with different toxicity effects than the chlorinated triazines.

5.2 Food Residue Profile

Propazine metabolism data in plants and livestock are adequate for identification of the residues of concern in these matrices. The plant metabolism studies demonstrate that residues are generally low, but translocate throughout the plants. Sorghum field trial residue data showed residue levels below the limit of quantitation for propazine and DEA in sorghum forage, grain, and stover. DACT was found only in sorghum forage at a maximum level of 0.087 ppm.

Field trials are of adequate number and geographic representation. Data analyses employed validated analytical methods and are supported by adequate storage stability data. Multiresidue method (MRM) testing for DEA and DACT should be submitted. Analytical standards for propazine and its regulated metabolites are currently available in the EPA National Pesticide Standards Repository. Sufficient studies were submitted to elucidate the fate of propazine in processed commodities. Analysis of potential residue levels in livestock feedstuffs from sorghum show that there is no reasonable expectation of finite residues in livestock commodities, i.e., 40 CFR §180.6(a)(3) applies; thus, livestock tolerances for propazine are not needed. Rotational crop studies support the current rotational crop restrictions on the propazine label.

5.3 Water Residue Profile

Determination of EDWCs for the chlorotriazines (atrazine, propazine, and simazine) have been provided by the Environmental Fate and Effects Division (EFED) (J. Hetrick and M. Biscoe, D428938, 10/28/2015). The EDWCs were derived using a total toxic residue (TTR) approach and include all chlorotriazine residues of concern in drinking water from all the triazine uses [parent chlorotriazines (atrazine, simazine, and propazine), desisopropylatrazine (DIA), desethylatrazine (DEA), and diaminochlorotriazine (DACT)], referred to as TCT (total chlorotriazines). The TTR approach was also used for the hydroxytriazine residues of concern (hydroxysimazine, hydroxypropazine, hydroxyatrazine, desethylhydroxyatrazine (DIHA), desisopropylhydroxyatrazine (DIHA), and ammeline), referred to as THT (total hydroxytriazines). Separate ground water (monitoring data) and surface water (SWCC and FIRST modeling) concentrations were provided for TCT and THT for the daily peak (acute exposures), 4-day average (4-day exposures), and annual average (chronic exposures) for use in the individual triazine assessments (propazine, atrazine, and simazine) and for use in the cumulative triazine assessment. Since the EDWCs were based on total triazine residues, which include atrazine, propazine, and simazine, and all the related metabolites, and are not just based on propazine and its chlorinated and hydroxylated metabolites, these EDWCs may be considered high-end estimates for the propazine risk assessment.

The EDWC values are summarized in Table 5.3. See the drinking water assessment (J. Hetrick and M. Biscoe, D428938, 10/28/2015) for complete details regarding the EDWC derivations.

Table 5.3. EDWCs for Total Chlorotriazines and Total Hydroxytriazines.							
Source Water	Compound	EDWC Estimate Source	Crop Use Pattern	App Rate (lb ai/A)	EDWC (ppb)		
					Daily Peak	4-Day Avg	Annual Avg
					ppb		
Surface Water	TCT	SWCC	Sugarcane	10	610	585	104
	THT	FIRST	Sugarcane	10	265	265	76
Ground Water	TCT	Monitoring	NA	NA	100	100	5.11
	THT	PRZM-GW/Monitoring	Sorghum	1.2	92.6	92.6	7.33

Monitoring Data

Extensive and robust water monitoring data are available for triazines and have been included in the drinking water assessment. Surface and groundwater data for total chlorotriazines and total hydroxytriazines are available from a variety of government and state agency monitoring programs, as well as registrant-conducted monitoring programs. The details of the monitoring data can be found in D428938 (J. Hetrick and M. Biscoe, 10/28/2015) and are briefly summarized below.

Surface Water Monitoring

The distribution of maximum total chlorotriazine (TCT) concentrations in ambient surface water monitoring data range from 0.05 to 20,000 µg/L. The distribution of annual average TCT concentrations in ambient surface water monitoring data ranges from 0.01 to 322 µg/L. The spatial distribution on the TCT occurrence corresponds with the use data for chlorotriazine herbicides in the United States. As expected, the high TCT concentrations are from states with high corn and sorghum production.

The Maximum Contaminant Levels (MCLs) for atrazine and simazine are 3 and 4 µg/L, respectively, as an annual average. The distribution of maximum TCT concentrations in finished surface water monitoring data range from 0.02 to 65.20 µg/L. The annual average TCT concentrations range from 0.02 to 7.76 µg/L.

Surface Water Modeling/Monitoring Comparison

A comparison of the 1-in-10 year maximum TCT concentration from surface water concentration calculator (SWCC) simulations for atrazine and simazine applications to corn to the maximum TCT concentration in ambient surface water monitoring data shows that the results are similar. In all cases, the 1-in -10 year maximum TCT concentrations from modeling and the peak TCT concentrations from monitoring data are well within an order of magnitude (10X). It is noted that several states a have maximum TCT concentrations greater than the 1 in 10 year TCT concentrations from SWCC modeling.

The distribution of maximum hydroxytriazine concentrations in ambient surface water monitoring data range from 0.03 to 4.6 µg/L. The spatial distribution on the hydroxytriazine occurrence in surface water generally corresponds with use area for chlorotriazine herbicides in

the United States. A comparison of the Tier 1 FIRST modeling for corn at 2.5 lb ai/A and monitoring data clearly indicate the Tier 1 surface water modeling is conservative. The Tier 1 FIRST modeling predicts the maximum peak hydroxyatrazine concentration is 66.15 and 55.6 µg/L for atrazine and simazine, respectively. The monitoring data show the maximum peak hydroxytriazine concentration is 4.6 µg/L. Tier FIRST 1 modeling is within an order of magnitude of the monitoring data.

Groundwater Monitoring

The maximum TCT concentrations in groundwater range from 0.053 to 9,290 µg/L. However, the groundwater monitoring data show that maximum TCT concentrations are typically low (< 1 µg/L) across the United States. The data also show that extremely high TCT concentrations (> 100 µg/L) are associated with point source contamination from spills and mixing/loading facilities.

The annual average TCT concentrations in groundwater range from 0.07 to 5,755 µg/.. The high TCT concentration (5,755 µg/L) is attributed to point source contamination from a spill or mixing loading facility. Florida (1.2% of the drinking water wells) and WI (38% of the drinking water wells) are the only states with annual average concentrations exceeding the MCL for atrazine.

Groundwater Modeling/Monitoring Comparison

A comparison of the maximum daily TCT concentration from PRZM-GW simulations for atrazine and simazine applications on corn to the maximum TCT concentration from monitoring data shows that TCT concentrations from monitoring data are not comparable to PRZM-GW model predictions. In all cases except for the PRZM-GW WI scenario, the PRZM-GW TCT concentrations exceed the monitoring data by more than an order of magnitude (10X). The WI DATCP monitoring data has 274 site-years (3.2 % of the sites) with TCT concentrations greater than 100 µg/L. These sites are associated with point source contamination from spills and mixing/loading facilities. However, the majority of well site-years (60%) in the WI DATCP monitoring program have atrazine concentrations of less than or equal to 1 µg/L. These data indicate that PRZM-GW screening level model predictions are conservative when compared to the monitoring data. The PRZM-GW modeling represents TCT concentrations in groundwater at the surface of an unconfined aquifer from a private well in a site with long-term, continuous annual triazine use (30 years) in a sand or loamy sand soil with low organic matter content and a shallow well (< 30 feet). This scenario assumes TCT concentrations are representative of new water (i.e., water moved from the vadose zone in groundwater) without any mixing or dilution with old water (i.e., resident water in the aquifer). Although such situations are possible in private drinking wells, they do not seem to be representative of the wells in the extensive groundwater monitoring data for TCT. The model predictions, however, are more representative of TCT concentrations associated with point source contamination from spills and mixing/loading sites. Given the widespread monitoring data from a spatial and temporal context, peak TCT concentrations in groundwater are not expected to exceed 100 µg/L from agricultural uses of triazines.

The distribution of maximum annual average hydroxytriazine concentrations in groundwater monitoring data are generally equal to or less than 1 µg/L. The highest annual average hydroxytriazine concentration is 7.33 µg/L. This detection is from a well in Iowa. A comparison of the PRZM-GW modeling for corn at 2.5 lb ai/A and monitoring data clearly indicate the PRZM-GW modeling is comparable to monitoring data. The PRZM-GW modeling predicts the hydroxytriazine concentration range from 0-10.3 and 0-1.11 µg/L for atrazine and simazine, respectively. The monitoring data show the maximum hydroxytriazine concentration is 7.3 µg/L. PRZM-GW modeling is clearly within an order of magnitude of the monitoring data.

5.4 Dietary Risk Assessment

Dietary exposure to propazine and its chlorinated and hydroxylated metabolites may occur from ingestion of residues in foods and in drinking water. Dietary exposure durations may be acute (one day) or chronic. However, for the chlorotriazine herbicides, only acute and 4-day exposure durations for dietary exposures are applicable (4-day assessment will be protective of longer exposures). For acute assessment for propazine and its chlorinated metabolites, the toxicological endpoint is delayed ossification in fetuses and is only applicable to females of reproductive age (13-49 years old). For the 4-day assessment for propazine and its chlorinated metabolites, the endpoint is attenuation of LH surge and is applicable to all lifestages. The duration appropriate for assessing dietary risks for the hydroxypropazine and its hydroxylated metabolites is chronic. The chronic endpoint (kidney effects) is applicable to all lifestages.

5.4.1 Dietary (Food) Risk Assessment

Propazine is registered for use on grain sorghum. However, the 2003-2010 U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) reports no human consumption for sorghum grain, the only food commodity from grain sorghum in the Dietary Exposure Evaluation Model with Food Commodity Intake Database (DEEM-FCID). Field trial studies have demonstrated that residues of propazine and its regulated metabolites are less than the limit of quantitation (LOQ) of the analytical method in sorghum grain. Considering the low residues in sorghum combined with the expected limited consumption, human exposure to propazine residues from the sorghum use is considered negligible.

5.4.2 Dietary (Drinking Water) Risk Assessment

With insignificant exposure expected from propazine in food based on the current uses, the total dietary exposure to propazine is through drinking water. A drinking water level of comparison (DWLOC) approach is used to calculate the amount of exposure available in the total 'risk cup' for drinking water (HED SOP 99.5, *Updated Interim Guidance for Incorporating Drinking Water Exposure into Aggregate Risk Assessments,* 8/1/99). Typically, this approach would involve accounting for any exposures from food and/or residential use as well; since there are no anticipated food or residential exposures to propazine, the entire 'risk cup' is available for drinking water exposures. The DWLOCs are compared to the estimated concentrations in drinking water (EDWCs; See Table 5.3). If the DWLOCs are greater than the EDWCs, there is no risk of concern. The use of a DWLOC approach facilitates determining aggregate risks when

there are multiple EDWCs or when there are potential aggregate risk estimates of concern and is also the approach being used for the atrazine, simazine, and triazine cumulative risk assessments. The general DWLOC formula is as follows:

DWLOC (ppb) = PAD (mg/kg)/[water consumption (L/kg) * 0.001 mg/ug]

Water ingestion rates (in L/kg) are included in the DWLOC calculations. These values vary with population subgroup, the duration time of interest, and the exposure percentile applicable for regulation. These values were from the 2003-2008 NHANES/WWEIA consumption database, selecting the appropriate exposure durations and percentiles.

The formula above is used for the acute and chronic DWLOC calculations. However, for 4-day assessment the water consumption is already accounted for in the PBPK model when estimating the PODs (infants and children were assumed to consume water 6 times a day with a total consumption volume of 0.688557 L/day. Youths and female adults were assumed to consume water 4 times a day with a total consumption volume of 1.71062 L/day). The 4-day DWLOCs are equal to the 4-day PADs (PAD=POD/LOC).

5.4.2.1 Acute Dietary (Drinking Water) Risk Assessment

Propazine

The acute DWLOC for females 13-49 years old is 1800 ppb (Table 5.4.2.1). The acute DWLOC is greater than the acute EDWCs for TCTs in surface water or ground water (Table 5.3; EDWC range =100-610 ppb); there is no acute dietary risk of concern.

Table 5.4.2.1. Acute DWLOC Calculations- Propazine.

Age(years) /Population	Acute POD (mg/kg/day)	LOC	Acute PAD (mg/kg/ day)[1]	Water Ingestion Rate (L/kg)[2]	Acute DWLOC (ppb)[3]
Females 13-49 years old	10	100	0.1	0.0544	1800

[1]PAD=POD/LOC

[2]Water ingestion rate from 2003-2008 NHANES/WWEIA consumption database at 95th percentile (one-day value).

[2]DWLOC (ppb) = PAD(mg/kg/day)/[water consumption (L/kg) * 0.001 mg/ug]

Hydroxypropazine

No toxicological effects attributable to a single dose were identified for hydroxypropazine; therefore, no risk is expected from this exposure scenario.

5.4.2.2 Four-Day Dietary (Drinking Water) Risk Assessment

The 4-day DWLOCs for infants, children, youths, and adults are equal to their respective 4-day PADs. The lowest 4-day DWLOC was for infants (<1 year old) at 630 ppb (Table 5.4.2.2). The 4-day DWLOCs are all greater than the 4-day EDWCs for TCTs in surface water or ground water (Table 5.3; highest 4-day TCT EDWC = 585 ppb); there are no 4-day dietary risks of concern.

Table 5.4.2.2. 4-Day DWLOC Calculations-Propazine.				
Age(years) /Population	**4-Day POD (ppb)[1]**	**LOC**	**4-Day PAD (ppb)[2]**	**4-Day DWLOC (ppb)[3]**
All Infants (< 1 year old)	1.89E+04	30	630	630
Children 1-2 years old	4.58E+04	30	1500	1500
Children 6-12 years old	1.06E+05	30	3500	3500
Youth 13-19 years old	6.80E+04	30	2300	2300
Females 13-49 years old	8.06E+04	30	2700	2700

1. From Table 4.6.2.4.2.2
2. PAD=POD/LOC
3. DWLOC (ppb) = PAD (ppb)

5.4.2.3 Chronic Dietary (Drinking Water) Risk Assessment

Propazine
The 4-day dietary risk assessments (Section 5.4.2.2) are protective for chronic dietary exposures since the POD and endpoint used for the 4-day assessment are the most sensitive for any duration, and is therefore protective of longer durations of exposure.

Hydroxypropazine
The lowest chronic DWLOC for hydroxypropazine is for all infants (<1 year old) at 1300 ppb as shown in Table 5.4.2.3. The chronic DWLOCs are greater than the chronic EDWCs for THTs in surface water or ground water (Table 5.3; highest chronic THT EDWC = 76 ppb); there is no chronic dietary risk of concern.

Table 5.4.2.3. Chronic DWLOC Calculations- Hydroxypropazine					
Age(years) /Population	**POD (mg/kg/day)**	**LOC**	**Chronic PAD (mg/kg/day)[1]**	**Water Ingestion Rate (L/kg) [2]**	**Chronic DWLOC (ppb)[3]**
All Infants (< 1 year old)	6.76	100	0.0676	0.0540	1300
Children 1-2 years old	6.76	100	0.0676	0.0302	2200
Children 6-12 years old	6.76	100	0.0676	0.0184	3700
Youth 13-19 years old	6.76	100	0.0676	0.0153	4400
Females 13-49 years old	6.76	100	0.0676	0.0209	3200

[1] PAD=POD/LOC
[2] Water ingestion rates from 2003-2008 NHANES/WWEIA consumption database averaged values.
[3] DWLOC (ppb) = PAD (mg/kg/day) /[water consumption (L/kg) * 0.001 mg/ug]

6.0 Residential Exposure/Risk Characterization

There are no proposed or existing residential uses for propazine; therefore, a residential exposure assessment has not been conducted.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and

risks from three major sources: food, drinking water, and residential exposures. There are no residential uses of propazine and exposures to propazine in food are expected to be negligible. Exposures are only expected from drinking water and there are no risks estimates of concern for this pathway. There are no aggregate risks of concern for propazine.

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).
During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for propazine.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products. The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[25] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of propazine. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at

[25] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs).*
A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[26] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

9.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Propazine is used on sorghum and can be applied via groundboom and aerial application equipment. Spray drift is not expected from applications to greenhouse-grown ornamentals; applications occurring in greenhouses are unlikely to result in spray drift. Propazine is a soil-directed herbicide; therefore, applications via airblast sprayers are not anticipated. Therefore, the recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[27]

Although there are no chemical-specific TTR data for propazine, TTR data are available for atrazine (K. Rickard, D443002, 09/26/2017) and simazine (R. Travaglini, D261346, 08/15/2001). Simazine and atrazine TTR data are a suitable surrogate for propazine because all three chemicals are members of the *s*-triazine family, share a common mechanism of toxicity, and share similar physicochemical properties. The simazine TTR data provided the highest/most

[26] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift
[27] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

protective Day 0 residue estimates; therefore, the propazine non-occupational spray drift assessment incorporated simazine transferrable residues.

MRID 44958701: *Turf Transferrable Residues for Simazine Applied to Turf*

Study Summary: TTR data are available for simazine. The study was conducted in California and Florida on two different test plots in each state, for irrigated and non-irrigated plots using an emulsifiable concentrate type formulation of simazine. One application of 2.0 lb ai/A was applied to each test plot. Applications were made in California using a tractor-mounted, groundboom, broadcast tank sprayer. Applications were made in Florida using a backpack sprayer. Samples were collected at the following intervals: one day prior to the application (control and fortified samples), immediately after the application, 4 hours after application, and at Days 1, 3, 7, 10, 14, 21, 28 and 35 after the application. Four replicate samples were collected at each sampling interval. The turf transfer samples were "dislodged" as a part of the extraction phase of the analytical method. Therefore, the residues were not dislodged until the day of extraction (from 15 days to 72 days after sampling). The data from the non-irrigated California site was used in the non-occupational spray drift exposure and risk assessment because it provided the most conservative residues. The data and the results of the pseudo-first order statistical analysis for the non-irrigated California site are summarized below in Table 9.1.1 and in D428625 (K. Rickard, 06/12/2018) for all sites. These data were used to generate a 4-day average residue estimate (0.349 µg/cm^2) for use in the non-occupational spray drift assessment to estimate dermal and incidental oral exposures because the POD is based on decreased LH surge and available toxicity data indicate that the decrease occurs after a 4-day exposure. The 4-day average residue was adjusted in the assessment for any differences between the study application rate and the registered application rates for propazine.

Table 9.1.1. Summary Statistics for "Turf Transferrable Residues for Simazine Applied to Turf" (MRID No. 44958701, D261346).

Statistic	California
	Non-Irrigated
Application Rate (lb ai/A)	2.0
Measured Average Day 0 Residue (µg/cm^2)	0.2698
Predicted Day 0 Residue (µg/cm^2)	**0.385**
Slope	-0.068
Half-Life (days)	10.2
R^2	0.8515
4-Day Average Residue (µg/cm^2)	0.349

There were no dermal risk estimates of concern from indirect spray drift exposure to propazine at the field edge for adults; the screening-level MOEs range from 140 to 200 (LOC = 30). For children 1 to < 2 years old, dermal and incidental oral risk estimates were combined because the toxicity endpoint for each route of exposure is LH surge attenuation. The total applicable LOC is 30. There were no combined dermal and incidental oral risk estimates of concern from indirect spray drift exposure to propazine at the field edge for children 1 to < 2 years old; combined dermal and incidental oral screening-level MOEs range from 93 to 130 (LOC =30). Non-occupational spray drift risk estimates are provided in Table 9.1.2; and in D428625 (K. Rickard, 06/12/2018).

Table 9.1.2. Summary of Risk Estimates Resulting from Spray Drift At the Field Edge Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Propazine[2].								
Crop	Application rate (lb ai/A)	Distance From Field Edge	Adult Dermal MOEs[2]			Children 1 < 2 years old Combined Dermal + Incidental Oral MOEs[2]		
			LOC = 30			LOC = 30		
		(Feet)	Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Sorghum	1.2	0	140	200	N/A	93	130	N/A

1. Risk estimates presented assuming screening-level droplet sizes (fine to medium for aerial applications; very fine to fine for groundboom applications), sparse canopies for airblast applications; and high booms for groundboom applications. Assuming coarser droplet sizes and lower booms will reduce risks.
2. Algorithms, assumptions, and calculations for the non-occupational spray drift assessment are provided in Appendix B (D428625). "N/A" provided when equipment not applicable based on the use pattern.

10.0 Cumulative Exposure/Risk Characterization

A CRA begins with the identification of a group of chemicals that induce a common toxic effect by a common mechanism of toxicity called a CMG. Atrazine, simazine, and propazine, and the metabolites DEA, DIA, and DACT, are considered a CMG due to the common neuroendocrine mechanism of toxicity which results in both reproductive and developmental alterations (USEPA, 2002). This common mechanism determination was done in accordance with OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) which describes the process for establishing CMGs. In 2006, a CRA was conducted which combined atrazine, simazine, DEA, DIA, and DACT. At that time, propazine was not included in the cumulative assessment group (CAG) because the limited use pattern (import tolerance on sorghum; greenhouse use), which would not result in drinking water exposure, precluded any reasonable likelihood of co-exposure with other chlorotriazines.

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[28] and conducting CRA[29]. A separate updated CRA with atrazine, simazine, propazine, and their common metabolites is available (K. Rickard *et al.,* D447476, 07/10/2018). Propazine is included in the CAG based on the potential for food and drinking water exposures from the currently registered domestic use on sorghum.

[28] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)
[29] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

11.0 Occupational Exposure/Risk Characterization

11.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios listed in Table 11.1.1.

Occupational Handler Exposure Data and Assumptions

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

Application Rate: The registered application rates for propazine are provided in Table 3.3.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[30]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[31].

Area Treated or Amount Handled: The area treated/amount handled are based on ExpoSAC Policy 9.1.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or

[30] Available: https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[31] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For propazine, based on the registered use, both short- and intermediate-term exposures are expected for occupational handlers. Propazine is also registered for use in greenhouses, and while crops may be grown year round in greenhouses, occupational exposures are considered more like a series of short-term exposures, rather than a continuous long-term exposure. However, for the chlorotriazine herbicides, only 4-day exposure durations will be assessed since these are protective for longer durations of exposure.

Shower Timing: Occupational handler dermal PODs were derived in the PBPK model assuming a shower occurred 24 hours after initial exposure.

Mitigation/Personal Protective Equipment: The registered label requires occupational handlers to wear baseline attire (long sleeved shirt, long pants, shoes, and socks), chemical resistant gloves, and protective eyewear. A chemical-resistant apron must also be worn when mixing/loading, cleaning up spills, cleaning equipment, or when otherwise exposed to the concentrate. Mixer/loaders supporting aerial applications must use a closed system along with the PPE required for mixer/loaders. Flaggers supporting aerial applications must use an enclosed cab. Results are presented for "baseline attire," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks chemical resistant gloves, the lowest level of PPE consistently required for occupational handlers. Results are also presented with various levels of additional PPE as necessary (e.g., double layer of clothing, respirator, etc.).

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in D428625 (K. Rickard, 06/12/2018).

Combining Exposures/Risk Estimates:
Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes are the same. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
The occupational handler exposure and risk assessment indicates that the combined dermal and inhalation risk estimates are not of concern (MOEs > 30) with baseline attire + label specified PPE (chemical resistant gloves), except for the following scenarios:

- Mixing/loading/applying liquids via backpack spray equipment to greenhouse ornamentals (MOE = 26, LOC = 30).
    - *This scenario is not of concern with a double layer of clothing (MOE = 41, LOC = 30).*
- Mixing/loading/applying liquids with a mechanically pressurized handgun to greenhouse ornamentals (MOE = 3.1, LOC = 30).
    - *This scenario is **still of concern** assuming a double layer of clothing and a PF10 respirator (MOE = 7.7, LOC = 30).*

Dermal exposures are the highest contributors to the combined dermal + inhalation risk estimates.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propazine[1].

Exposure Scenario	Crop or Target	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal	Inhalation	Total
				MOE[4] (LOC = 30) [PPE/Mitigation]	MOE[5] (LOC = 30) [PPE/Mitigation]	MOE[6] (LOC = 30) [PPE/Mitigation]
Mixer/Loader						
Mixing/Loading Liquids for Aerial Application	Sorghum	1.2 lb ai/A	1,200 Acres	39 [SL/G]	390 [No R]	35 [SL/G, No R]
Mixing/Loading Liquids for Groundboom Application	Greenhouse Ornamentals	1.5 lb ai/A	60 Acres	620 [SL/G]	6,300 [No R]	560 [SL/G, No R]
	Sorghum	1.2 lb ai/A	200 Acres	230 [SL/G]	2,400 [No R]	210 [SL/G, No R]
Applicator						
Applying Sprays via Aerial Equipment	Sorghum	1.2 lb ai/A	1,200 Acres	700 [EC]	18,000 [EC]	670 [EC]
Applying Sprays via Groundboom Equipment	Greenhouse Ornamentals	1.5 lb ai/A	60 Acres	4,100 [SL/G]	4,100 [No R]	1,000 [SL/G, No R]
	Sorghum	1.2 lb ai/A	200 Acres	540 [SL/G]	1,500 [No R]	400 [SL/G, No R]
Flagger						
Flagging for Aerial Sprays	Sorghum	1.2 lb ai/A	350 Acres	420 [SL/G]	850 [No R]	280 [SL/G, No R]
Mixer/Loader/Applicator						
Mixing/Loading/Applying Liquids via Backpack Sprayers	Greenhouse Ornamentals	0.15 lb ai/gal	40 gals	31 [SL/G] 56 [DL/G]	150 [No R]	**26 [SL/G, No R]** 41 [DL/G, No R]
Mixing/Loading/Applying via Manually-Pressurized Handwand			40 gals	810 [SL/G]	690 [No R]	370 [SL/G, No R]
Mixing/Loading/Applying via Mechanically-Pressurized Handguns			1,000 gals	**5.6 [SL/G]** **8.7 [DL/G]**	**6.9 [No R]** 34 [PF5] 69 [PF10]	**3.1 [SL/G, No R]** **4.8 [SL/G, PF5]** **5.2 [SL/G, PF10]** **7.7 [DL/G, PF10]**
				31 [SL/G] 56 [DL/G]	150 [No R]	**26 [SL/G, No R]** 41 [DL/G, No R]

1 Results are presented assuming baseline attire and chemical resistant gloves unless otherwise specified. Applying via aerial application equipment is considered in a closed system/engineering control (EC). Risk estimates of concern are in bold.
2 Based on EPA Reg. No. 42750-148.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (30.4 mg/kg/day) ÷ Dermal Dose (mg/kg/day). Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).
5 Inhalation MOE = Inhalation POD (1.8 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

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

11.2 Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Dermal Post-Application Risk

Occupational Post-application Dermal Exposure Data and Assumptions

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

Exposure Duration: For propazine, both short- and intermediate-term post-application exposure could occur for the proposed agricultural use. Propazine is also registered for use in greenhouses, and while crops may be grown year round in greenhouses, occupational exposures are considered more like a series of short-term exposures, rather than a continuous long-term exposure. However, for the chlorotriazine herbicides, only 4-day exposure durations are applicable.

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the

absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[32]" which, along with additional information about the ARTF data, can be found at the Agency website[33]. Table 8.2.2.2 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

Application Rate: The registered application rates are provided in Table 3.3.

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

Shower Timing: Occupational post-application dermal PODs were derived in the PBPK model assuming a shower occurred 24 hours after initial exposure.

Dislodgeable Foliar Residues: Chemical-specific dislodgeable foliar residue (DFR) data have not been submitted for propazine; however, chemical-specific DFR data on field corn are available for atrazine. Atrazine DFR data are suitable surrogates for simazine because both chemicals share many physicochemical properties, they are both members of the *s*-triazine family, and share a common mechanism of toxicity. Therefore, this assessment uses DFR data available on corn foliage treated with atrazine. The DFR study was secondary reviewed and found to be acceptable for risk assessment (K. Rickard, D442405, 09/26/2017). The predicted day 0 residues were adjusted in the occupational post-application assessment for any differences between the study application rate and the registered application rates for propazine.

MRID 44883601: *Dissipation of Dislodgeable Foliar Residues of Atrazine on Field Corn*

Study Summary: The corn DFR study was conducted at one site in Missouri. Atrazine was applied once to field corn in two different formulations; Atrazine 4L is a suspension concentrate containing 4.0 lb ai/gallon and Atrazine 90 DF is a water dispersible granular formulation containing 90% atrazine. Atrazine 4L was applied at a rate of 2.0 lb ai/A and Atrazine DF was applied at a rate of 2.5 lb ai/A. Applications were made with CO_2-pressurized backpack sprayers equipped with flat fan 8002 nozzles. Samples were collected when corn was 12 inches high. Leaf punch samples were collected at the following intervals: 4 and 12 hours after application, and 1, 2, 3, 5, and 7 day(s) after treatment (DAT). Each of the treated plots were divided into three subplots and at each sampling interval, one sample was taken from each subsection. Random samples were collected from both the control and the two treated test plots at each sampling interval. The dislodging procedure was started within one hour of sample collection. Average residues of atrazine were 2.638 µg/cm^2 four hours after application and declined to 0.0937 µg/cm^2 7DAT. The data and the results of the pseudo-first order statistical analysis are summarized below in Table 11.2.1.1. The predicted DAT0 residue value of 2.486 µg/cm^2 was used to estimate dermal risk from contact with treated sorghum and greenhouse ornamentals. The

[32] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[33] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

DFR values from the atrazine liquid formulation were used as a surrogate for the registered liquid formulations of propazine.

Table 11.2.1.1. Review of Dissipation of Dislodgeable Foliar Residues of Atrazine on Field Corn (D442405)	
Corn DFR (liquid) MRID # 44883601	
Statistic	**Atrazine 4L (Missouri)**
Application Rate (lb ai/A), Target Application Rate = 2.5 lb ai/A	2
Measured Average Day 0 Residue (µg/cm^2)	2.638
Predicted Day 0 Residue (µg/cm^2)	2.486
Slope	-0.449
Half-Life (days)	1.5
R^2	0.95

Occupational Post-Application Non-Cancer Dermal Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in D428625 (K. Rickard, 06/12/2018).

Occupational Post-Application Non-Cancer Dermal Risk Estimates

Using atrazine-specific DFR data and assuming predicted TTR and DFR residues on the day of application because post-application workers (especially scouters) could move from field to field encountering day 0 residue estimates, the occupational post-application MOEs are not of concern for the registered uses of propazine on the day of application for all scenarios. The occupational post-application MOEs range from 120 to 2,500 (LOC = 30). All post-application risk estimates are presented in Table 11.2.1.2. Although the atrazine data represent outdoor applications, they were also used to represent the use of propazine in greenhouses, which could result in residues dissipating more slowly. Because both chemicals share many physicochemical properties, they are both members of the *s*-triazine family, and share a common mechanism of toxicity, these data were considered appropriate for use in the propazine post-application assessment.

Table 11.2.1.2. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Propazine[1].

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	DFR[1]	Dermal Dose (mg/kg/day)[2]	MOE[3]
Greenhouse Vegetables	Hand Harvesting, Pinching, Pollination, Hand Pruning, Scouting, Turning, Tying/training, Hand Weeding, Propagating	1,200	1.86	0.2594	120
	Irrigation (Hand Watering)	230		0.0050	610
Greenhouse Ornamentals	Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training				
Sorghum	Scouting	210	1.49	0.03631	840
	Hand Weeding	70		0.012104	2,500

1 DFR = From MRID 44883601 (study application rate = 2.0 lb ai/A, day 0 concentration = 2.636 ug/cm^2) and adjusted for the registered application rates (1.5 lb ai/A for greenhouse crops and 1.2 lb ai/A for sorghum).
2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).
3 MOE = POD (30.4 mg/kg/day) ÷ Daily Dermal Dose.
4 DAT = Day after Treatment/Application for MOE to be greater than the LOC (30).

Restricted Entry Interval

Propazine is classified as Toxicity Category IV for acute dermal toxicity, eye irritation, and skin irritation potential. It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Post-application risk estimates were not of concern on the day of application. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to atrazine. All REIs on the propazine labels are 24 hours; therefore, are considered protective of post-application exposure.

11.2.2 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for propazine.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

12.0 Incident Data Review

HED performed an updated Tier I review of human incidents for the triazine herbicides (atrazine, propazine and simazine) using the following sources: OPP Incident Data System (IDS); the National Pesticide Information Center (NPIC); the California Pesticide Illness Surveillance Program (CA PISP); and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases (S. Recore *et. al*., D444041, 11/01/2017). The Agricultural Health Study (AHS) findings and epidemiological investigations for the triazines are reviewed in separate documents (A. Aldridge, D447696, 07/09/2018 and A. Aldridge, D447697, 07/09/2018).

No propazine incidents were reported to IDS, NPIC, CA PISP, or SENSOR-Pesticides and there does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

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Appendix A. Toxicology Profile and Executive Summaries

A.1.1 Toxicology Data Requirements - Propazine

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

Table A.1.1. Summary of Toxicological Data Requirements for Propazine.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Nonrodents	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	waived[1]
870.3250	90-Day Dermal Toxicity	yes	waived[1]
870.3465	90-Day Inhalation Toxicity	yes	waived[1]
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b	Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5385	Mutagenicity—Mammalian Bone Marrow Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Unscheduled DNA Synthesis	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	waived[1]
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	waived[1]
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

1. K. Rury, TXR# 0056587, 04/16/2013

A.2.1 Toxicity Profiles - Propazine

Table A.2.1.1. Acute Toxicity Profile - Propazine technical				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral	43474101	LD_{50} > 5050 mg/kg	IV
870.1200	Acute Dermal	43474102	LD_{50} > 5050 mg/kg	IV
870.1300	Acute Inhalation	43474103	LC_{50} > 1.22 mg/L	III
870.2400	Primary Eye Irritation	43474104	Slight irritant	IV
870.2500	Primary Dermal Irritation	43474105	Negative	IV
870.2600	Dermal Sensitization	43474106	Negative	N/A

Table A.2.1.2 Subchronic, Chronic and Other Toxicity Profile for Propazine		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200 21/28-Day ghupdo#wr{lflw| (rat)	7745:734# 3/#43/#433#u#4333#pj2nj2gd|#	# v|whpl f#QRDHO#@#433#pj2nj2gd|# # v|whpl f#ORDHO#@#4333#edvhg#rq#ghfuhdvhg#erg|#zhljkw#jdlq
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.
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 ≥ 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 ≥ 50 mg/kg/day LOAEL: not identified)
870.4100b Chronic toxicity (dog)	46654401 0, 50, 200, or 750 ppm (1.64, 6.50, and 23.94 mg/kg/day for males and 1.65, 6.72, and 23.98 mg/kg/day for females, respectively)	LOAEL: not established ♂ LOAEL: decreased body weight ♀ NOAEL: ≥ 23.04 mg/kg/day ♂ NOAEL: 6.72 mg/kg/day ♀
870.4200	00041408	NOAEL = 5.2 mg/kg/day (M); 6.4 mg/kg/day (F)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Carcinogenicity (rat)	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	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
870.7485 Metabolism and pharmacokinetics (rat)	43689801 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.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		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

A.2.3 Toxicity Profiles – Hydroxyatrazine

Table A.2.5. Subchronic, Chronic and Other Toxicity Profile for Hydroxyatrazine.

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.

Table A.2.5. Subchronic, Chronic and Other Toxicity Profile for Hydroxyatrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
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.

A.3 Additional Evaluation Information on the PBPK Model

In the 2015 PBPK model, the values of metabolism-related parameters were derived from an *in vitro* approach that described the time-course concentration profiles of atrazine, DIA, DEA and DACT in incubation media for an intact hepatocyte suspension assay. The rat *in vitro* model was optimized to fit the measured decline in cell viability over time during the incubations. The *in vitro* model is comprised of four differential equations describing the rate of metabolism of atrazine, the rate of formation of DIA and DEA from atrazine, and the rate of formation of DACT from DIA and DEA. As in the previous work with atrazine (McMullin et al, 2007a,b), competitive metabolic inhibition was included to account for the interactions between atrazine, DIA, and DEA. The metabolism of atrazine was described with a single set of parameters and the rates of formation of DIA and DEA were set as a fraction of total atrazine metabolism. Parameters included in the *in vitro* model are shown in Table 4.6.2.4.1 To simplify the estimation of metabolic rates, the affinity constants published in McMullin et al. (2007b) were fixed as constants in this *in vitro* model. The only parameters optimized to fit the data were the fraction of DIA produced from atrazine and the maximum rates of metabolism (Vmax) for atrazine, DIA and DEA. DACT formation was described as the sum of DIA and DEA metabolism. Parameter estimation was conducted in the following order: first, the Vmax for atrazine and the fraction metabolized to DIA and DEA were estimated. Then, the Vmax's for metabolism of DEA and DIA to DACT were estimated. After fitting the DIA and DEA data, there appeared to be an additional clearance of DACT based on the declining slope in the terminal phase of the incubations. Thus, a first-order elimination rate for DACT was added to the model to account for this loss, which was presumably due to glutathione conjugation. The estimated maximum velocities were scaled to rat and human whole body based on the estimated rate multiplied by the number of hepatocytes in the whole liver, and then divided by the body weight to the ¾ power. The resulting rates were input into the PBPK model with the units of µmol/hr/kg $BW^{0.75}$. Overall, the *in vitro* intact hepatocyte model was able to predict both the Syngenta and McMullin et al. (2007b) intact hepatocyte *in vitro* assay data (Figures A.3.1 – A.3.3).

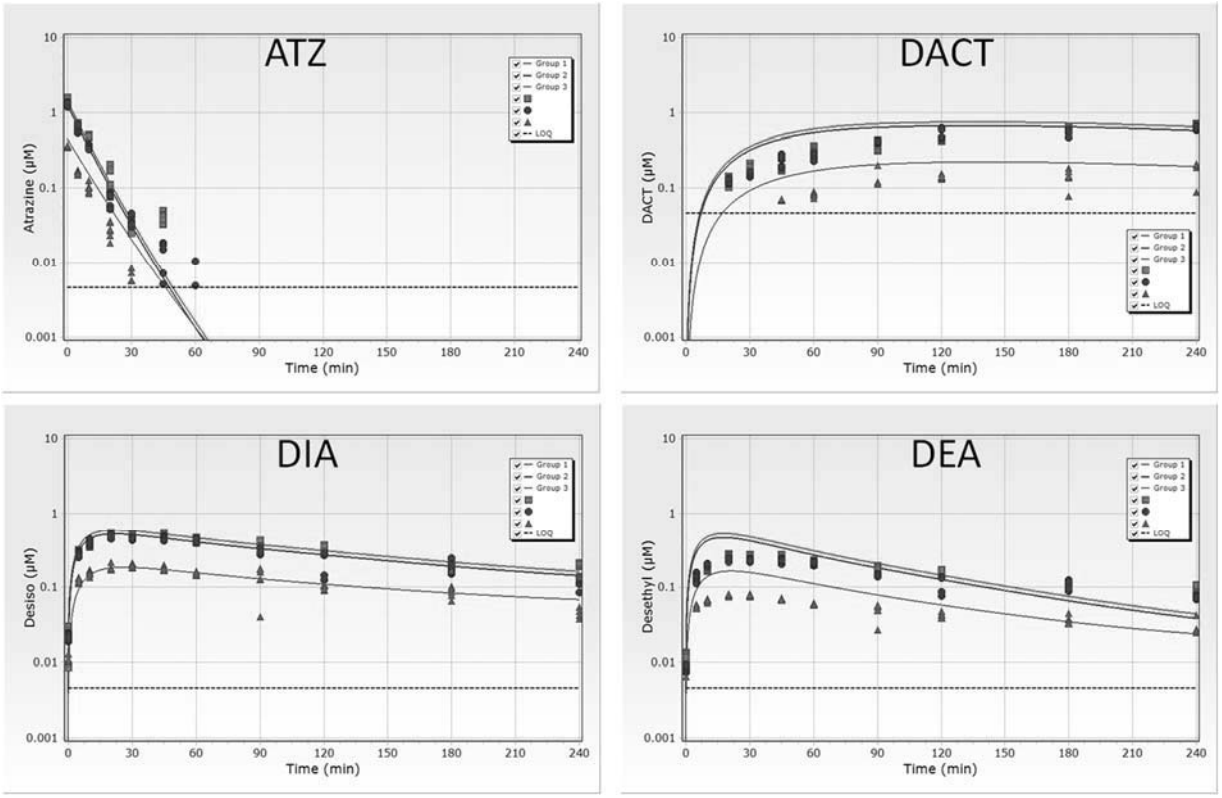

Figure A.3.1. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.26 µM – Group 2, and 0.45 µM – Group 3).

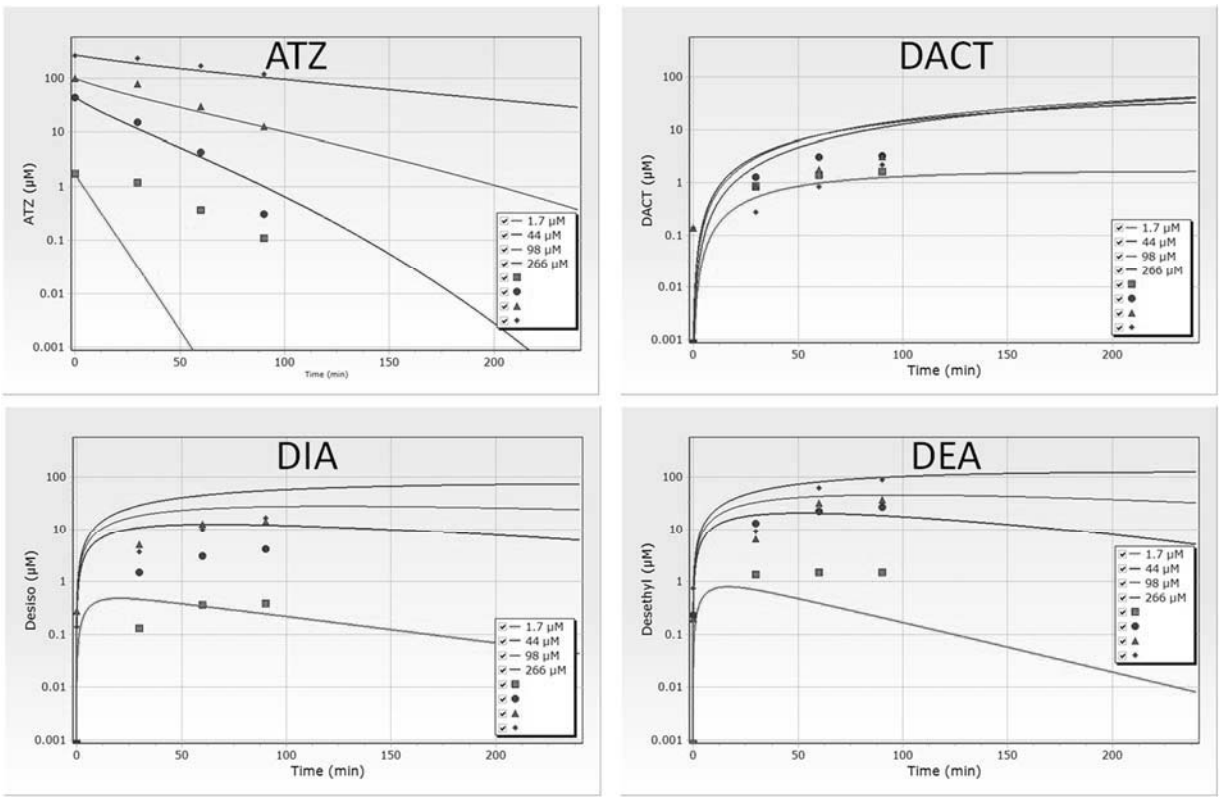

Figure A.3.2. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (McMullin et al., 2007).

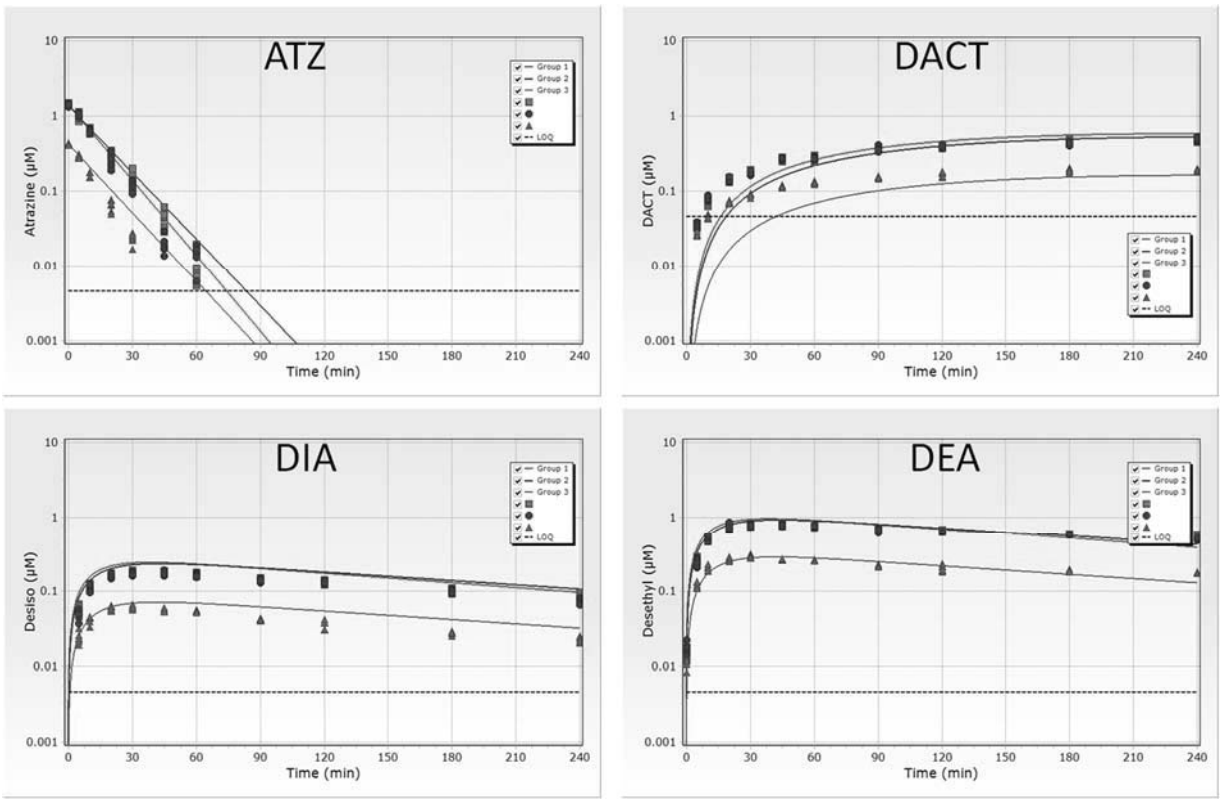

Figure A.3.3. Model prediction of intact human hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.38 µM – Group 2, and 0.42 µM – Group 3).

To evaluate the performance of the PBPK model, model-predicted time course plasma concentrations after single bolus dosing and repeated dosing in rats were compared to observed data (Figures A.3.4 – A.3.6). Overall, the model was able to predict oral bolus and dietary intake with the same set of rate constants and the assumption of complete bioavailability of ATZ, DIA and DEA. For both the single and multiple oral dose studies, the model adequately described the measured plasma concentrations of ATZ, DIA, DEA, and DACT (Figures A.3.4 and A.3.5), even though there was a transient over-prediction of the peak DEA concentrations compared to the experimental data. For the dietary study, the model provided good fits to the measured data during the exposure, including the slow increase to pseudo-steady state concentrations for DACT (Figure A.3.6). The model prediction of the initial clearance following withdrawal from exposure was also acceptable. While the terminal phase of the clearance appears to be over-predicted, almost all data points were at or below the limit of quantification (LOQ) for the analytical methods; therefore, it is not possible to determine whether the discrepancy is of a biological or analytical nature. Moreover, the difference represents an extremely small fraction of the dose (<0.1%). In addition to rat model simulations, the human model was used to simulate humans exposing to atrazine via a single oral dose at 100 µg/kg, and the predicted plasma concentrations were compared to measured DIA and DACT concentrations in a human study (Figure A.3.7).

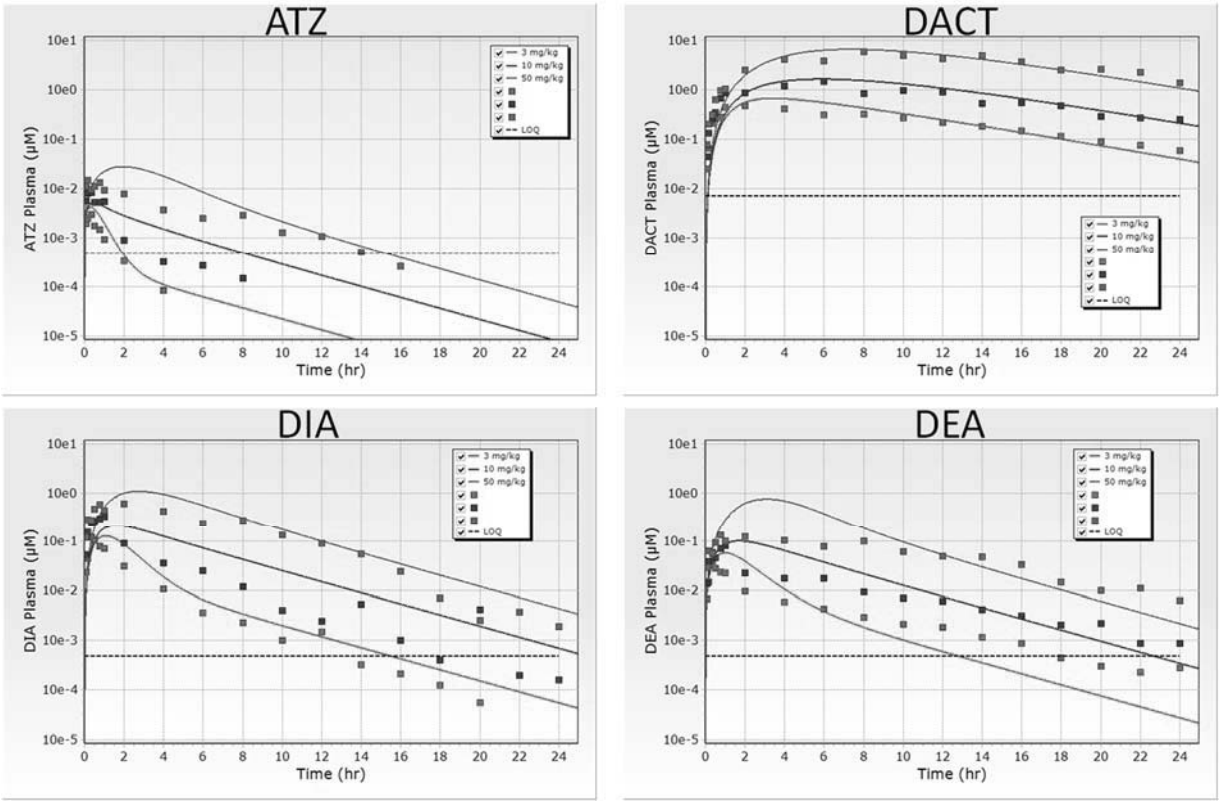

Figure A.3.4. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats after a single gavage dose of atrazine at 3, 10 and 50 mg/kg.

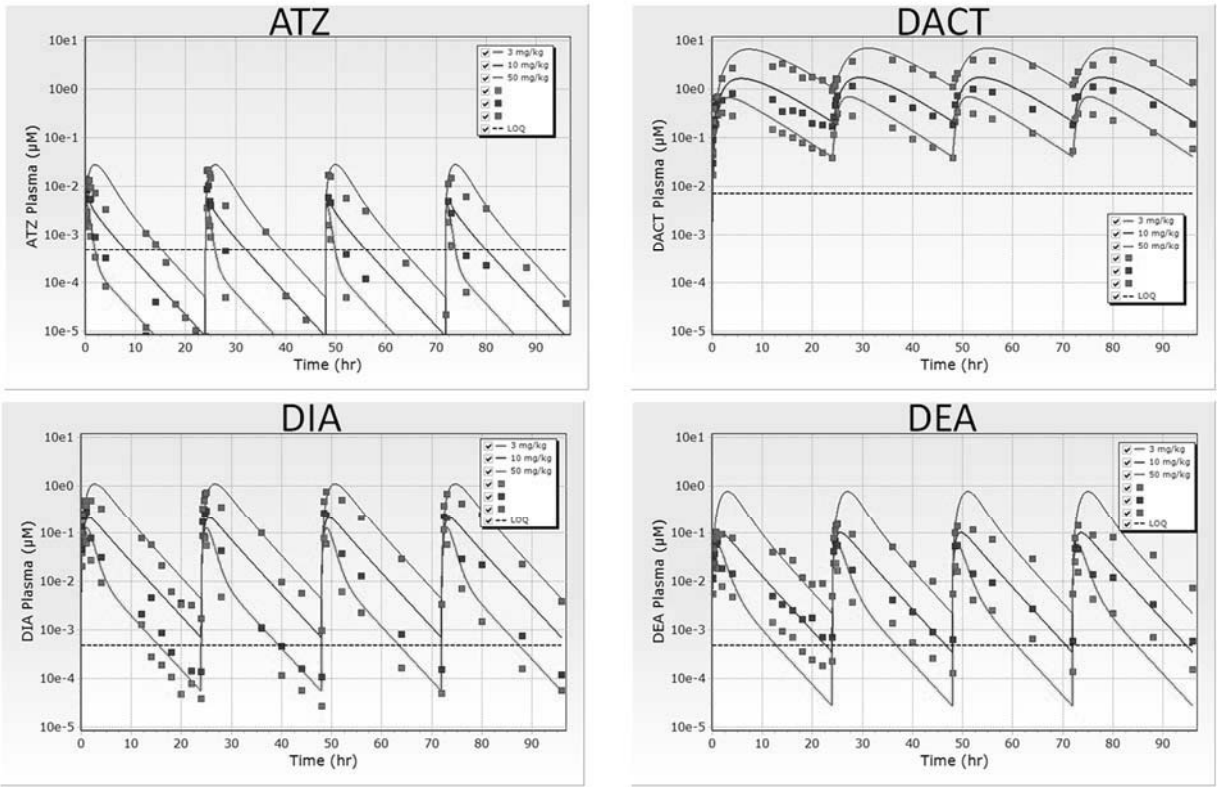

Figure A.3.5. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated daily gavage doses of atrazine at 3, 10 and 50 mg/kg.

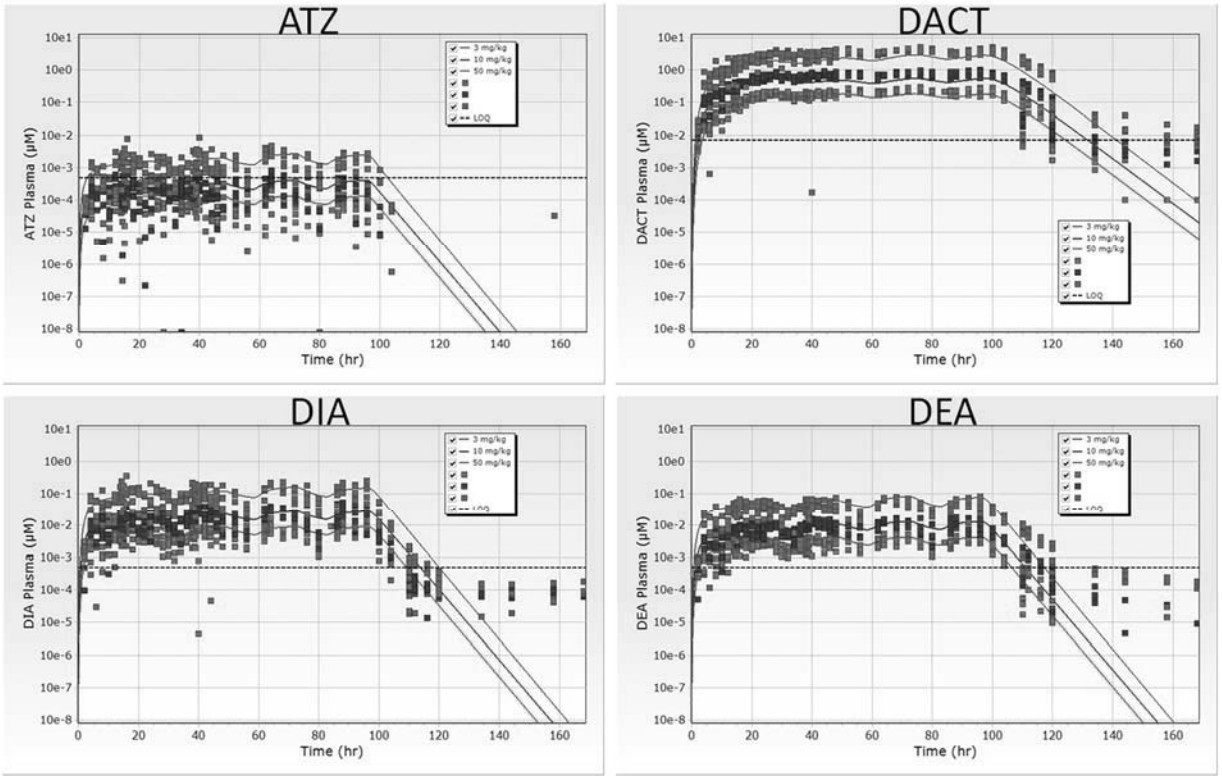

Figure A.3.6. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated dietary exposure to atrazine at 3, 10 and 50 mg/kg.

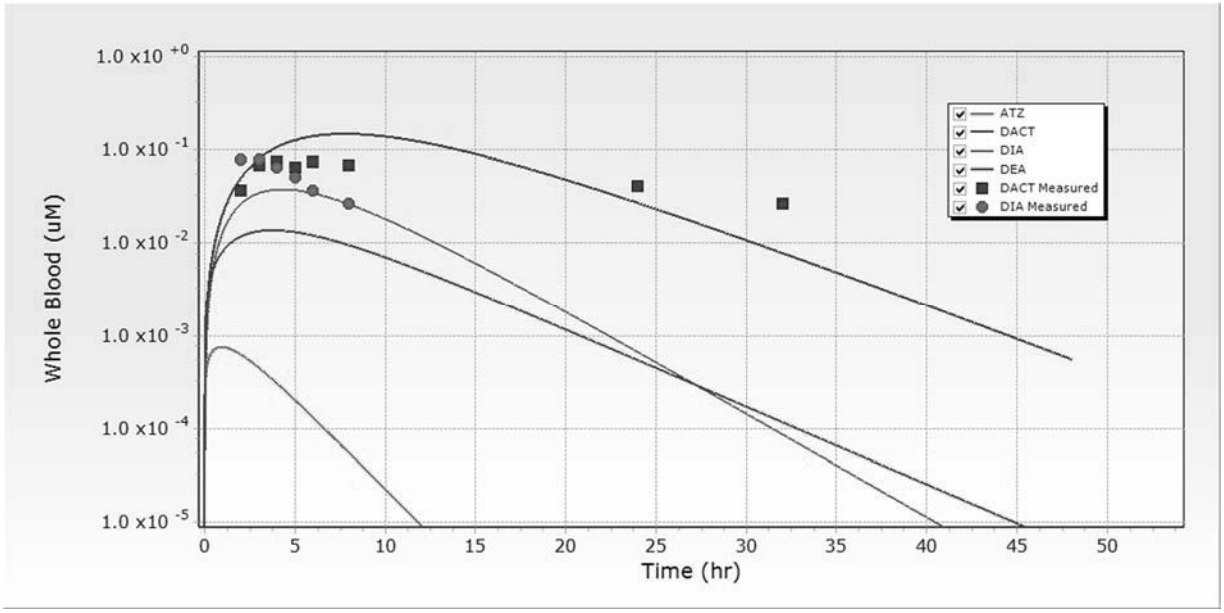

Figure A.3.7. Model simulations of atrazine, DIA, DEA, and DACT concentrations in the plasma of humans exposed to a single oral dose of 100 µg/kg atrazine.

An independent external review of the model code and parameter values was performed by the Health Impacts and Exposure Science Group at the Pacific Northwest National Laboratory (PNNL). The PNNL is one of the U.S. Department of Energy's ten national laboratories to support national needs in nuclear energy, environmental management, and national security. After the first review, PNNL identified multiple areas for improvement. In response to PNNL's comments, researchers at the Hamner Institutes and Syngenta have updated and refined the model. EPA confirmed that PNNL's recommended changes were incorporated and, in addition, has performed additional evaluation of the model inputs and outputs which led to additional improvements. All model code and parameters for the PBPK model are provided in the public docket for the triazine risk assessment.

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Propazine.		
Parameter	Value	Reference
Melting point	217.7 °C	RD S. Malak, D219079, 09/26/1995
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 S. Malak, D219079, 09/26/1995
Dissociation constant, pK	Not applicable; practically insoluble in water.	RD S. Malak, D219079, 09/26/1995
Octanol/water partition coefficient	P = 1234.7 Log P = 3.08	
UV/visible absorption spectrum	Not available	

Appendix C. Tolerance/MRL Tables

Propazine (PC Code 080808)

Table C.1 Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR § 180.243 (a) General: the sum of propazine, 6-chloro-N,N'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine, and its metabolites 6-chloro-2-N-(1-methylethyl)-1,3,5-triazine-2,4-diamine, and 6-chloro-1,3,5-triazine-2,4-diamine, calculated as the stoichiometric equivalent of propazine, in or on the commodity.		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Sorghum, grain, forage	0.20			
Sorghum, grain, grain	0.15			
Sorghum, grain, stover	0.15			
Completed: W. Donovan; 07/10/2018				

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

Appendix D. Benchmark Dose Analysis for Hydroxyatrazine: Chronic Dietary Endpoint Based on Renal Histopathological Effects in Rats

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using all available dichotomous models for incidence data for various histopathological renal lesions in male and female rats from a combined chronic toxicity/oncogenicity study (MRID 43532001) in the rat. Criteria used to assess the best fit included statistical (goodness-of-fit) values, model criteria (Akaike Information Criteria; AIC), BMD/BMDL ratios, visual inspection of fits, and comparison of male and female dose-response relationships. The benchmark dose response (BMR) level of 10% extra risk for quantal incidence data was chosen as a biologically significant change. Table D.1 summarizes the results of BMD analyses of the various renal lesions. The female rat data provided a slightly lower POD (a $BMDL_{10}$ of 6.76 mg/kg/day) based on renal lesions, specifically, fibrosis of the papillary interstitium. The incidence of fibrosis of the renal papillary interstitium that was modeled are summarized in Table D.2. Based on the criteria to assess the best fit, the Log-logistic model resulted in the best fit of the data. Figures D.1 and D.2 present the BMDS outputs for male and female rats.

Table D.1. BMD modeling results for various renal histological lesions in the rat after exposure to hydroxyatrazine in the diet for 2 years.

Kidney Lesion	Males		Females	
	BMD_{10}	**$BMDL_{10}$**	**BMD_{10}**	**$BMDL_{10}$**
Dilation with crystal deposits	7.979 Gamma AIC 49.05	7.353	7.924 Gamma AIC 94.96	6.797
Inflammation, acute	14.61 Multistage AIC 111.77	11.92	17.34 Multistage AIC 96.73	12.91
Intrinsic arteries, mineralization	no reliable fits		19.21 Multistage AIC 108.379	15.67
Mineralization	13.65 Multistage AIC 265.88	7.572	12.22 Multistage AIC 306.176	7.563
Nephropathy, progressive	no reliable fits		no reliable fits	
Papilla, accumulation interstitial matrix	no reliable fits		no reliable fits	
Papilla, fibrosis interstitial	7.582 LogLogistic AIC 104.798	6.967	7.724 LogLogistic AIC 97.83	6.760
Pelvis, dilatation with crystal deposits	7.510 Multistage AIC 129.35	6.585	8.630 Multistage AIC 166.72	6.537
Transitional cell erosion	22.88 Quantal-Linear AIC 67.05	13.84	23.27 Quantal-Linear AIC 74.45	14.72
Transitional cell hyperplasia	13.29 Logistic AIC 304.18	9.199	10.14 Logistic AIC 243.98	8.749

Table D.2. Incidence of fibrosis of the renal papillary interstitium in male and female rats following administration of hydroxyatrazine in the diet for 2 years.					
Sex	**Dose and incidence**				
Male	0 mg/kg/day	0.388 mg/kg/day	0.962 mg/kg/day	7.75 mg/kg/day	17.4 mg/kg/day
Male	1/79	2/69	1/70	11/70**	80/80**
Female	0 mg/kg/day	0.475 mg/kg/day	1.17 mg/kg/day	9.53 mg/kg/day	22.3 mg/kg/day
Female	0/79	0/70	0/68	20/69**	79/80**

** Significantly different from control, $p \leq 0.01$

Figure D.1. BMDS Output for the Log-Logistic model of fibrosis of the renal papillary interstitium incidence data for male rats administered hydroxyatrazine in the diet for 2 years

```
 ================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/Users/jliccion/BMDS260/BMDS2601_20150629/BMDS2601/Data/lnl_Dax_Setting.(d)
        Gnuplot Plotting File:
C:/Users/jliccion/BMDS260/BMDS2601_20150629/BMDS2601/Data/lnl_Dax_Setting.plt
                                            Wed Nov 04 11:40:47 2015
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0126582
                     intercept =     -4.08858
                         slope =       2.3427


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by
the user,
```

and do not appear in the correlation matrix)

	background	intercept
background	1	-0.18
intercept	-0.18	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0183485	0.00908927	0.000533865	0.0361632
intercept	-38.6622	0.370829	-39.3891	-37.9354
slope	18	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-50.1002	5			
Fitted model	-50.3992	2	0.598094	3	0.8969
Reduced model	-210.17	1	320.14	4	<.0001
AIC:	104.798				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0183	1.450	1.000	79.000	-0.377
0.3880	0.0183	1.266	2.000	69.000	0.658
0.9620	0.0183	1.284	1.000	70.000	-0.253
7.7500	0.1571	11.000	11.000	70.000	-0.000
17.4000	1.0000	80.000	80.000	80.000	0.015

Chi^2 = 0.64 d.f. = 3 P-value = 0.8873

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.58244

BMDL = 6.96693

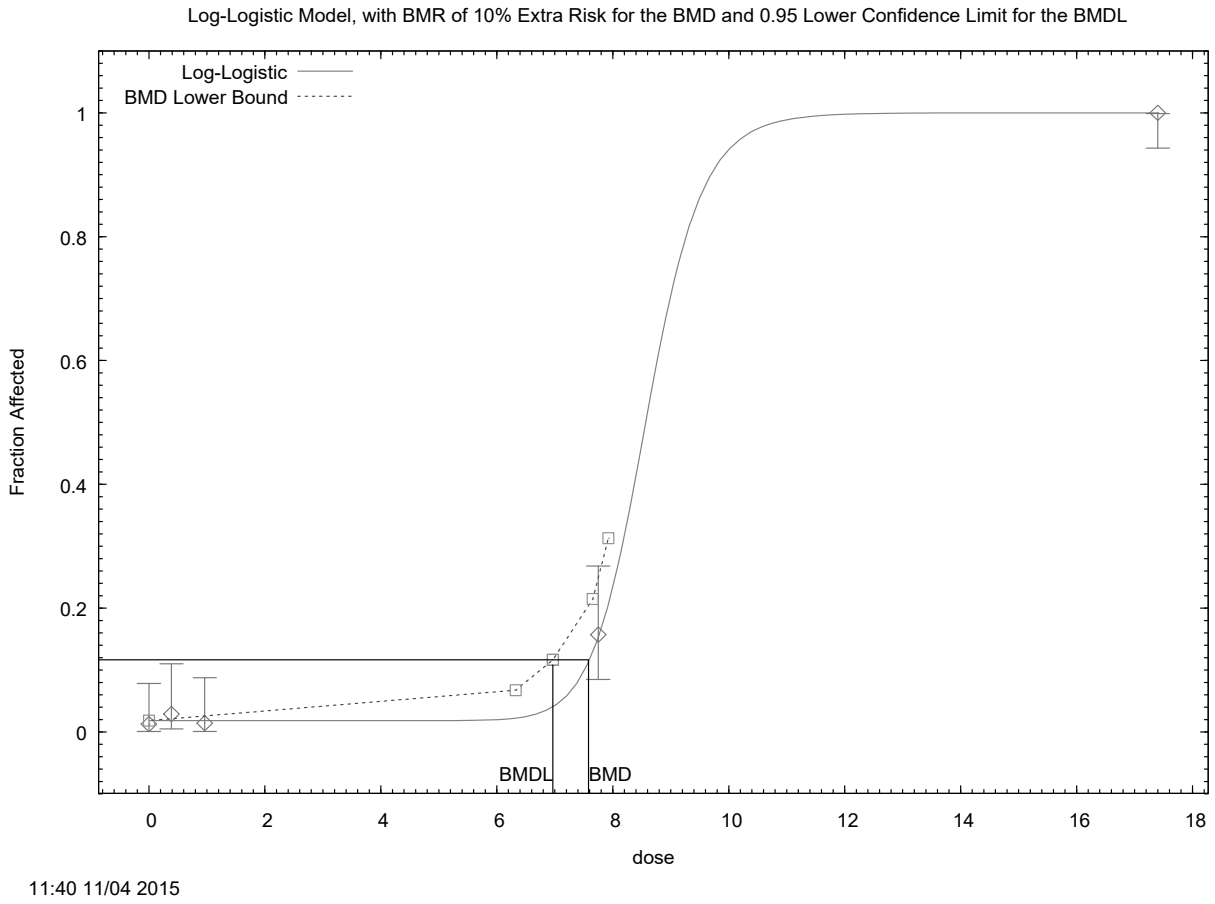

Figure D-2. BMDS Output for the Log-Logistic model of fibrosis of the renal papillary interstitium incidence data for female rats administered atrazine in the diet for 2 years

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        Logistic Model. (Version: 2.14; Date: 2/28/2013)
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        Gnuplot Plotting File:
C:/Users/jliccion/BMDS260/BMDS2601_20150629/BMDS2601/Data/lnl_Dax_Setting.plt
                                          Wed Nov 04 10:05:10 2015
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -4.34101
                         slope =      2.29874


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1           -1

     slope           -1            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -14.8599         2.83863           -20.4236           -
9.29633
          slope          6.19392         1.22398            3.79497
8.59287

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -46.9153         5
   Fitted model        -46.9153         2   0.000127078      3              1
  Reduced model        -213.652         1       333.473      4         <.0001

           AIC:         97.8306


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
```

```
 ------------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000      79.000        0.000
   0.4750     0.0000         0.000     0.000      70.000       -0.000
   1.1700     0.0000         0.000     0.000      68.000       -0.008
   9.5300     0.2899        20.000    20.000      69.000       -0.000
  22.3000     0.9875        79.000    79.000      80.000       -0.000

Chi^2 = 0.00      d.f. = 3        P-value = 1.0000


   Benchmark Dose Computation

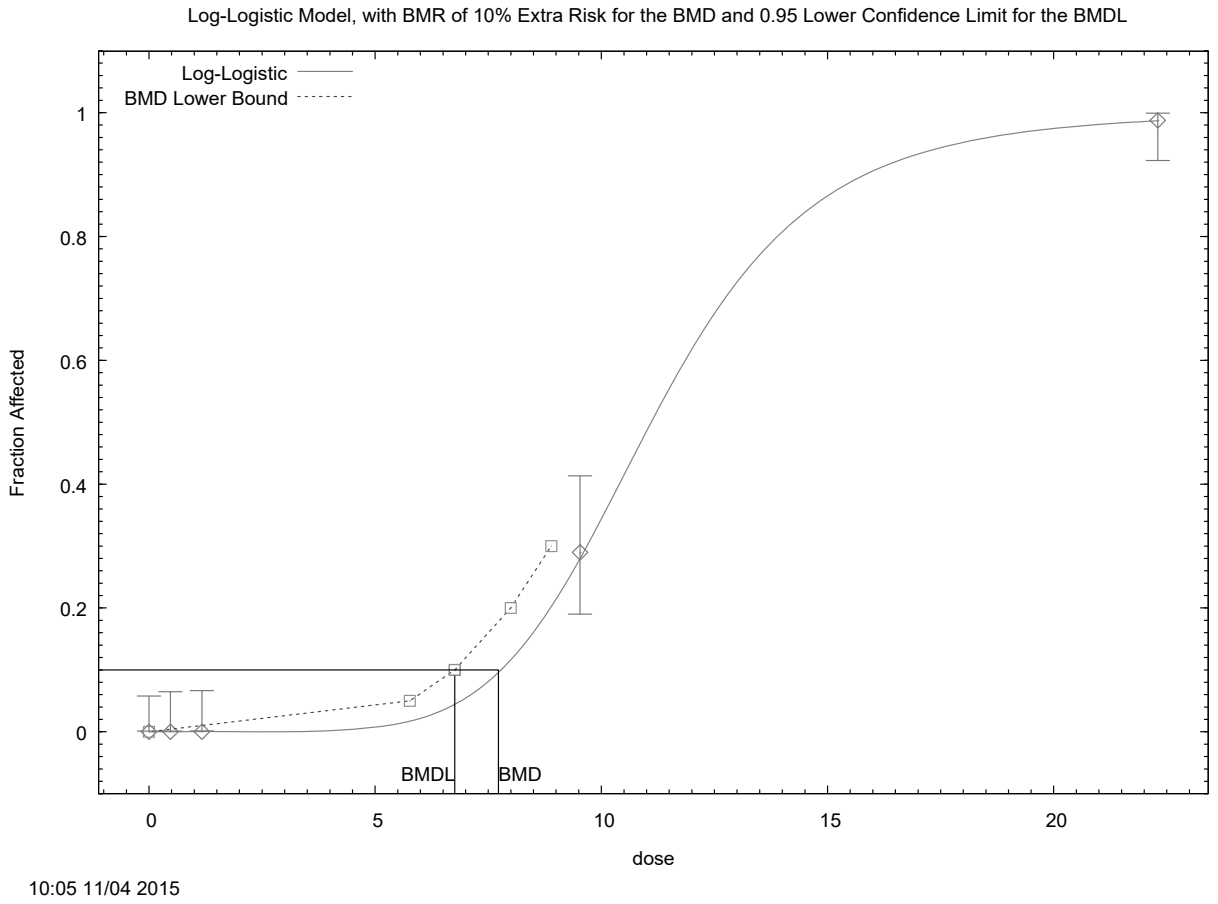
Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       7.72435

            BMDL =       6.75969
```



Appendix E. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1; the AHETF database; the ARTF database; the Residential SOPs (lawns/turf for the non-occupational spray drift assessment), and MRID 44152114 (human dermal absorption study[34]), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[35].

[34] This intentional exposure human study underwent an ethics review in 2006, at which time it was confirmed that it meets all requirements under EPA's Human Studies Rule at 40 CFR part 26 for EPA reliance on the study.
[35] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix F. Summary of Dermal Points of Departure Derived Assuming a Shower Occurs 8 hours After Initial Exposure and Risk Assessment Results

Table F.1. Propazine PBPK Modeled External Doses (PODs) Corresponding to a $BMDL_{1SD}$ for LH Surge Attenuation Assuming a Shower Occurs 8 Hours After Initial Exposure.

RA Type	Exposure Pathway (all triazines unless noted)	Young Children (1 - 2 years old)	Children (Residential: 6-11 years old)	Youths (Residential:11-16 years old)	Females (13 – 49 years old)
		Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)
Non-Occupational (Spray Drift)	Dermal (mg/kg/day)	131.56			91.12
Occupational	Dermal (mg/kg/day)				91.30

Table F.2. Summary of Risk Estimates Resulting from Spray Drift At the Field Edge Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Propazine Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure [2].

Crop	Application rate (lb ai/A)	Distance From Field Edge	Adult Dermal MOEs[2]			Children 1 < 2 years old Combined Dermal + Incidental Oral MOEs[2]		
			LOC = 30			LOC = 30		
		(Feet)	Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Sorghum	1.2	0	430	590	N/A	190	260	N/A

1. Risk estimates presented assuming screening-level droplet sizes (fine to medium for aerial applications; very fine to fine for groundboom applications), sparse canopies for airblast applications; and high booms for groundboom applications. Assuming coarser droplet sizes and lower booms will reduce risks.
2. Algorithms, assumptions, and calculations for the non-occupational spray drift assessment are provided in Appendix B (D428625). "N/A" provided when equipment not applicable based on the use pattern.

Table F.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propazine Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure [1].

Exposure Scenario	Crop or Target	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal	Inhalation	Total
				MOE[4] (LOC = 30) [PPE/Mitigation]	MOE[5] (LOC = 30) [PPE/Mitigation]	MOE[6] (LOC = 30) [PPE/Mitigation]
Mixer/Loader						
Mixing/Loading Liquids for Aerial Application	Sorghum	1.2 lb ai/A	1,200 Acres	120 [SL/G]	390 [No R]	92 [SL/G, No R]
Mixing/Loading Liquids for Groundboom Application	Greenhouse Ornamentals	1.5 lb ai/A	60 Acres	1,900 [SL/G]	6,300 [No R]	1,500 [SL/G, No R]
	Sorghum	1.2 lb ai/A	200 Acres	700 [SL/G]	2,400 [No R]	540 [SL/G, No R]
Applicator						
Applying Sprays via Aerial Equipment	Sorghum	1.2 lb ai/A	1,200 Acres	2,100 [EC]	18,000 [EC]	1,900 [EC]
Applying Sprays via Groundboom Equipment	Greenhouse Ornamentals	1.5 lb ai/A	60 Acres	4,300 [SL/G]	4,100 [No R]	2,100 [SL/G, No R]
	Sorghum	1.2 lb ai/A	200 Acres	1,600 [SL/G]	1,500 [No R]	770 [SL/G, No R]
Flagger						
Flagging for Aerial Sprays	Sorghum	1.2 lb ai/A	350 Acres	1,300 [SL/G]	150 [No R]	58 [SL/G, No R]
Mixer/Loader/Applicator						

Table F.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propazine Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure [1].

Exposure Scenario	Crop or Target	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal	Inhalation	Total
				MOE[4] (LOC = 30) [PPE/Mitigation]	MOE[5] (LOC = 30) [PPE/Mitigation]	MOE[6] (LOC = 30) [PPE/Mitigation]
Mixing/Loading/Applying Liquids via Backpack Sprayers	Greenhouse Ornamentals	0.15 lb ai/gal	40 gals	94 [SL/G]	150 [No R]	58 [SL/G, No R]
Mixing/Loading/Applying via Manually-Pressurized Handwand			40 gals	2,400 [SL/G]	690 [No R]	540 [SL/G, No R]
Mixing/Loading/Applying via Mechanically-Pressurized Handguns			1,000 gals	**17** [SL/G]	**6.9** [No R]	**4.9** [SL/G, No R]
				26 [DL/G]	34 [PF5]	**15 [DL/G + PF5]**
					69 [PF10]	**19 [DL/G + PF10]**

1 Results are presented assuming baseline attire and chemical resistant gloves unless otherwise specified. Applying via aerial application equipment is considered in a closed system/engineering control (EC). Risk estimates of concern are in bold.
2 Based on EPA Reg. No. 42750-148.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (91.3 mg/kg/day) ÷ Dermal Dose (mg/kg/day). Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).
5 Inhalation MOE = Inhalation POD (1.8 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Table F.4. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Propazine Using PODs that Assume a Shower Occurs 8 Hours After Initial Exposure[1].

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	DFR[1]	Dermal Dose (mg/kg/day)[2]	MOE[3]
Greenhouse Vegetables	Hand Harvesting, Pinching, Pollination, Hand Pruning, Scouting, Turning, Tying/training, Hand Weeding, Propagating	1,200	1.86	0.2594	350
	Irrigation (Hand Watering)	230		0.0050	1,800
Greenhouse Ornamentals	Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training				
Sorghum	Scouting	210	1.49	0.03631	2,500
	Hand Weeding	70		0.012104	7,500

1 DFR = From MRID 44883601 (study application rate = 2.0 lb ai/A, day 0 concentration = 2.636 ug/cm^2) and adjusted for the registered application rates (1.5 lb ai/A for greenhouse crops and 1.2 lb ai/A for sorghum).
2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).
3 MOE = POD (91.3 mg/kg/day) ÷ Daily Dermal Dose.