UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: July 10, 2018

SUBJECT: **Simazine.** Human Health Risk Assessment for Registration Review and to Support the Registration of Proposed Uses on Citrus Fruit (Crop Group 10-10), Pome Fruit (Crop Group 11-10), Stone Fruit (Crop Group 12-12), Tree Nuts (Crop Group 14-12), and Tolerance Amendment for Almond Hulls.

PC Codes: 080807
Decision Nos.: 462917, 507874
Petition No.: 2F8006
Risk Assessment Type: Single Chemical
TXR No.: NA
MRID No.: NA

DP Barcodes: D402163, D428603
Registration No.: NA
Regulatory Action: Section 3, Registration Review
Case No.: 7280
CAS Nos.: 122-34-9
40 CFR: §180.213

FROM: Kristin Rickard, Risk Assessor
Danette Drew, Chemist
William Donovan, Ph.D., Chemist
John Liccione, Ph.D., Toxicologist
Risk Assessment Branch V/VII (RAB V/VII)
Health Effects Division (HED) (7509P)
Office of Pesticide Programs (OPP)

And

David Miller, Chief, Toxicology and Epidemiology Branch (TEB)
Elizabeth Mendez, Ph.D., Senior Scientist, Immediate Office
Ashlee Aldridge, MPH, Epidemiologist, Toxicology and Epidemiology Branch (TEB)
Health Effects Division (HED) (7509P)
Office of Pesticide Programs (OPP)

And

Anna Lowit, Ph.D., Senior Science Advisor
Immediate Office
Office of Pesticide Programs (OPP)

And

Cecilia Tan, Ph.D.
National Exposure Research Laboratory (NERL)
Office of Research and Development E-205-01
Research Triangle Park, NC

THROUGH: Michael S. Metzger, Chief
Risk Assessment Branch V/VII (RAB V/VII)
Health Effects Division (HED) (7509P)
Office of Pesticide Programs (OPP)

And

Michael Doherty, Chemist
Shalu Shelat, Environmental Health Scientist
HED Risk Assessment Review Committee (RARC)

TO: Christian Bongard, Chemical Review Manager
Risk Management and Implementation Branch III
Pesticide Re-Evaluation Division (7508P)

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 of the dietary, residential, aggregate, and occupational exposures and risks from the registered uses of simazine.

Syngenta Crop Protection, LLC (Syngenta) has proposed uses and tolerances of simazine on the following agricultural commodities: citrus fruit (crop group 10-10), pome fruit (crop group 11-10), stone fruit (crop group 12-12), and tree nuts (crop group 14-12); and a tolerance amendment has been proposed for almond hulls. Therefore, this memorandum also serves as HED's Section 3 human health risk assessment of the dietary, residential, aggregate, and occupational exposures from the proposed uses of simazine.

The most recent human health risk assessment for the chlorotriazine herbicides (atrazine, simazine, and propazine) was completed in 2006 (J. Morales *et al.*, 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 made:

- The non-acute toxicity points of departure (PODs) and uncertainty factors have been updated using a rat and human physiologically-based pharmacokinetic (PBPK) model;
- The drinking water exposure assessment has been updated;
- The dietary exposure assessment has been updated to incorporate the proposed new uses of simazine;
- Aggregate exposure assessments were completed, including updated dietary and residential exposure estimates;
- Non-occupational spray-drift exposure/risk assessment and bystander exposure assessments were completed where applicable; and
- An occupational exposure assessment for the registered and proposed uses was completed reflecting recent updates to the simazine PODs, and policy changes for body weight, unit exposure, and area/amount treated assumptions.

A summary of the findings and an assessment of human risk resulting from the registered and proposed uses of simazine is provided in this document.

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 simazine. Atrazine, propazine, and the cumulative risk assessment (CRA) for all of the chlorotriazine herbicides are addressed in separate documents.

Use Profile

Proposed Uses

Simazine is a systemic herbicide that is usually applied to the soil, and is absorbed through leaves and roots. Syngenta has proposed simazine for use on the following agricultural commodities and crop groups: citrus fruit (Crop Group 10-10), pome fruit (Crop Group 11-10), stone fruit (Crop Group 12-12), and tree nuts (Crop Group 14-12). Syngenta has also proposed a tolerance amendment for almond hulls. These uses are requested to be added to two end-use product labels (EPA Reg. Nos. 100-526 and 100-603); a liquid and water dispersible granule (WDG)/dry flowable (DF) formulation, respectively. Applications can be made using ground and handheld application equipment; chemigation and aerial application methods are prohibited. Both product labels require occupational handlers to wear baseline attire (long sleeved shirts, long pants, shoes, and socks) and chemical resistant gloves. EPA Reg. No. 100-603 (WDG/DF) requires mixer/loaders and others supporting groundboom applications to wear baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, socks, chemical resistant apron, and a National Institutes for Occupational Safety and Health (NIOSH) dust/mist respirator. The restricted entry interval (REI) for the proposed uses of simazine is 12 hours.

Existing Uses

Simazine is currently registered for use on various agricultural crops, Christmas trees, golf course turf, nursery crops, residential turf, and turf for sod. Simazine is formulated into liquid and DF/WDG end-use products. Simazine may be applied using ground, chemigation, and handheld application equipment; aerial application is prohibited. The registered labels vary with respect to personal protective equipment (PPE) requirements. All of the DF/WDG labels require mixer/loaders for groundboom applications and/or mixer/loaders, cleaners of equipment or spills, or other handlers otherwise exposed to the concentrate to wear: baseline attire (long sleeved shirts, long pants, shoes, and socks), chemical resistant gloves, and a dust/mist respirator. Some labels also require mixer/loaders to wear a double layer of clothing or coveralls. All other handlers of DF/WDG products must wear baseline attire and chemical resistant gloves. All of the registered liquid labels require handlers to wear baseline attire and waterproof or chemical resistant gloves. All registered labels, regardless of formulation, list REIs of 48 hours for Christmas trees and 12 hours for all other crops.

Hazard Characterization

Simazine has a similar structure, and shares a common mechanism of neuroendocrine toxicity with atrazine, as well as propazine 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 luteinizing hormone (LH) surge after 4 days of exposure, an effect which also protects for other downstream adverse endocrine-related toxicological effects. *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 simazine and its metabolites.

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). 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 simazine to atrazine, and the shared common chlorinated metabolites, the atrazine PBPK model was extrapolated to simazine by utilizing specific parameter values for simazine. Another recent refinement to the atrazine PBPK model is the addition of dermal and inhalation routes. The PBPK model was used to estimate human equivalent doses and toxicological points of departure (PODs) for repeated dose exposures to simazine. 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. In addition, longer durations would not lead to greater toxicity. PODs for simazine for relevant lifestages (infants, children, youths, and adults) were derived for the standard routes of exposure (oral, dermal, and inhalation) (excluding acute dietary for simazine and its chlorinated metabolites and the chronic dietary for hydroxysimazine and its hydroxy metabolites as described 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 in the PBPK model 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 simazine toxicity data was 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 toxiciological 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 hydroxysimazine and its hydroxy metabolites. Dermal and inhalation exposures are not expected for hydroxysimazine. 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

Proposed and Existing Uses

Non-occupational spray drift, occupational handler, and occupational post-application exposures are expected from the proposed and existing uses of simazine. Residential handler and post-application exposures are expected from the existing uses of simazine, only; there are no proposed residential uses of simazine. The durations of exposure are expected to be short-term (1 to 30 days) for residential handler, residential post-application, and non-occupational spray drift scenarios; and both short- (1 to 30 days) and intermediate-term (1 to 6 months) for occupational handlers and post-application workers. However, currently available toxicity data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats following atrazine exposure. This is also the length of the estrous cycle in rats and also the exposure duration needed for the triazines to reach a time-to-effect. Therefore, for the purposes of the occupational, non-occupational, and residential risk assessments, only the 4-day duration is relevant. Although the chlorometabolites of atrazine (DEA, DIA, and DACT) may be found in plants, non-dietary exposure is not expected since these metabolites are a product of plant metabolism and are unlikely to be present on plant surfaces, reducing the likelihood for exposure.

The residues of toxicological concern for simazine neuroendocrine risk assessment are parent compound simazine and its chlorinated and hydroxylated metabolites. Simazine and its chlorinated metabolites are assumed to have equivalent toxicity. The residues of concern for risk assessment for kidney effects are simazine's metabolite hydroxysimazine, along with the

associated hydroxylated metabolites, DIHA, and ammeline. These hydroxylated residues of concern are assumed to have equal toxicity. Dietary exposure to simazine 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 simazine and its chlorotriazine metabolites, the toxicological endpoint is delayed ossification in fetuses and is only applicable to females 13-49 years old. For the 4-day assessment, the endpoint is attenuation of the LH surge (the most sensitive endpoint) and is applicable to all lifestages; a 4-day assessment is appropriate since the toxicological effect occurs after four days of exposure and is protective of exposures of longer durations. The duration appropriate for assessing dietary risks for the hydroxysimazine 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 simazine may occur from occupational, residential, and non-occupational exposure sources; exposure to the chlorinated and hydroxylated metabolites are not expected to occur. Based on the currently registered uses of simazine, the durations of exposure are expected to be both short- and intermediate-term for occupational handler and post-application workers. Residential exposures and exposures from non-occupational spray drift from application are expected to be short-term only. 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 and proposed uses of simazine. Adequate field trial data has been submitted for the established and proposed crop uses of simazine. The residue definition for tolerance enforcement includes the parent simazine and its chlorinated metabolites, while that for risk assessment also includes the corresponding hydroxy metabolites. As noted above, these are assessed separately from the parent compound and chlorinated metabolites.

Acute and 4-day dietary (food-only) exposure to simazine and its chlorinated metabolites do not exceed HED's level of concern (LOC; 100% of the population adjusted dose (PAD)). The acute dietary risk estimate for females 13-49 years old is <1% of the acute population adjusted dose (aPAD); the acute toxicological endpoint is only applicable to females of reproductive age. The 4-day dietary risk estimate for children 1-2 years old, the most highly exposed subpopulation, is 2.3% of the 4-day PAD. As simazine has been classified as "Not likely to be carcinogenic to humans," cancer risk is not a concern and a quantitative cancer risk assessment was not conducted.

The chronic dietary (food only) exposure to hydroxyatrazine and its hydroxylated metabolites does not exceed the level of concern. The chronic dietary risk estimates for children 1 -2 years old, the most highly exposed subpopulation, is < 1% cPAD.

Residential Exposure and Risk Assessment

Residential Handler Exposure and Risk Assessment - Existing Uses

All registered simazine product labels with residential use sites (e.g., residential lawns) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use PPE (chemical resistant gloves). However, one of these labels (EPA Reg. No. 19713-60) contains a separate sub-label for "residential use". Despite the statement regarding PPE, HED has assumed that this product may be marketed for homeowner use, and has conducted a quantitative residential handler assessment. This product has been assessed to reflect the updates in HED's 2012 Residential SOPs[1]. There were no residential handler combined (dermal + inhalation) risk estimates of concern for the existing uses of simazine.

Residential Post-Application Exposure and Risk Assessment

Simazine-specific turf transferable residue (TTR) data are available. These data were incorporated into the residential post-application assessment for evaluating exposures to turf treated with liquid and DF/WDG formulations of simazine. A 4-day average TTR 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. Using the available chemical-specific data and a 4-day average TTR, there were post-application dermal risk estimates of concern for adults and children 1 to < 2 years old and combined (dermal + incidental oral) risk estimates of concern for children 1 to < 2 years old (LOC = 30) from high contact activities on treated turf. There were no dermal post-application risk estimates of concern for adults, children 11 to < 16 years old, and children 6 to < 11 years old from golfing or mowing activities; and no incidental oral post-application risk estimates of concern for children 1 to < 2 years old (MOEs > LOC of 30).

Aggregate Exposure and Risk Assessment

The durations of exposure identified for simazine aggregate assessment are acute and 4-day. The duration of exposure identified for hydroxysimazine aggregate assessment is chronic. The acute and chronic aggregate assessments include food and drinking water only. The 4-day aggregate assessment includes food, drinking water, and residential exposures.

A drinking water level of comparison (DWLOC) approach to aggregate risk was used to calculate the amount of exposure available in the total 'risk cup' for drinking water after accounting for any exposures from food and/or residential use. The DWLOCs can then be compared to the estimated concentrations in drinking water (EDWCs). EDWCs were derived using a total toxic residue 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.

For simazine, the acute DWLOC for females 13-49 years old (the acute toxicological endpoint is only applicable to females of reproductive age) is greater than the acute EDWCs for TCTs in surface water or ground water. There is no acute aggregate risk of concern.

[1]Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Simazine 4-Day Aggregate DWLOCs
The calculated 4-day DWLOCs for infants, children, and adults are all greater than the 4-day EDWCs for TCTs in surface water or ground water; there are no 4-day aggregate risks of concern for the included residential scenarios. However, this aggregate assessment excluded residential exposure scenarios/uses that were of risk concern alone; specifically, adults and children 1 to < 2 years old contacting treated turf via high contact activities were not included since there is a risk estimate of concern for dermal and combined dermal and oral exposures when assuming the maximum labeled rate for spray applications (2.0 lb ai/A). However, if the application rate for turf spray is reduced to 0.70 lb ai/A, the 4-day aggregate DWLOC is 630 ppb for children 1-2 years old and 1,800 ppb for females 13-49 years of age, which would not be of risk concern.

Non-Occupational Spray Drift Exposure and Risk Assessment
Typically, a quantitative spray drift assessment would not be conducted when the residential turf application exceeds the target crop application (after adjusting for drift). However, since the simazine residential post-application assessment on residential turf resulted in risk estimates of concern, a quantitative spray drift assessment was conducted. There were no combined dermal and incidental oral risk estimates of concern from indirect spray drift exposure to simazine at the field edge for children 1 to < 2 years old using chemical-specific TTR data and a 4-day average residue; except for applications to grapefruit and oranges at 8.0 lb ai/A (combined dermal + incidental oral MOE = 22, LOC = 30). Non-occupational spray drift exposure and risk estimates resulting from applications to grapefruit and oranges were not of concern for children 1 to < 2 years old 10 feet from the field edge (combined dermal + incidental oral MOE = 44, LOC = 30). There were no non-occupational spray drift risk estimates of concern for adults at the field edge.

Non-Occupational Bystander Exposure and Risk Assessment
A non-occupational bystander exposure and risk assessment was conducted using the available application site and ambient air monitoring data for simazine. There are no risk estimates of concern for adults and children (MOEs $\geq$ 30) using either the maximum air concentration data from application site monitoring or using the average air concentration from all ambient air monitoring.

Occupational Exposure and Risk Assessment
Occupational Handler - Proposed Uses
There were combined (dermal + inhalation) occupational handler exposure and risk estimates of concern (MOE > 30) with baseline attire and chemical resistant gloves (lowest level of PPE on the proposed labels) for some of the proposed uses of simazine. Dermal exposures were the highest contributors to the combined (dermal + inhalation) risk estimates.
Mixing/loading/applying DF/WDG and liquid formulations for backpack sprayer application to grapefruit and oranges (0.4 lb ai/gal) and resulted in risk estimates not of concern with the addition of a double layer of clothing. However, mixing/loading/applying DF/WDG and liquid formulations using mechanically pressurized handgun sprayers resulted in risk estimates of concern for all proposed use sites assuming label-specified PPE; and risk estimates were still of concern with the addition of a double layer of clothing and a PF10 respirator (maximum available PPE).

Occupational Handler Exposure - Existing Uses
There were no occupational handler risk estimates of concern for the existing uses of simazine except for some of the mixing/loading/applying using handheld spray equipment scenarios. In all cases, dermal exposures were the highest contributors to the combined (dermal + inhalation) risk estimates.

Some scenarios require a double layer of clothing, a double layer of clothing and a PF5 respirator, or engineering controls to be not of concern (MOE > LOC of 30). Most mixing/loading/applying scenarios for DF/WDG and liquid formulations remain of concern (MOE < LOC of 30) assuming baseline attire, label-specified PPE (gloves), a double layer of clothing and a PF10 respirator (maximum available PPE/mitigation.

Occupational Post-Application Exposure - Proposed and Existing Uses
In addition to the available simazine TTR data, atrazine dislodgeable foliar residue (DFR) data are available, and are considered appropriate for use in the simazine risk assessment. Predicted TTR and DFR residues on the day of application were used in the occupational post-application assessment because post-application workers (especially scouters) could move from field to field encountering day 0 residue estimates. Therefore, use of an average residue may not be appropriate. Using the atrazine DFR and simazine TTR data, there are no occupational post-application MOEs are of concern for the registered and proposed uses of simazine on the day of application, except for hand-set irrigation for highbush and lowbush blueberries; this scenario is not of concern 1 day after application.

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"[2].

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 G 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 (see Appendix G).

2.0 Risk Assessment Summary & Conclusions

Residential Handler Exposure and Risk Assessment
There were no residential handler combined (dermal + inhalation) risk estimates of concern for the existing uses of simazine.

Residential Post-Application Exposure and Risk Assessment

[2] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

There were no incidental oral risk estimates of concern for children 1 to < 2 years old (MOEs > LOC of 30) using chemical-specific TTR data. However, there are dermal risk estimates of concern for adults and combined (dermal + incidental oral) risk estimates of concern for children 1 to < 2 years old from the registered uses of simazine for high contact activities on treated turf.

Aggregate Exposure and Risk Assessment
The simazine 4-day aggregate assessment excluded residential exposure scenarios that were already of risk concern (i.e., high contact activities for adults and children 1-2 years old on treated turf sprayed with simazine). Excluding these scenarios, there were no aggregate risk estimates of concern at the maximum registered application rates. However, there are no risk estimates of concern for all subpopulations, including children 1 to < 2 years old if the maximum application rate for turf spray is reduced to 0.70 lb ai/A.

Non-Occupational Spray Drift Exposure and Risk Assessment
There were no combined dermal and incidental oral risk estimates of concern from indirect spray drift exposure to simazine at the field edge for children 1 to < 2 years old; except for applications to grapefruit and oranges at 8.0 lb ai/A; these risk estimates were not of concern for children 1 to < 2 years old 10 feet from the field edge. There were no non-occupational spray drift risk estimates of concern for adults at the field edge.

Occupational Handler Exposure and Risk Assessment – Proposed Uses
There were combined (dermal + inhalation) occupational handler exposure and risk estimates of concern (MOE > 30) with baseline attire and chemical resistant gloves (lowest level of PPE on the proposed labels) for some of the proposed uses of simazine for some scenarios.

Occupational Handler Exposure and Risk Assessment – Existing Uses
Many of the combined (dermal + inhalation) occupational handler exposure and risk estimates were of concern (MOE > 30) with baseline attire and chemical resistant gloves (lowest level of PPE consistently required across all registered and proposed labels). Some scenarios require a double layer of clothing to be not of concern (MOE > LOC of 30). Most mixing/loading/applying scenarios for DF/WDG and liquid formulations remain of concern (MOE < LOC of 30) assuming baseline attire, label-specified PPE (gloves), a double layer of clothing and a PF10 respirator (maximum available PPE/mitigation.

Occupational Post-Application Exposure and Risk Assessment – Proposed and Existing Uses
Using atrazine DFR and simazine TTR data, one occupational post-application scenario was of concern on the day of application (handset irrigation to highbush and lowbush blueberries). This scenario is not of concern 1 day after application.

2.1 Data Deficiencies

There are no multiresidue method testing results (OCSPP 860.1360) for the regulated chloro metabolites of simazine: G-28279 (DIA) and G-28273 (DACT) (see Figure 3.1.1).

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Suitable analytical enforcement methods are available for simazine and its two regulated chloro metabolites: G-28279 (DIA), and G-28273 (DACT). Method AG-539 has demonstrated adequate recoveries in a variety of crop matrices and has undergone successful independent laboratory validation. However, the preferred tolerance enforcement method is LC-MS/MS Method GRM052.01A since it has a lower limit of quantification (LOQ) of 0.01 ppm for each residue of concern. Method GRM052.01A uses essentially the same methanol/water extraction procedure as Method AG-539. Briefly, samples of homogenized plants are extracted with methanol/water (80:20, v:v) on a reflux apparatus for 120 minutes. After cooling, each sample is filtered through a Reeve Angel 802 filter fluted inside a Whatman 2V filter into an 8-ounce amber-colored bottle. To 1.0 mL of this filtrate of the plant extract, 4.0 mL of water/methanol (90:10, v:v) + 0.1% formic acid is added before analysis by LC-MS/MS using a TurboSpray Ionization mass spectrometer (MS) run in positive (+) ion mode using the multiple reaction monitoring (MRM). The primary transitions used for quantitation of simazine, G-28273, and G-28279 are m/z 202.1→132.0, m/z 146.0→104.0, and m/z 174.1→104.0, respectively.

No enforcement methods for livestock commodities are needed for simazine.

According to the Food and Drug Administration's (FDA's) Pesticide Analytical Manual (PAM) Volume I, Appendix II, simazine is successfully recovered using Section 302 (Protocol D), but not recovered using Sections 303 (Protocol E) or 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-28279 (DIA) or G-28273 (DACT), and these data should be submitted.

Analytical standards for residues of concern for simazine 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.

Table 2.2.1. Analytical Standard Status for Simazine and its Residues of Concern.

Analytical Standard	CAS#	Expiration Date
Atrazine	1912-24-9	8/28/24
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 §180.213 for the combined residues of simazine and its two chlorinated metabolites in/on a variety of crops and livestock commodities. HED

recommends that the residue definition for the tolerance expression for simazine be modified in accordance with current policy to read:

> *"Tolerances are established residues of the herbicide simazine, 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 simazine, 6-chloro-N,N'-diethyl-1,3,5-triazine-2,4-diamine, and its metabolites 6-chloro-N-ethyl-1,3,5-triazine-2,4-diamine, and 6-chloro-1,3,5-triazine-2,4-diamine, calculated as the stoichiometric equivalent of simazine, in or on the commodity."*

A summary of the established and recommended tolerances for simazine is listed in Table 2.2.2. The registrant should submit a revised Section F consistent with the recommended tolerance levels and crop group designations indicated.

Table 2.2.2. Tolerance Summary for Simazine.

Commodity	Established Tolerance (ppm)	Recommended Tolerance[2] (ppm)
Almond	0.25	Remove (group 14-12)
Almond, hulls	0.25	3.0
Apple	0.20	Remove (group 11-10)
Avocado	0.20	0.20
Blackberry	0.20	0.20
Blueberry	0.20	0.20
Cattle: meat and meat byproducts[1]	0.03	Remove (180.6(a)(3))
Cherry	0.25	Remove (group 12-12)
Corn, field, forage	0.20	0.20
Corn, field, grain	0.20	0.20
Corn, field, stover	0.25	0.25
Corn, pop, grain	0.20	0.20
Corn, pop, stover	0.25	0.25
Corn, sweet, forage	0.20	0.20
Corn, sweet, kernel plus cob with husks removed	0.25	0.20
Corn, sweet, stover	0.25	0.25
Cranberry	0.25	0.25
Currant	0.25	0.25
Egg	0.03	Remove (180.6(a)(3))
Fruit, citrus, group 10-10	--	0.04
Fruit, pome, group 11-10	--	0.03
Fruit, stone, group 12-12	--	0.10
Grape	0.20	0.20
Grapefruit	0.25	Remove (group 10-10)
Hazelnut	0.20	Remove (group 14-12)
Lemon	0.25	Remove (group 10-10)
Loganberry	0.20	0.20
Milk	0.03	Remove (180.6(a)(3))
Nut, macadamia	0.20	Remove (group 14-12)
Nut, tree, group 14-12	--	0.05
Olive	0.20	0.20
Orange	0.25	Remove (group 10-10)
Peach	0.20	Remove (group 12-12)
Pear	0.25	Remove (group 11-10)
Pecan	0.20	Remove (group 14-12)
Plum	0.20	Remove (group 12-12)
Raspberry	0.20	0.20
Strawberry	0.25	0.03

Table 2.2.2. Tolerance Summary for Simazine.		
Commodity	**Established Tolerance (ppm)**	**Recommended Tolerance[2] (ppm)**
Walnut	0.2	Remove (group 14-12)

[1] Cattle, goat, hog, horse, and sheep.

[2] Where revocation of tolerances are recommended, the reason is indicated in parenthesis. Thus, individual crop tolerances should be removed when they are covered by establishment of crop group tolerances; and tolerances for meat, milk, poultry, and eggs should be removed because 40 CFR §180.6(a)(3) applies.

Note to RD: Upon establishment of the recommended crop group tolerances, the established individual crop tolerances in the new crop groups should be removed to avoid unnecessary duplicative listings (i.e., there is no need for an individual walnut tolerance since walnuts are included in tree nuts group 14-12).

2.2.3 Revisions to Petitioned-For Tolerances

The submitted residue data support a tolerance level of 0.04 ppm for the citrus fruit crop group. The proposed tolerance level of 0.05 ppm is computed if the maximum combined residue level of 0.038 ppm (one grapefruit sample) is included in the Organisation for Economic Co-operation and Development (OECD) tolerance calculation procedures. However, using the average field trial value of 0.034 ppm, as specified by HED protocol, a tolerance of level of 0.04 ppm is recommended. Also, although the proposed tolerance level of 0.07 ppm for crop group 14-12 is supported by OECD tolerance calculations, a level of 0.05 ppm is recommended to harmonize with the Canadian MRL.

2.2.4 International Harmonization

No Codex Maximum Residue Limits (MRLs) have been established for simazine. Canada has set an MRL of 0.05 ppm for individual nuts that are members of the tree nut crop group. The recommended tolerance for tree nuts is harmonized with the Canadian MRL, so there are no harmonization issues at this time.

2.3 Label Recommendations

2.3.1 Recommendations from Residential Assessment

- HED notes that there are residential post-application scenarios for registered uses that have risk estimates of concern where potential mitigation may impact label language.
- HED notes that there is one registered (EPA Reg. No. 19713-60) label containing a separate sub-label for "residential use." Despite the statement regarding PPE, HED has assumed that this product may be marketed for homeowner use, and has conducted a quantitative residential handler assessment. If the label is not intended for homeowner use, the text should be updated.

2.3.2 Recommendations from Occupational Assessment

- HED notes that there are several occupational handler scenarios for the registered uses of

simazine that result in a risk of concern with current label PPE requirements.

- One occupational post-application scenario (handset irrigation for highbush and lowbush blueberries) resulted in risk estimates of concern on the day of application. Therefore, the REIs on the registered labels may need to be revised to address those concerns.

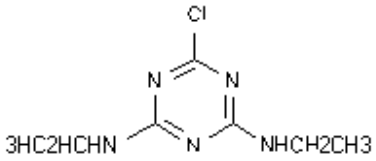
2.3.3 Recommendations from Residue Chemistry Assessment

- HED recommends that the registrant restrict crop rotation to labeled crops only. Alternatively, the registrant may propose tolerances for unlabeled rotational crops reflecting residues incurred at the intended plant back interval.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Simazine Nomenclature.

Chemical structure	
Empirical Formula	$C_7N_5H_{12}Cl$
Common name	Simazine
Company experimental name	G-27692
IUPAC name	6-chloro-N^2,N^4-diethyl-1,3,5-triazine-2,4-diamine
Other systematic	2-chloro-4,6-bis(ethylamino)-*s*-triazine
CAS name	6-chloro-N,N'-diethyl-1,3,5-triazine-2,4-diamine
CAS registry number	122-34-9

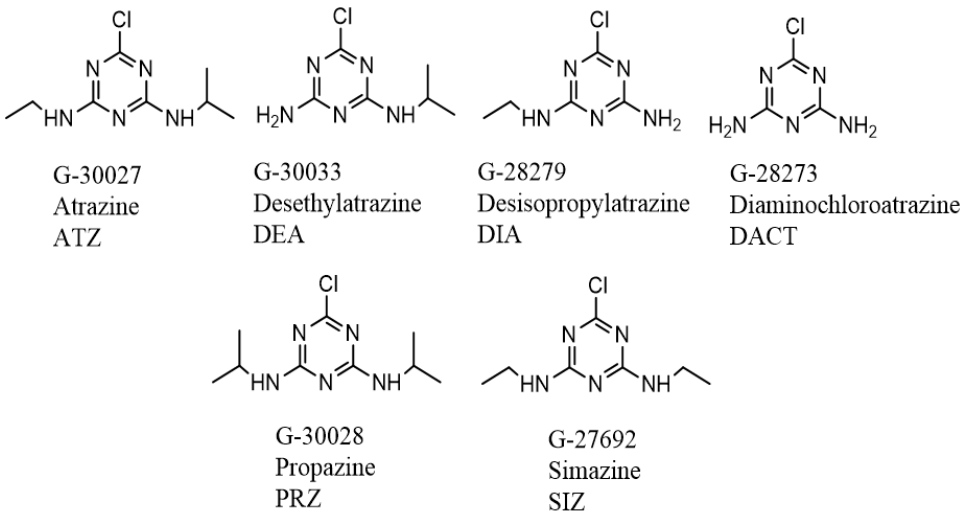


Figure 3.1.1. Chemical Structures for the Total Chlorinated Triazines (TCTs).

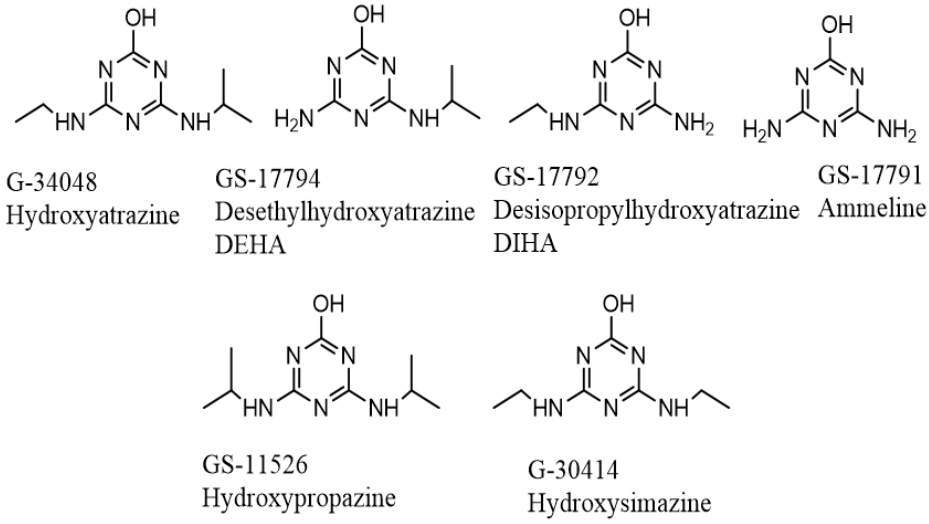


Figure 3.1.2. Chemical Structures for the Total Hydroxy Triazines (THTs).

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 simazine are provided in Appendix C.

3.3 Pesticide Use Pattern

Use Profile – Proposed Uses

Simazine is a systemic herbicide that is usually applied to the soil, and is absorbed through leaves and roots. Syngenta has proposed simazine for use on the following agricultural commodities and crop groups: citrus fruit (Crop Group 10-10), pome fruit (Crop Group 11-10), stone fruit (Crop Group 12-12), and tree nuts (Crop Group 14-12). Syngenta has also proposed a tolerance amendment for almond hulls. These uses are requested to be added to two EUP labels (EPA Reg. Nos. 100-526 and 100-603); a liquid and DF formulation, respectively. Applications can be made using ground and handheld application equipment; chemigation and aerial application methods are prohibited.

The proposed uses of simazine are summarized in Table 3.3.1.

Table 3.3.1. Summary of the Proposed Uses of Simazine.

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
Grapefruit, Orange						
Ground, Handheld	Liquid [100-526] DF [100-603]	8.0 lb ai/A (0.4 lb ai/gal)	1-2	8.0 lb ai/A	1	Apply in 20 gals/A by ground. Aerial application and application through irrigation is prohibited.
Lemon, Pome Fruit (Crop Group 11-10), Stone Fruit (Crop Group 12-12), Filberts, Macadamia Nuts, Pecans, Walnuts						
Ground, Handheld	Liquid [100-526] DF [100-603]	4.0 lb ai/A (0.2 lb ai/gal)	1-2	4.0 lb ai/A	Lemon: 1 Pome fruit, Stone Fruit: 21 Filberts, Macadamia Nuts, Pecans, Walnuts: 30	Apply in 20 gals/A by ground. Aerial application and application through irrigation is prohibited.
Almonds						
Ground, Handheld	Liquid [100-526] DF [100-603]	2.0 lb ai/A (0.1 lb ai/gal)	1	2.0 lb ai/A	30	Apply in 20 gals/A by ground. Aerial application and application through irrigation is prohibited.

Use Profile – Existing Uses

Simazine is currently registered for use on various agricultural crops (almonds, apples, avocadoes, blackberries, blueberries, boysenberries, field and sweet corn, filberts, grapefruit, grapes, lemons, loganberries, macadamia nuts, nectarines, olives, oranges, peaches, pears, pecans, plums, raspberries, strawberries, sweet cherries, tart cherries, walnuts), nursery crops, Christmas trees, golf course turf, residential turf, and turf for sod.

The registered uses of simazine, and the label providing the highest single application rate and least restrictive application methods, are summarized in Table 3.3.2. All uses are restricted to one or two applications per year. To avoid crop injury, observe the following precautions. 1) If rotating treated land the year following application, plant only corn, unless stated otherwise on this label. 2) if replanting perennial crops or if rotating land to crops other than corn, do not apply this product in the year preceding planting of these crops.

Table 3.3.2. Summary of the Existing Uses of Simazine.						
Application Timing, Type, and Equip.	**Representative Formulation [EPA Reg. No.]**	**Application Rate**	**Max. No. Applications per Season or Growing Cycle**	**Max. Seasonal Application Rate**	**PHI (days)**	**Use Directions and Limitations**
Christmas Tree Farms & Shelterbelts						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.2 lb ai/gal)	2	4.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Ground	Liquid [19713-273]					Aerial application is prohibited.
Turf Grass on Fairways, Lawns, and Similar Areas						
Ground	DF/WDG [100-603]	2.0 lb ai/A (0.13 lb ai/gal)	2	3.0 lb ai/A	NA	Aerial application and application through irrigation is prohibited.
Ground	Liquid [19713-273]					Aerial application is prohibited.
Field Corn, Sweet Corn						
Ground	Liquid [9779-296]	2.5 lb ai/A (0.13 lb ai/gal)	2	2.5 lb ai/A	NS	Aerial application and application through irrigation is prohibited. May also be used as a winter weed control.
	DF/WDG [100-603]	2.0 lb ai/A	2	2.5 lb ai/A	Field Corn: 60 Sweet Corn: 45	
Ground, Chemigation	Liquid [19713-273]					Aerial application is prohibited. May also be used as a winter weed control.
	DF/WDG [19713-553]	1.0 lb ai/A (0.05 lb ai/gal)	2			
Lowbush Blueberries						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.1 lb ai/gal)	2	4.0 lb ai/A	Do not apply when fruit is present	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]					Aerial application is prohibited.
Strawberries						
Ground	DF/WDG [100-603]	1.0 lb ai/A (0.05 lb ai/gal)	1	1.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]		1	1.0 lb ai/A	NS	Aerial application is prohibited.
Cranberries						
Ground	DF/WDG [19713-252]	4.0 lb ai/A (0.2 lb ai/gal)	1	4.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]		1	4.0 lb ai/A	NS	Aerial application is prohibited.
Nursery Crops						
Ground	DF/WDG [100-603]	3.0 lb ai/A (0.15 lb ai/gal)	1	3.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]		1	3.0 lb ai/A	NS	Aerial application is prohibited.
Grapefruit, Oranges						
Ground	DF/WDG [100-603]	8.0 lb ai/A (0.4 lb ai/gal)	1	8.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
	Liquid [100-526]					

Table 3.3.2. Summary of the Existing Uses of Simazine.						
Application Timing, Type, and Equip.	**Representative Formulation [EPA Reg. No.]**	**Application Rate**	**Max. No. Applications per Season or Growing Cycle**	**Max. Seasonal Application Rate**	**PHI (days)**	**Use Directions and Limitations**
Ground, Chemigation	Liquid [19713-273]	4.0 lb ai/A (0.2 lb ai/gal)	2	8.0 lb ai/A	NS	Aerial application is prohibited.
Lemons						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.2 lb ai/gal)	2	4.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]	4.0 lb ai/A (0.2 lb ai/gal)	2	8.0 lb ai/A	NS	Aerial application is prohibited.
Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.2 lb ai/gal)	1-2	4.0 lb ai/A	Apples: 150 Do not apply when nuts on ground	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]					Aerial application is prohibited.
Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.1 lb ai/gal)	1-2	4.0 lb ai/A	Do not apply when fruit is present or when nuts are on the ground	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]					Aerial application is prohibited.
Almonds, Peaches, Nectarines						
Ground	DF/WDG [100-603]	2.0 lb ai/A (0.1 lb ai/gal)	2.0 lb ai/A	1	NS	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]					Aerial application is prohibited
Turf Grass for Sod						
Ground	DF/WDG [100-603]	4.0 lb ai/A (0.3 lb ai/gal)	2	6.0 lb ai/A	30	Aerial application and application through irrigation is prohibited.
Ground, Chemigation	Liquid [19713-273]		2	6.0 lb ai/A	30	Aerial application is prohibited
Tree Plantations for Timber						
Ground	DF/WDG [33270-26]	4.0 lb ai/A	1	4.0 lb ai/A	NS	Aerial application and application through irrigation is prohibited.
Aquatic Areas[1]						
Handheld	Liquid [9712-8]	0.00000625 lb ai/gal water 0.19 lb ai/A	NS	NS	NA	Use in aquariums and containerized ornamental fish ponds and fountains that are 1000 gallons or less. Wear long-sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves made of any waterproof material.
Residential Turf (Sub-label indicated "For Residential Use")						
Handheld	Liquid [19713-60]	2.0 lb ai/A (0.0844 lb ai/gal) 0.00124 lb ai/ft^2	NS	2.0 lb ai/A	NA	Handlers must wear baseline attire and chemical resistant gloves.

1. Density of product was not provided. Rate calculated as follows: 8 fl oz product/720 gal water x 0.9% ai x 8.34 lb product/gal water (density of water) x 1 gal/128 oz. Rate was not given in area treated, only that the product should

treat ponds/fountains that contain 1,000 gallons or less of water. Therefore, based on available information on pond/pool size in gallons[3], it was conservatively assumed that the size of the pond was 30' x 50' (1500 ft^2) and only 1,000 gallons was needed to fill the pond: 0.00000625 lb ai/gal x 1000 gal/1500 ft^2 x 43560 ft^2/A = 0.19 lb ai/A.

3.4 Anticipated Exposure Pathways

Humans may be exposed to simazine and its chlorinated metabolites in food and drinking water since simazine may be applied directly to growing crops and application may result in these residues reaching surface and ground water sources of drinking water. Adults and children may be exposed to simazine in residential settings due to the existing uses on residential turf. Non-occupational bystanders may be exposed to spray drift/volatilization from occupational applications. Occupational exposures are expected from the application of simazine and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all the existing and proposed uses of simazine.

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. Simazine is considered to be equivalent in neuroendocrine toxicity to the chlorotriazines atrazine and propazine as well as their shared chlorinated metabolites (see

[3] http://news.poolandspa.com/how-many-gallons-of-water-are-in-my-pool/

Section 4.1). The database for simazine'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 simazine, because simazine, propazine, and atrazine share a common mechanism of toxicity for neuroendocrine effects. Separate risk assessments for atrazine and propazine have been developed.

The risks associated with exposure to the hydroxylated metabolites of simazine 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, 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 and Epidemiologic Analysis and 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 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 simazine database is not as robust as the atrazine database. However, atrazine data can be used to bridge data for simazine because they share a common mechanism of toxicity based on neuroendocrine effects. The toxicology database for 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 support 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 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; 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 13 epidemiology studies identified in the literature that generally met one or more of the following criteria: reported a statistically significant estimate of effect for

simazine; originated from a prospective cohort; and/or were otherwise of a moderate or high-quality study design[4]; or were often referenced in the epidemiology literature and were unavailable at the time of the recent 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 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 routes 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, are provided in Section 4.6.2. of this document.

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

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

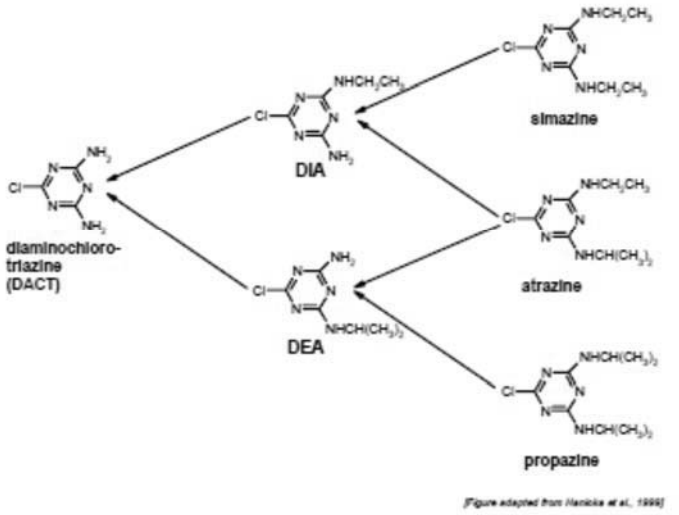
Characterization of the pharmacokinetics and internal dosimetry of atrazine and its metabolites represents a critical step for elucidating the link between exposure and attenuation of the pre-ovulatory LH surge for the application of a MOA approach to risk assessment. Atrazine is quickly metabolized via the oral route to its dealkylated chlorinated metabolites (DEA, DIA, and

[4] 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

DACT) as illustrated in Figure 4.3. DACT is the major metabolite (MRID 44713802; McMullin, 2003). All three metabolites 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)[5] 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.

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 curves (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.

[5] 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

A single-dose human oral pharmacokinetic study (MRIDs 43598603 & 43598604)[6] 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 hr. 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 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 simazine 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)[7], 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 hr (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

[6] 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.

[7]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.

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, 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 simazine 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).

4.5.1 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[8], 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

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

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[9] 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 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.

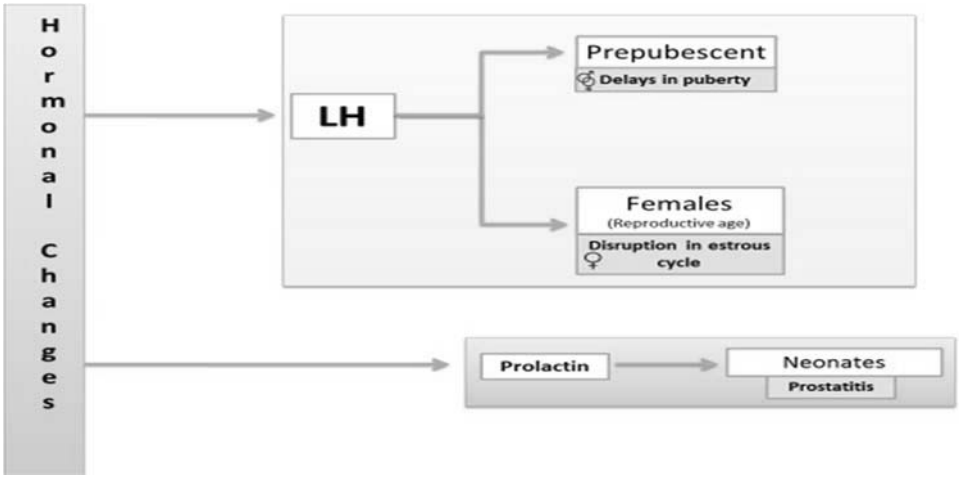
4.5.1.2 LH Changes as a Sentinel Effect for Adverse Health Outcomes

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;

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

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 4.4.1.2). 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.



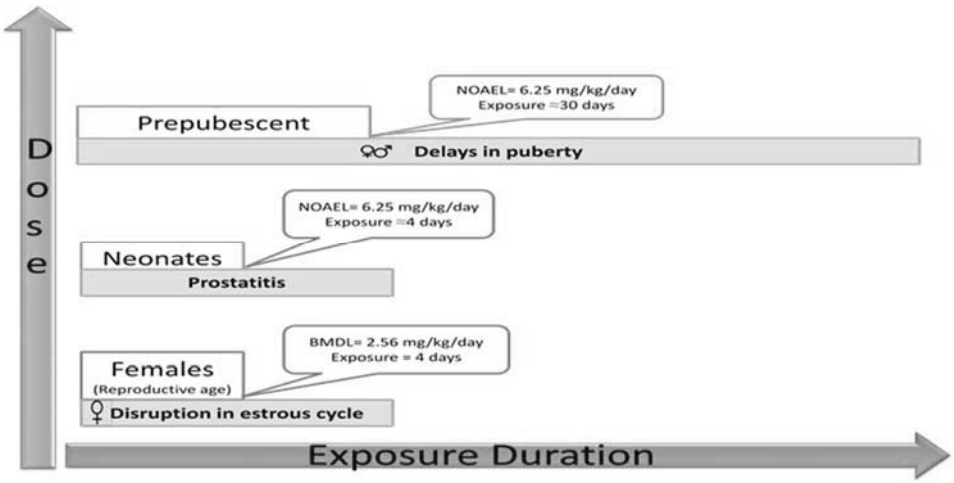


Figure 4.5.1.2. LH Suppression and Adverse Outcomes Observed in Rats

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 or what has been termed as "minipuberty." 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**

$BMDL_{1SD}$ 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 = 2.442/4.92 mg/kg/day

4.5.2 Hydroxysimazine

For this assessment, it is assumed that hydroxysimazine has a toxicity profile identical to hydroxyatrazine. Therefore, the risk assessment for hydroxysimazine relies on toxicity data available on hydroxyatrazine (K. Rickard *et al.,* D418316, 07/10/2018). Unlike the chlorotriazines and their chlorinated metabolites, hydroxysimazine 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.

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 simazine.

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

Over the past several decades, there have been a number of experimental toxicological as well as epidemiologic evaluations of the carcinogenic and non-carcinogenic potential of the triazine herbicides, including atrazine and simazine. With respect to epidemiology, EPA has presented its evaluation of then-available epidemiological information regarding various triazines numerous times to the SAP, and the panel members considered that information in developing their thoughts, recommendations, and advice. These have included the following EPA presentations:

- in June 2000, focusing on breast, ovarian, prostate and NHL cancers;
- in July 2003, focusing on prostate cancer in the triazine manufacturing plant worker studies;
- in February 2010, focusing on the draft framework for incorporating epidemiologic and human incident data in health risk assessment, and its preliminary reviews of several atrazine epidemiology studies on birth outcomes and other health effects;
- in September 2010, focusing on non-cancer epidemiology studies;
- and in July 2011, focusing on cancer epidemiology studies.

The Agency recently conducted an updated epidemiology systematic literature review to investigate evidence on the human health effects potentially associated with exposure to atrazine, simazine, and/or propazine (Appendix B). Ninety-three publications from 1990 – 2017 were identified for inclusion in the epidemiology literature review. These publications investigated carcinogenic and noncarcinogenic effects (43% and 58%, respectively; not mutually exclusive). Most (88%) reported an effect estimate for atrazine, 14% reported an effect estimate for simazine (not mutually exclusive: some articles reported estimates for both chemicals, while other articles reported estimates for only one). No publications reported an effect estimate for propazine. Various study designs, including cohort, case-control, cross-sectional, and ecologic, were represented in the epidemiology material. Included publications were restricted to English language articles that reported effect estimates (*e.g.*, odds ratio, p-trend, regression or correlation coefficients) for atrazine and/or simazine specifically, and included study populations from the USA, France, England, Canada, and Spain.

Of particular interest to the current weight of evidence for the risk assessment of simazine were the 3 epidemiology publications that originated from the 13 epidemiology studies that were assessed in the current Atrazine DRA report, that generally met one or more of the following criteria: reported a statistically significant estimate of effect for simazine; originated from a prospective cohort; and/or were otherwise of a moderate or high quality study design[10]; or were often referenced in the epidemiology literature and were unavailable at the time of the recent SAPs (Appendix B). These 3 studies included: Chevrier *et al.* (2011) which investigated birth and reproductive system health effects, Hoppin *et al.* (2016) which reported on allergic and nonallergic wheeze, and Garcia-Perez *et al.* (2015) which evaluated childhood leukemia. Additional detail on these 3 studies is provided in Appendix B, but brief summaries are provided below:

> Chevrier *et al*. (2011) reported no evidence of a significant positive association between simazine exposure and adverse birth outcomes including FGR, SHC, and congenital malformations such as male genital anomalies. Several study limitations mentioned above including the use of the backward selection technique for the data analysis, and the lack of routine urine sampling from the study participants to assess chronic exposure (only a single urine sample was collected for the duration of the study), reduced the reliability of the study and overall confidence in interpreting the findings of this study.

[10] 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

Garcia-Perez *et al.* (2015) reported a positive association between living within 2.5 km of a facility that released simazine and risk of childhood leukemia; however, due to several limitations including the limited number of exposed cases observed (n = 30), the use of distance to a pollution source as a proxy of exposure, and the different methods for residential classification for cases and controls, limited the ability to draw conclusions from the study.

Hoppin *et al.* (2016) reported evidence of a significant positive association between simazine exposure and allergic wheeze, and no evidence of a positive association between simazine exposure and nonallergic wheeze among male pesticide applicators. Although this study benefited from the large AHS participant cohort with data collected on specific pesticide usage, the study was limited due to the small number of exposed cases observed for both allergic and nonallergic wheeze (n = ~ 40 exposed cases (or n = 1 - 3 % of cases) for both allergic and nonallergic wheeze). Furthermore, the cross-sectional study design was considered a study limitation, as temporality could not be determined. These study limitations limit the reliability of the study, and overall confidence in interpreting the findings of this study.

4.6 Toxicity Endpoint and Point of Departure (POD) Selections

4.6.1 Durations of Exposure, Critical Windows of Exposure, and 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 single day 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[11]). 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 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[12]). 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[13]). 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)[14]. 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

[11] 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

[12] 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

[13] 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

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

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 2003 assessment, the drinking water assessment was conducted using a 90-day duration of concern. However, as described above, the 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.***

4.6.2 Dose Response Assessment

4.6.2.1 Acute/Single Day Dietary Exposure Point of Departure

For the acute dietary endpoint for simazine (summarized in Table 4.6.2.2), a POD of 30 mg/kg/day for females 13-49 years of age was selected from a simazine developmental toxicity study (MRID 40614403. In this study, simazine was administered to CR1 rats (19-23/dose) by gastric intubation at dose levels of 0, 30, 300, or 600 mg/kg/day from days 6 through 15 of gestation. The developmental NOAEL of 30 mg/kg/day was based on unossified teeth, head, centra vertebrae, sternebrae, and rudimentary ribs seen at 300 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 doses 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.

4.6.2.2 Acute/Single Day Dietary Exposure Uncertainty Factors

In the acute dietary assessments, the Agency is applying the typical 10-fold factors for inter- and intra-species extrapolation. Thus, the total uncertainty factor for acute dietary is 100X. The FQPA Safety Factor of 10X was reduced to 1X based on lack of increased sensitivity for infants and children, as supported by the SAP and discussed in Section 4.6. 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 Simazine for Use in Acute Dietary Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure (POD)**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-49 years of age)	NOAEL = 30 mg/kg/day	UF_A= 10X UF_H=10X FQPA SF= 1X	Acute RfD = 0.3 mg/kg/day	Developmental Study in Rats LOAEL = 300 mg/kg/day based on increased incidence of unossified teeth, head, centra vertebrae, sternebrae, and also on rudimentary ribs

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.

4.6.2.3 Four-Day Repeated Exposure (Oral, Dermal, Inhalation) Points of Departure

In the human health risk assessment that supported the 2006 simazine risk assessment (D. Soderberg, D325433, 01/12/2006), 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 simazine 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.

4.6.2.3.1 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)[15]; 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 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[16] 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 4.6.2.3.1). **This $BMDL_{1SD}$ = 2.42 mg/kg/day provides the animal POD used in extrapolating to humans.**

[15] 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.

[16] 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*.

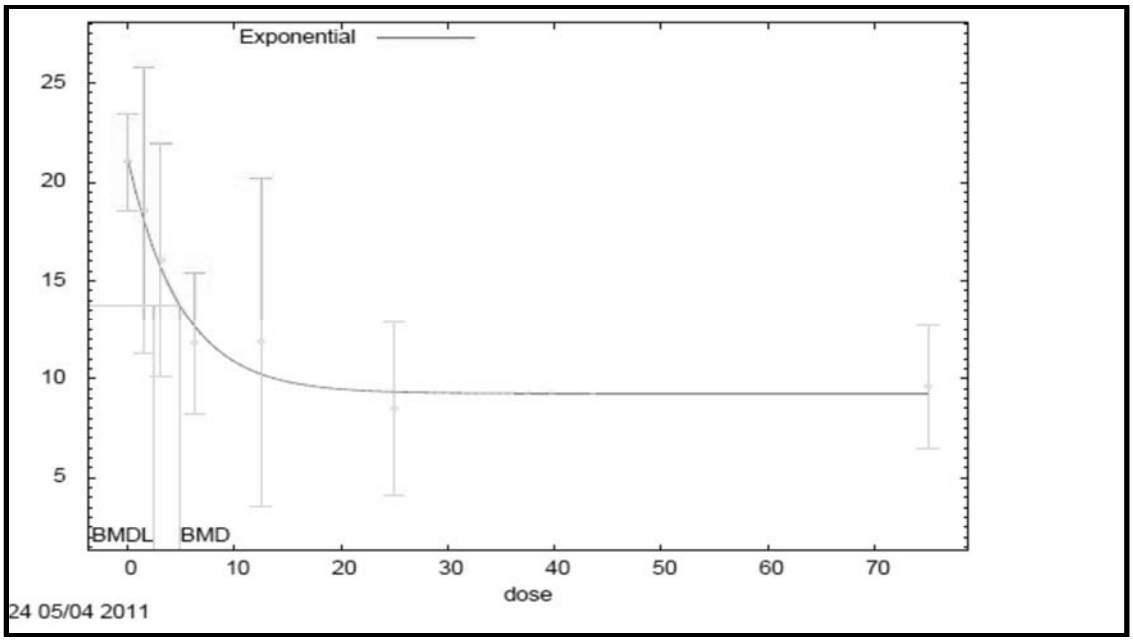


Figure 4.6.2.3.1. Plot of benchmark dose analysis from Cooper *et al.*, (2010) using the exponential model.

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 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 simazine-specific parameters where applicable. The only differences between the three models are the molecular weights 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 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 from an *in vivo* human study 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.

4.6.2.4 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- 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.

4.6.2.4.1 Description and 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).

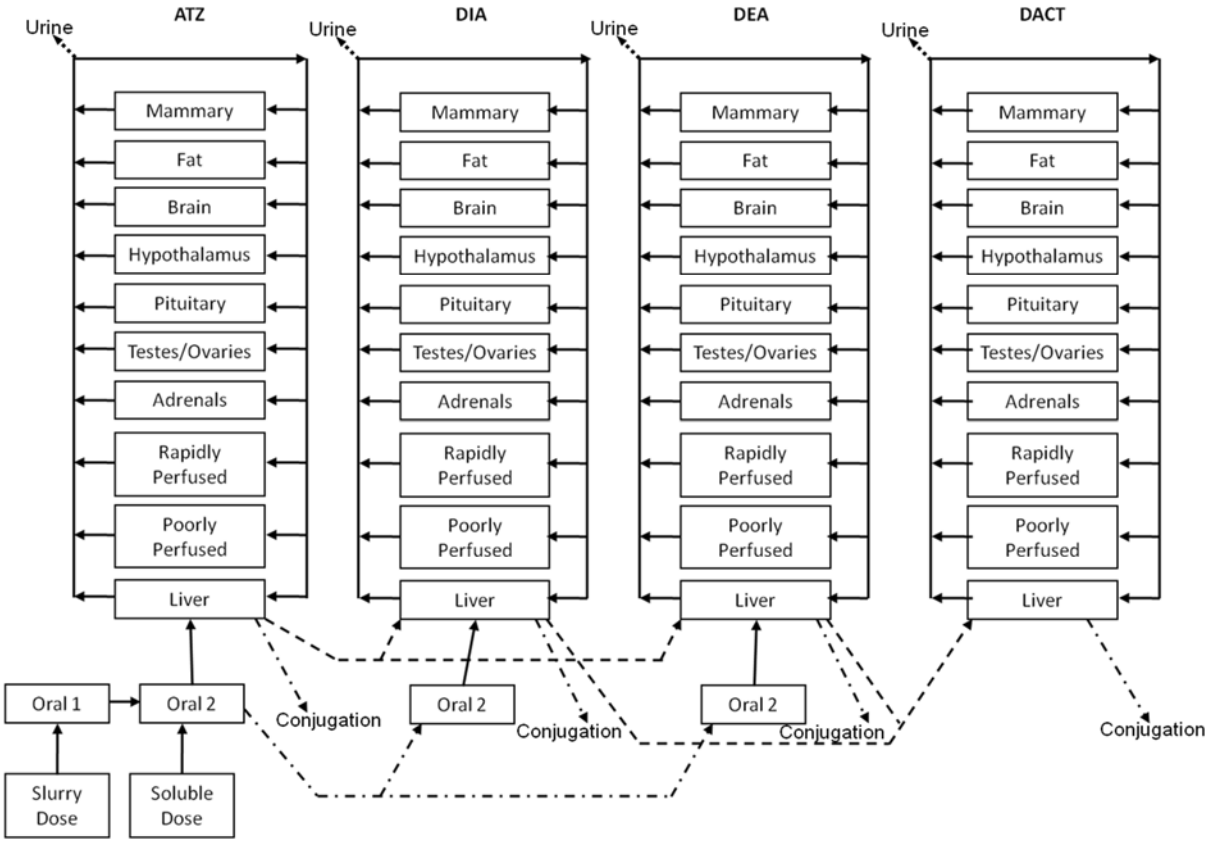


Figure 4.6.2.4.1. Schematic of the PBPK model for atrazine and triazine metabolites (dashed line represents metabolism in liver of atrazine to DIA and DEA and conversion of DIA and DEA to DACT)

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 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 simazine, 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 DEA in Oral 2 (/hr*BW$^{0.75}$)	KMETATRA_ETHYL_OR2C	0.393	0.693	0.26
Absorption rate DEA in Oral 2 (/hr*BW$^{0.25}$)	KAOR2ETHYLC	0.6	0.6	0.6
Metabolism				
Elimination of ATZ (/hr*BW$^{0.25}$)	KELIMATRAC	41.0	41.0	41.0
Affinity constant for ATZ (µmol/L)	KMATRA	30.0	30.0	30.0
Maximum velocity liver ATZ to DEA (µmol/hr/kg$^{0.75}$)	VMAXCATRA_ETHYL	236.3	236.3	752.6
Elimination of DIA (/hr*BW$^{0.25}$)	KELIMISOC	48.4	48.4	48.4
Elimination of DEA (/hr*BW$^{0.25}$)	KELIMETHYLC	7.07	7.07	7.07
Maximum velocity liver DEA (µmol/hr/kg$^{0.75}$)	VMAXCETHYL	25.3	25.3	25.1
Affinity constant for DEA (µmol/L)	KMETHYL	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
Vmax (µmol/min/10^6 hepatocytes)	VMAXCETHYL	0.00015	0.00004	0.00015
Affinity constant DEA (µM)	KMETHYL	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)[17], 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 4.5.2.2.2.2.1) 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[18] (Luecke *et al.,* 2007, Young *et al.,* 2009, Smith *et al.,* 2014[19]). 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.

[17] 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.

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

[19] 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)[20], 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

[20] 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.

4.6.2.4.2 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 Simazine.

Exposure Scenario	Exposure Pathway	Population & Body Weight (kg)				
		All 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]
Residential (Handler)	Dermal					69[4]
	Inhalation					69[4]
Residential (Contact with Treated Turf)	Oral		11[3]			
	Dermal			32[5]	57[6]	69[4]
Residential (Golfing)	Dermal			32[5]	57[6]	69[4]
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.
6 (Exposure Factors Handbook, Table 8-3, mean body weight for the 11 to < 16 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.

For non-dietary dermal exposures, showers were assumed to occur in the PBPK model after one day (24 hours) to account for any residues left on the skin following exposure time. Available information in the Exposure Factors Handbook[21] indicates that the median frequency for baths and showers was estimated to be 7 times per week (i.e., once per day) for children[22]. 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[23]. 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 G.

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

For residential handlers (adults only), the dermal PODs were estimated assuming 50% of the skin's surface was exposed, and that a shower occurred 24 hours after initial exposure; and the

[21] Available at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252
[22] 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
[23] 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

inhalation POD's were estimated assuming 1 hour/day exposure. For golfers (including adults, children 6-11 years old, youth 11-16 years old), the dermal PODs were estimated assuming 50% of the skin's surface was exposed, and that a shower occurred 24 hours after initial exposure. For residential mowers (adults and children 11-16 years old), the dermal PODs were estimated assuming 50% of the skin's surface was exposed, and a shower occurred 24 hours after initial exposure. For adults and children 1 to < 2 years old engaged in other turf activities (including residential and non-occupational exposures), dermal PODs were estimated assuming that 50% of skin surface was exposed, and that a shower occurred 24 hours after initial exposure. The incidental oral PODs for children 1 to < 2 years old for other turf activities was estimated assuming that there were six events, 15 minutes apart, per day. For residential bystanders (adults and children 1 to < 2 years old), the inhalation POD was estimated assuming 24 hours/day of exposure for 1-day.

For occupational handlers and post-application workers, the dermal PODs were estimated assuming a body weight of 69 kg (to 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 summarizes the simazine PBPK modeled external doses (PODs) corresponding to LH surge attenuation.

Table 4.6.2.4.2.2. Simazine PBPK Modeled External Doses (PODs) Corresponding to 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)	21,226	51,446	119,390	77,730	93,054
	Food (mg/kg/day)	3.08	3.26	2.59	2.35	2.32
Residential Handlers	Dermal (mg/kg/day)					35.53
	Inhalation (concn. in air mg/m^3)					231 (5.57 mg/kg/day)[1]
Residential (Golfers)	Dermal (mg/kg/day)			39.41	35.58	35.05
Residential (Mowing)	Dermal (mg/kg/day)				36.07	35.53
Residential (Other Turf Scenarios)	Dermal (mg/kg/day)		50.45			35.41
	Oral (mg/kg/day)		3.34			

Table 4.6.2.4.2.2. Simazine PBPK Modeled External Doses (PODs) Corresponding to 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)**
Residential Bystander	Inhalation (mg/m^3)		2.14			9.34
Non-Occupational Spray Drift	Dermal (mg/kg/day)		50.45			35.41
	Oral (mg/kg/day)		3.34			
Occupational	Dermal (mg/kg/day)					34.8
	Inhalation (concn. in air mg/m^3)					18.1 36.2 10.4 (2.09 mg/kg/day)[2]

1. Residential handler:
   a. 5.57 mg/kg/day = 231 mg/m^3 (POD derived from the PBPK model) × 0.83 m^3/hr (or 13.8 L/min) × 2 hr/day ÷ 69 kg.
2. Occupational handler breathing rates and results:
   a. 2.09 mg/kg/day = 18.2 mg/m^3 × 1 m^3/hr (or 16.7 L/min) × 8 hr/day ÷ 69 kg.
   b. 2.09 mg/kg/day = 36.2 mg/m^3 × 0.5 m^3/hr (8.9 L/min) × 8 h/day ÷ 69 kg.
   c. 2.09 mg/kg/day = 10.4 mg/m^3 × 1.74 m^3/hr (or 29 L/min) × 8 hr/day ÷ 69 kg.

4.6.2.5 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).

4.6.3 Recommendation for Combining Routes of Exposure for Risk Assessment

The acute and chronic dietary aggregate 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; and occupational exposures from the dermal and inhalation routes since the same endpoint was selected.

4.6.4 Cancer Classification and Risk Assessment Recommendation

In 1989, the HED Cancer Peer Review Committee (CPRC) classified simazine as a **Group C Carcinogen (possible human carcinogen)** with a linear low-dose approach (Q_1*) for human risk characterization (E. Rinde, TXR 0052670, 07/31/1989). The Q_1*was $1.2x10^{-1}$. The CPRC met again on October 25, 1989 to discuss recommendations from a September 28, 1989 Science Advisory Panel meeting. The October, 1989 CPRC meeting maintained the Category C classification and the Q_1* of $1.2x10^{-1}$ (H. Spencer, TXR 0052671, 05/24/1990).

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. The CARC evaluated the possibility that any mode of action which may be selected for atrazine would apply for simazine.

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

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

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

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

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

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

On April 14, 2005, the CARC reevaluated the carcinogenic potential of simazine and reclassified simazine as "Not Likely To Be Carcinogenic To Humans." The reclassification was based on the weight of evidence conclusion that simazine is not genotoxic and operates via a mode of action for the development of mammary and pituitary tumors in the female SD rat similar to atrazine. See TXR 0052664 (J. Kidwell, 04/14/2005).

Epidemiology
In 2017, the Agency conducted a formalized literature review to collect, evaluate, and integrate evidence from recent epidemiological literature on the association between chlorotriazines including simazine exposure and human health outcomes including cancer (Appendix B).

This epidemiology literature review identified 93 publications from 1990 – 2017 for inclusion. Of particular interest to the current weight of evidence for the risk assessment of simazine were the 3 epidemiology publications identified in the literature that generally met 1 or more of the following criteria: reported a statistically significant estimate of effect for simazine; originated from a prospective cohort and/or were otherwise of a moderate or high quality study design[24]; or were often referenced in the epidemiology literature and were unavailable at the time of the recent SAPs. Of the three simazine studies, one study (Garcia-Perez *et al.* 2015) reported a positive association between living within 2.5 km of a facility that released simazine and risk of childhood leukemia (OR = 1.66; 95% CI: 1.08, 2.54 with 29 cases and 423 controls living within 2.5 km of a facility; 22 facilities reported 8 kg simazine released into water and no facilities reporting simazine released into air). However, several study limitations included the limited number of exposed cases observed (n = 30), the use of distance to a pollution source as a proxy of exposure, and the different methods for residential classification for cases and controls. As a result, we are unable to conclude that a causal or clear associative relationship exists between simazine exposure and childhood leukemia.

4.7 Hydroxysimazine Toxicity Endpoint and Point of Departure Selection and Uncertainty Factors

Although no toxicity data are available on the hydroxysimazine metabolite, specific toxicity data for the hydroxyatrazine metabolite can be bridged to the hydroxysimazine metabolite. For the hydroxyatrazine metabolite, only the chronic dietary endpoint was applicable, the only relevant duration of exposure associated with a toxic effect. Hydroxyatrazine is a plant metabolite, and to a lesser extent a livestock metabolite; therefore, hydroxysimazine residues are not expected on the surfaces of plants limiting the potential for non-dietary exposures in residential and occupational settings. However, dietary exposures to hydroxysimazine will be 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-

[24] 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

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 E.

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.

4.8 Safety Factor for Infants and Children (FQPA Safety Factor)[25]

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.

[25] 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).

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[26]). 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 exposure assessment is described in detail in Section 5.3. The exposure databases and modeling are sufficient to assure that residues in drinking water will not be underestimated. The drinking water exposure assessment 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[27] 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 the subject of three reviews by the SAP between 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.

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

[27] 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

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:
Two research articles (Chevrier *et al.* 2011, Garcia-Perez *et al.* 2015) identified in the epidemiological literature were considered as part of the FQPA Safety Factor determination.

Chevrier *et al.* 2011 investigated the association between prenatal simazine exposure and risk of adverse birth outcomes, and reported no evidence of a significant positive association. In Garcia-Perez *et al.* 2015, residential proximity to industrial and urban pollutants including simazine was used to evaluate whether an association with childhood leukemia was observed. Although study results suggested a positive association between living within 2.5 km of a facility that released simazine and the risk of childhood leukemia, several study limitations included potential misclassification bias from the use of distance to a pollution source as a proxy of exposure, selection bias from possible geocoding errors, and the use of different methods for residential classification for cases and controls that likely biased the observed outcomes. Due to these limitations, this study (Garcia-Perez *et al.* 2015) does not provide adequate evidence to evaluate whether a causal relationship between simazine exposure and childhood leukemia exists at this time.

Based on review of these two studies mentioned above, no evidence was found that would lead the Agency to conclude that there is a causal association between exposure to simazine and adverse birth outcomes or childhood leukemia.

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.

4.8.1 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.

4.8.2 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 Feb. 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. The Agency continues to monitor the scientific literature and will, as appropriate, incorporate high quality, reliable data that helps further our understanding of atrazine.

4.8.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal[28]

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

[28] 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**
Peripubertal		• 6.25/12.5 mg/kg/day; increased prostatitis, delayed PPS • 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

4.8.4 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 simazine residue chemistry databases 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 residential exposure assessments are based upon the 2012 Residential Standard Operating Procedures (SOPs) and incorporate chemical-specific DFR data. These assessments of exposure are not likely to underestimate the resulting estimates of risk from exposure to simazine.

4.9 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 review 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[29] 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.

Simazine is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see Docket # EPA-HQ-OPP-2013-0251).

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[30].

The EDSP data were considered in the simazine human health risk assessment.

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 simazine is well understood. In general, simazine is metabolized in plants through replacement of the chlorine atom with either a hydroxy group or 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 chlorine 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

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

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 residues absorbed through the foliage. Simazine'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. Hydroxy-metabolites of simazine are not produced in tissues of animals dosed with simazine, per se. As in plants, all metabolic routes in the animal leave the central triazine ring intact.

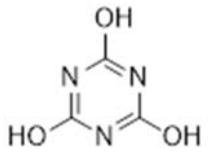
5.1.2 Summary of Environmental Degradation

Similar environmental degradation pathways are operative for atrazine, propazine, and simazine. These chemicals are considered moderately persistent and 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, chlorotriazine use may result in ground water contamination. Consequently, extensive monitoring data have been collected for these chemicals.

The chlorinated and hydroxylated metabolites observed in the plant and/or 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 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 and other terminal breakdown products also occurs (Figure 5.2.1).



Cyanuric Acid

Figure 5.2.1 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 simazine. Risks are quantified separately for the hydroxylated metabolites, based on different toxicological endpoints as compared to simazine and the chlorinated metabolites. As a result, simazine parent plus its chlorinated and hydroxylated metabolites comprise the residues of concern for risk assessment. For tolerance enforcement, the residues of concern are simazine 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 Simazine Risk Assessment and Tolerance Expression.

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

[1] desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT). See Figure 3.1.1.
[2] hydroxysimazine, desisoprpylhydroxyatrazine (DIHA), 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

The residue chemistry database for simazine is considered complete for the purposes of Registration Review and for the proposed new uses. Plant and livestock metabolism studies have successfully established the metabolic profile of simazine and supported identification of the reside of concern for enforcement and risk assessment purposes. Sufficient field trial data have been provided to support the established and proposed tolerances for plant commodities. Extensive field trial data for citrus includes exaggerated rate applications, which indicate that residues are mostly <LOQ and not rate dependent over the range tested. Thus, establishment of the requested crop groups was determined to be supported. Further, adequate analytical methods are available for tolerance enforcement in plant commodities. Storage stability studies are adequate to support sample storage intervals from field trial studies. Sufficient studies were submitted to elucidate the fate of simazine in processed commodities. Livestock feeding studies combined with dietary burden considerations indicate that there is no reasonable expectation of finite residues in livestock commodities; thus, livestock tolerances for simazine are not needed and the established livestock tolerances should be revoked. Rotational crop studies indicate that detectable levels of residues may be taken up by rotational crops at plant back intervals as long as 12 months. The registrant should limit crop rotational to labeled crops or conduct extensive field rotational crop studies and propose tolerances for unlabeled rotational crops at the intended plant back interval.

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 are based on total triazine residues, which include atrazine, propazine, and simazine, and all the related metabolites, and are not just based on simazine and its chlorinated and hydroxylated metabolites, these EDWCs may be considered high-end estimates for the simazine 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 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

5.4.1 Description of Residue Data Used in Dietary Assessment

Separate dietary (food only) assessments were performed for: 1) simazine and its chlorinated metabolites, and 2) hydroxysimazine and hydroxylated metabolites because different toxicity endpoints were observed for these compounds. Drinking water residues were not directly incorporated into the dietary assessment because a DWLOC approach to aggregate risk was used to calculate the amount of exposure available in the total 'risk cup' for drinking water after accounting for any exposures from food and/or residential use (See Section 7.0).

For simazine and its chlorinated metabolites, separate (food only) acute, 4-day, and chronic dietary exposure assessments were completed; the chronic dietary exposure assessment was completed to assess background dietary exposures for use in the aggregate assessment. The acute and 4-day dietary assessments were partially refined, assuming residue levels from field trial studies, default processing factors, and assumed that 100% of the proposed and registered commodities were treated. The background dietary exposure assessment was also partially refined, assuming residue levels from field trial studies, default processing factors, and average percent crop treated data.

For the hydroxysimazine and hydroxylated metabolites, the only relevant toxicity endpoint selected was for chronic dietary exposures. The chronic dietary assessment was refined, and incorporated residue levels from metabolism studies, default processing factors, and average percent crop treated information for simazine.

5.4.2 Summary of Toxicological Points of Departure for Dietary (Food) Assessment

The toxicological PODs, uncertainty factors, and PADs are summarized in the tables below.

Table 5.4.2.1. Summary of Toxicological Doses and Endpoints for Simazine for Use in Dietary Human Health Risk Assessments.

Exposure Scenario	Point of Departure (POD)	Uncertainty/ FQPA Safety Factors	RfD, PAD for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49)	NOAEL = 30 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1X	aRfD = 0.30 mg/kg/day aPAD = 0.30 mg/kg/day	Developmental Study in Rats LOAEL = 300 mg/kg/day based on increased incidence of unossified teeth, head, centra vertebrae, sternabrae, and also on rudimentary ribs
Acute Dietary (All Populations)	No toxic effect attributable to a single dose was identified for the general population.			
4-Day Infants <1 yr	3.08 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.10 mg/kg/day	National Health and Environmental Effects Research Laboratory (NHEERL) 4-day atrazine study (Oral Gavage Rat Study) $BMDL_{1SD}$ = 2.42 mg/kg/day based on attenuation of LH surge. PODs for population subgroups indicated were derived via PBPK modeling.
4-Day Children 1-2	3.26 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.11 mg/kg/day	
4-Day Children 6-12	2.59 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.086 mg/kg/day	
4-Day Youth 13-19	2.35 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.078 mg/kg/day	
4-Day Females13-49	2.32mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.073 mg/kg/day	
Cancer	Classification: "Not likely to be Carcinogenic to Humans".			

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

5.4.3 Percent Crop Treated Used in Dietary Assessment

The acute and 4-day assessments for simazine and its chlorinated metabolites assumed 100% crop treated for all registered crops.

The chronic (background) assessments for simazine and its chlorinated metabolites and for hydroxysimazine and its hydroxylated metabolites incorporated average percent crop treated estimates as provided by the Biological and Economic Analysis Division (BEAD; See Attachment 1 of D442822: Simazine Screening Level Usage Analysis (SLUA), 8/15/2017). The following average percent crop treated estimates were used in the background (chronic) assessment for the following crops: almond: 10%; apple: 10%; avocado: 5%; blueberry: 15%; caneberry: 45%; cherry: 5%; field corn: 5%; sweet corn: 2.5%; grapefruit: 20%; grape: 25%; hazelnut: 35%; lemon: 10%; nectarine: 5%; olive: 15%; orange: 25%; peach: 15%; pear: 10%; pecan: 5%; plums/prunes: 2.5%; strawberry: 5%; tangerine: 5%; and walnut: 20%. For commodities not included in the SLUA, 100% CT was assumed.

5.4.4 Acute Dietary Risk Assessment

Simazine and its chlorinated metabolites
A partially refined acute dietary assessment was conducted using residue levels from field trial studies, default processing factors, and 100% crop treated assumptions. At the 95th percentile of exposure, the estimated food risk is < 1% of the acute population adjusted dose (aPAD) for females 13-49 years old (the acute toxicological endpoint is only applicable to females of reproductive age).

Hydroxysimazine and its hydroxylated metabolites
No toxicological effects attributable to a single dose were identified for hydroxysimazine or the other hydroxylated metabolites of concern; therefore, no risk is expected from this exposure scenario.

5.4.5 4-Day Dietary Risk Assessment

For the 4-day exposure assessment, the acute (two-day) DEEM module was used as the most appropriate module available in DEEM for approximating four days of consumption/exposure; there is no module reflecting four days of consumption. The use of two-day average food consumption data is considered a high-end approximation to the intended four-day time frame appropriate for the luteinizing hormone (LH) surge toxicity endpoint.

Simazine and its chlorinated metabolites
A partially refined 4-day dietary assessment was conducted using residue levels from field trial studies, default processing factors, and 100% crop treated assumptions. At the 95th percentile of exposure, the estimated food risk is 2.3% of the 4-day population adjusted dose (4-day PAD) for children 1-2 years old, the most highly exposed population subgroup.

Hydroxysimazine and its hydroxylated metabolites

A toxic effect specifically attributable to a 4-day exposure time was not found in the toxicity database; therefore, a 4-day exposure endpoint has not been identified for hydroxysimazine. The chronic dietary assessment is protective for any multi-day or long-term exposures.

5.4.6 Background and Chronic Dietary Risk Assessment

Simazine and its chlorinated metabolites
To support an aggregate (dietary plus residential exposures) risk assessment, a partially refined chronic dietary assessment was conducted to assess background (average) dietary exposures using residue levels from field trial studies, default processing factors, and average percent crop treated data; input into the chronic DEEM module. The highest estimated food exposure is 0.000144 mg/kg/day for the children 1-2 years old population subgroup (See Table 5.4.8 for exposure estimates for all population subgroups).

Hydroxysimazine and its hydroxylated metabolites
A refined chronic dietary assessment was conducted using residue levels from metabolism studies, default processing factors, and average percent crop treated data; input into the chronic DEEM module. The highest estimated food exposure is 0.000085 mg/kg/day for the children 1-2 years old population subgroup. This exposure level corresponds to < 1% cPAD for chronic exposures to hydroxysimazine.

5.4.7 Cancer Dietary Risk Assessment

As simazine has been classified as "Not likely to be carcinogenic to humans," cancer risk is not a concern and a quantitative cancer dietary risk assessment was not conducted.

5.4.8 Summary Tables

Table 5.4.8.1. Summary of Dietary (Food only) Exposure and Risk for Simazine and its Chlorinated Metabolites.[1]

Population Subgroup	Acute Dietary (95th Percentile)		4-Day Dietary (95th Percentile)			Background Dietary Exposure (for Use in Aggregate Assessment)
	Dietary Exposure (mg/kg/day)	% aPAD	4-day PAD[2]	Dietary Exposure (mg/kg/day)	% 4dPAD	Dietary Exposure (mg/kg/day)
All Infants (< 1 year old)	N/A	N/A	0.10	0.001749	1.8	0.000062
Children 1-2 years old			**0.11**	**0.002536**	**2.3**	**0.000144**
Children 6-12 years old			0.086	0.001113	1.3	0.000043
Youth 13-19 years old			0.078	0.000599	< 1	0.000023
Females 13-49 years old	0.000624	< 1	0.077	0.000542	< 1	0.000025

1. Highest exposures identified in bold.
2. PAD = 4-day dietary POD for each subpopulation (Table 4.6.2.4.2.2) ÷ Total Uncertainty Factor of 30X.

Table 5.4.8.2. Summary of Chronic Dietary (Food Only) Exposure and Risk for Hydroxysimazine and its Metabolites.[1]

Population Subgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD
All Infants (< 1 year old)	0.000042	< 1

Table 5.4.8.2. Summary of Chronic Dietary (Food Only) Exposure and Risk for Hydroxysimazine and its Metabolites.[1]		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD**
Children 1-2 years old	**0.000085**	**< 1**
Children 6-12 years old	0.000026	< 1
Youth 13-19 years old	0.000015	< 1
Females 13-49 years old	0.000016	< 1

1. Highest exposure identified in bold.

6.0 Residential Exposure/Risk Characterization

There are no proposed residential uses of simazine at this time; however, there are existing residential uses that have been reassessed in this document to reflect updates to HED's 2012 Residential SOPs[31] along with policy changes for body weight assumptions. The revision of residential exposures will impact the human health aggregate risk assessment for simazine.

6.1 Residential Handler Exposure/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 tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

All registered simazine product labels with residential use sites (e.g., residential lawns) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use PPE (chemical resistant gloves). However, one of these labels (EPA Reg. No. 19713-60) contains a separate sub-label for "residential use". This label includes a statement regarding PPE; however, HED has assumed that this product may be marketed for homeowner use, and has conducted a quantitative residential handler assessment.

The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- Mixing/loading/applying liquid formulations for application to turf via hose-end sprayers, manually pressurized handwand sprayers, sprinkler cans, and backpack sprayers.

Residential Handler Exposure Data and Assumptions

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

[31] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Application Rate: There are no proposed uses that would result in residential handler exposures; however, there is one registered label that has been assumed for use by residential handlers (EPA Reg. No. 19713-60). A summary of the registered application rates is provided in Table 3.3.2.

Unit Exposures and Area Treated or Amount Handled: Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[32].

Exposure Duration: Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners. Currently available toxicity data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats. Therefore, for the purposes of the residential risk assessments, only the 4-day duration is assessed since it will be protective for longer durations of exposure.

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

Residential Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[33].

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 Residential Handler Non-Cancer Exposure and Risk Estimates
As shown below in Table 6.1.1, all residential handler combined (dermal + inhalation) risk estimates were not of concern (MOEs > LOC of 30) and ranged from 44 to 180.

[32] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide
[33] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.1.1. Residential Handler Exposure and Risk Estimates for Simazine.										
Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[3]	MOE[4]	Dose (mg/kg/day)[5]	MOE[6]	MOE[7]
Mixer/Loader/Applicator										
Liquid formulations to Lawns/Turf with a Hose-End Sprayer	30	13.4	0.022	2.0 lb ai/A	0.5 A	0.19	180	0.00032	17,000	180
Liquid formulations to Lawns/Turf with a Manually Pressurized Handwand		63	0.018	0.0844 lb ai/gal	5 gals	0.39	92	0.00011	51,000	92
Liquid formulations to Lawns/Turf with a Sprinkler Can		13.4	0.022	0.00124 lb ai/ft^2	1,000 ft^2	0.24	148	0.0004	14,000	150
Liquid formulations to Lawns/Turf with a Backpack Sprayer		130	0.14	0.0844 lb ai/gal	5 gals	0.80	45	0.0086	6,500	44

1 See Table 3.3.2.
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (69 kg).
4 Dermal MOE = Dermal POD (35.52 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (69 kg).
6 Inhalation MOE = Inhalation POD (5.56 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
7 Total MOE = Total MOE = 1 ÷ [(1 / Dermal MOE) + (1 /Inhalation MOE)].

6.2 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with simazine. The quantitative exposure/risk assessment for residential post-application exposures is based on dermal and incidental oral contact to turf following liquid and DF/WDG applications.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[34]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-Application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[34].

Application Rate: There are no proposed uses that would result in residential post-application exposure; however, there are existing uses of simazine that would result in post-application exposures for adults and children. The maximum single application rate for each registered formulation is listed in Table 3.3.2.

Exposure Duration: Residential exposures to treated turf are expected to be short-term in duration. As noted above, currently available toxicity data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats and the exposure duration needed for the triazines to reach a pseudo steady-state. Therefore, for the purposes of the residential risk assessments, only the 4-day steady-state duration is assessed since it will be protective for longer durations of exposure.

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

Turf Transferrable Residues: Chemical-specific TTR data have been submitted for simazine. The TTR study was reviewed and found to be acceptable for risk assessment (R. Travaglini, D261346, 08/15/2001).

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

Study Summary: The study was conducted in California and Florida on two different test plots (irrigated and non-irrigated) in each state 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

[34] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

in California using a tractor-mounted, groundboom, and broadcast tank sprayer. Applications were made in Florida using a backpack sprayer. Samples were collected using the modified California Cloth Roller technique developed by the Outdoor Residential Exposure Task Force (ORETF). 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 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 6.2.1, and in D428623 (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 residential post-application 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. This value was not adjusted for any difference between the study application rate (2.0 lb ai/A) and the registered turf application rate (2.0 lb ai/A) because these rates are the same. However, because risk estimates of concern were identified for adults and children 1 to < 2 years old using the maximum application rate for spray applications (2.0 lb ai/A), the 4-day residue was adjusted to evaluate lower application rates.

Table 6.2.1. 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

Residential Post-Application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure can be found in the 2012 Residential SOPs[35].

Combining Exposure and Risk Estimates

Since dermal and incidental oral exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. Combining both of these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each

[35] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 < 2 years old are the dermal and hand-to-mouth scenarios. This combination is considered a protective estimate of children's exposure.

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

Simazine-specific TTR data are available. These data were incorporated into the residential post-application assessment for evaluating exposures to turf treated with liquid and DF/WDG formulations of simazine.

Using the available chemical-specific data and 4-day average turf transferrable residues, there were post-application dermal risk estimates of concern from the registered use of simazine on residential turf for adults and children 1 to < 2 years old and combined (dermal + incidental oral) risk estimates of concern for children 1 to < 2 years old (LOC = 30). There were no dermal post-application risk estimates of concern for children 11 to < 16 years old and children 6 to < 11 years old; and no incidental oral post-application risk estimates of concern for children 1 to < 2 years old (MOEs > LOC of 30). The dermal MOEs ranged from 26 to 1,300 for adults and from 330 to 1,300 for children 11 to < 16 years old. The dermal MOE was 310 for children 6 to < 11 years old. The combined (dermal + incidental oral) MOE for children 1 to < 2 years old was 17 (LOC = 30).

Because risk estimates of concern were identified adults and children 1 to < 2 years old for the maximum application rate for spray applications (2.0 lb ai/A), the application rate that would not result in risk estimates of concern was back-calculated. A maximum rate of 1.0 lb ai/A on residential turf results in no risk estimates of concern for adults and children 1 to < 2 years old.

Table 6.2.2. Residential Post-Application Exposure and Risk Estimates for Simazine.

Lifestage	Use Site	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs[3]	Combined Routes (X indicates included in Combined MOE)	Combined MOEs[4]
		Activity	Route of Exposure					
Adult	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.107	330		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.028	1,300		
	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	1.37	**26**		
Adult	Treated Turf	High Contact Activities after Spray Application	Dermal	1.0 lb ai/A[5]	0.683	52		
Children 11 to < 16 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.108	330		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.0276	1,300		
Children 6 to < 11 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.127	310		
Children 1 to < 2 Years Old	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	2.33	**22**	X	**17**
			Hand-to-Mouth		0.048	70	X	

Table 6.2.2. Residential Post-Application Exposure and Risk Estimates for Simazine.								
Lifestage	**Use Site**	**Post-application Exposure Scenario**		**Application Rate[1]**	**Dose (mg/kg/day)[2]**	**MOEs[3]**	**Combined Routes (X indicates included in Combined MOE)**	**Combined MOEs[4]**
		Activity	**Route of Exposure**					
		Contact after Spray Application	Object-to-Mouth		0.0015	2,300		
			Soil Ingestion		0.000067	49,000		
Children 1 to < 2 Years Old	Treated Turf	High Contact Activities after Spray Application	Dermal	1.0 lb ai/A[5]	1.17	43	X	33
			Hand-to-Mouth		0.024	140	X	
			Object-to-Mouth		0.000726	4,600		
			Soil Ingestion		0.0000339	99,000		

1 See Table 3.3.
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day). Scenario-specific PODs provided in Table 4.6.2.4.2.2.
4 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/incidental oral MOE)], where applicable.
5 Presented because risk estimates of concern identified assuming the maximum application rate (2.0 lb ai/A).

6.3 Residential Risk Estimates for Use in Aggregate Assessment

As identified in Section 5.2, some exposure scenarios on treated turf resulted in risk estimates of concern for adults and children 1 to < 2 years old. Therefore, the scenarios resulting in risk estimates of concern from simazine use on residential turf have not been considered for the purpose of performing an aggregate assessment since additional exposure from food and water would only increase the risk estimates.

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for simazine.

- Adults: post-application dermal exposures from golfing on treated turf.
- Children 11 to < 16 years old: post-application dermal exposures from golfing on treated turf.
- Children 6 to < 11 years old: post-application dermal exposures from golfing on treated turf.
- Children 1 to < 2 years old: risks of concern were identified from contact with treated turf using the maximum registered application rate; therefore, a residential exposure scenario has not been recommended for aggregate risk assessment.

Table 6.3.1. Recommendations for the Residential Exposures for the Simazine Aggregate Assessment.									
Lifestage	**Exposure Scenario**	**Dose (mg/kg/day)[1]**				**MOE[2]**			
		Dermal	**Inhalation**	**Oral**	**Total**	**Dermal**	**Inhalation**	**Oral**	**Total**
Adults	Golfing after Spray Application	0.107	N/A	N/A	0.107	330	N/A	N/A	330
Children 11 to < 16 Years Old	Golfing after Spray Application	0.108			0.108	330			330

Table 6.3.1. Recommendations for the Residential Exposures for the Simazine Aggregate Assessment.									
Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Children 6 to < 11 Years Old	Golfing after Spray Application	0.127			0.127	310			310
Children 1 to < 2 Years Old	Risks of concern identified – therefore, a scenario has not been recommended for aggregate assessment.								

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + incidental oral (where applicable).

2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Incidental Oral MOE), where applicable.

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. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be aggregated. The durations of exposure identified for simazine aggregate assessment are acute and 4-day. The duration of exposure identified for hydroxysimazine aggregate assessment is chronic. The acute and chronic aggregate assessments include food and drinking water only. The 4-day aggregate assessment includes food, drinking water, and residential exposures.

A drinking water level of comparison (DWLOC) approach to aggregate risk was used to calculate the amount of exposure available in the total 'risk cup' for drinking water after accounting for any exposures from food and/or residential use (HED SOP 99.5, *Updated Interim Guidance for Incorporating Drinking Water Exposure into Aggregate Risk Assessments,* 8/1/99). The DWLOCs are then compared to the estimated concentrations in drinking water (EDWCs). If the DWLOCs are greater than the EDWCs, there is no aggregate 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 atrazine, propazine, and triazine cumulative risk assessments.

For the acute and chronic aggregate assessments, the formula for calculating the DWLOC is as follows:

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

Water ingestion rates (in L/kg) are included in the acute and chronic DWLOC calculations. These values vary with population subgroup, the duration time of interest, and the exposure percentile applicable for regulation. These values were determined directly from the NHANES/WWEIA water consumption data, making use of the appropriate exposure durations and percentiles.

For the simazine 4-day aggregate assessments, the DWLOC approach used a reciprocal MOE

calculation method since the target MOEs (level of concern based on the total uncertainty factor) are the same for all relevant sources of exposure, i.e., 30X for residential (dermal, oral, and inhalation), food, and drinking water, and because the points of departure are different for food, drinking water, and residential exposures. This entailed calculating the MOE for water (MOE_{water}) by deducting the contributions from food (MOE_{food}) and residential (MOE_{dermal}, MOE_{oral}, and $MOE_{inhalation}$) from the target MOE (MOE_{agg}) of 30. The DWLOC is then calculated by dividing the POD_{water} by the MOE_{water}. The general reciprocal MOE formula is as follows:

$$MOE_{agg} = 1/ [(1/MOE_{water}) + (1/MOE_{food}) + (1/MOE_{dermal}) + (1/MOE_{oral}) + (1/MOE_{inhalation})]$$

$$MOE_{water} = 1/ [(1/MOE_{agg}) – ((1/MOE_{food}) + (1/MOE_{dermal}) + (1/MOE_{oral}) + (1/MOE_{inhalation}))]$$

$$DWLOC= POD_{water}/ MOE_{water}$$

For the 4-day assessment, water consumption is accounted for in the PBPK model when deriving the drinking water PODs and is not included in the above DWLOC calculation. 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.

7.1 Acute Aggregate Risk

Simazine

The acute aggregate assessment considers food and water exposures. The acute DWLOC for females 13-49 years old is 5,500 ppb (Table 7.1). 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 aggregate risk of concern.

Table 7.1. Acute Aggregate Risk Calculations- Simazine.

Age (years) /Population	Acute Scenario						
	POD (mg/kg/day)	LOC	Acute PAD (mg/kg/day)	Water Ingestion Rate (L/kg) [1]	Residential Exposure (mg/kg/day)	Acute Food Exposure (mg/kg/day)[2]	Acute DWLOC (ppb)[3]
Females 13-49	30	100	0.3	0.0544	--	0.000624	5,500

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

2 Table 5.3.7.1.

3 DWLOC = [(aPAD – Food Exposure)]/[water consumption (L/kg) * 0.001 mg/ug]

Hydroxysimazine

No toxicological effects attributable to a single dose were identified for hydroxysimazine; therefore, an acute endpoint has not been identified and no risk is expected from this exposure scenario.

7.2 Four-Day Aggregate Risk

Simazine
The 4-day aggregate assessment includes background dietary exposures from food (Table 5.4.8.1) together with the maximum exposures from residential uses of simazine (Tables 6.3.1 and 6.3.2 for selected turf scenarios).

Aggregate DWLOCs
The calculated 4-day DWLOCs are all greater than the 4-day EDWCs for TCTs in surface water or ground water; there are no 4-day aggregate risks of concern for the included turf scenarios (Table 7.2.1). The lowest 4-day DWLOC is for all infants < 1 year old at 700 ppb. The highest 4-day EDWC is 585 ppb based on ground water modeling.

This aggregate assessment excluded residential exposure scenarios that were of risk concern. Specifically, adults and children 1 to < 2 years old contacting treated turf via high contact activities were not included since there is a risk estimate of concern for dermal and combined dermal and oral exposures when assuming the maximum labeled rate for spray applications (2.0 lb ai/A). Excluding these scenarios, there were no aggregate risk estimates of concern at the maximum registered application rates.

However, because risk estimates of concern were identified adults and children 1 to < 2 years old for the maximum application rate for spray applications (2.0 lb ai/A), the application rate that would not result in aggregate risk estimates of concern was back-calculated. A maximum rate of 0.70 lb ai/A on residential turf results in a 4-day DWLOC of 630 ppb for children 1 to < 2 years old and 1,800 ppb for females 13-49 years old, which would not be of risk concern.

Table 7.2.1. Simazine 4-Day Aggregate Risk Calculations.

Lifestage	Turf Exposure Scenario	LOC for Aggregate Risk	MOE Food Exposure[1]	MOE Dermal Residential Exposure[2]	MOE Oral Residential Exposure[3]	MOE Inhalation Residential Exposure	Minimum Allowable MOE for Drinking Water Exposure[4]	4-Day DWLOC[5] (ppb)
All Infants (< 1 year old)	N/A	30	50,000	N/A	N/A	N/A	30	700
Children 1 to < 2 years old	Risks of concern were identified for the non-dietary exposure scenarios – therefore, an aggregate assessment has not been conducted.							
Children 6-12 years old	Golfing after Spray Application	30	60,000	310	N/A	N/A	33	3,600
Youth 13-19 years old	Golfing after Spray Application	30	102,000	330			33	2,400
Females 13-49 years old	Golfing after Spray Application	30	93,000	330			33	2,800

1 **Food:** MOEfood = PODfood (mg/kg/day) (from Table 4.6.2.4.2.2)/ *Background* Food Exposure (mg/kg/day) (from Table 5.4.8.1).
2 **Dermal:** MOEdermal = PODdermal (mg/kg/day) (from Table 4.6.2.4.2.2)/ Dermal Exposure (mg/kg/day) (from Table 6.3.1).
3 **Oral:** MOEdermal = PODoral (mg/kg/day) (from Table 4.6.2.4.2.2)/ Oral Exposure (mg/kg/day) (from Table 6.3.1).
4 **Water:** MOEwater = 1/ [(1/MOEagg) – ((1/MOEfood) + (1/MOEdermal) + (1/MOEoral) + (1/MOEinhalation))]; Where MOEagg =LOC.

5 **DWLOC:** DWLOC ppb= PODwater ppb; from Table 4.6.2.4.2.2) /MOEwater.

7.3 Chronic Aggregate Risk

Simazine
The 4-day aggregate risk assessments (Section 7.2) are protective for chronic aggregate risks since the POD and endpoint used for the 4-day assessment are the most sensitive for any duration, and are, therefore, protective of longer durations of exposure.

Hydroxysimazine
The chronic aggregate risk assessment for the hydroxysimazine considers food and water exposures**.** No residential exposures to the hydroxysimazine metabolite are expected from the simazine uses. The lowest chronic DWLOC for hydroxysimazine is for all infants (<1 year old) at 1300 ppb as shown in Table 7.3. The chronic DWLOCs are greater than the chronic EDWCs for THTs in surface water or ground water (Table 5.3; EDWC range = 7.33-76 ppb); there is no chronic aggregate risk of concern.

Table 7.3. Chronic Aggregate Risk Calculations- Hydroxysimazine.

Population Subgroup	Chronic Scenario						
	POD (mg/kg/day)	LOC	Chronic PAD (mg/kg/day)	Water Ingestion Rate (L/kg) [1]	Residential Exposure (mg/kg/day)	Chronic Food Exposure (mg/kg/day)[2]	Chronic DWLOC (ppb)[3]
All Infants (< 1 year old)	6.76	100	0.0676	0.0540	N/A	0.000042	1,200
Children 1 to < 2 years old				0.0302		**0.000088**	2,200
Children 6-12 years old				0.0184		0.000026	3,600
Children 6-12 years old				0.0153		0.000015	4,400
Youth 13-19 years old				0.0208		0.000017	3,200

[1] Water ingestion rates from 2003-2008 NHANES/WWEIA consumption database averaged values.
[2] Hydroxyatrazine food exposure values are from Table 5.4.6.2.
[3] DWLOC = [cPAD – (Food)]/[water consumption (L/kg) * 0.001 mg/ug]

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 (https://www.regulations.gov/document?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/docket?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 simazine.

In addition to this screen, the Agency has developed a preliminary bystander volatilization inhalation exposure assessment for simazine utilizing the currently available inhalation toxicity data and air monitoring data.

The simazine bystander volatilization inhalation exposure assessment compares the maximum and average air concentrations detected in each of the monitoring studies to the steady state inhalation PBPK modeled POD for residential bystanders. Use of the maximum air concentration is meant to represent a potential resident who lives next to a treated field and may be exposed to the peak concentration of simazine volatilizing off the field over a 24-hour period. Use of the steady-state inhalation POD for this 1-day scenario is considered a conservative approach because LH surge is not considered an acute/single dose effect; therefore, this assessment provides a screening level risk estimate. Use of the arithmetic mean simazine air concentration from each study is meant to represent a potential seasonal exposure. The following data sources provide air concentration measurements for simazine:

1. **Ambient site study conducted in Lompoc, CA by the California Department of Pesticide Regulation (CDPR) under the Toxic Air Contaminant Program[36].**

Although simazine was monitored by CDPR in 2000, there were no detectable concentrations of simazine found in the study (no concentrations above the method detection limit of 0.6 ng/m^3). Therefore, a quantitative bystander assessment was not conducted using these data; however, a quantitative bystander assessment was conducted using available detectable air concentration data and there were no risk estimates of concern for adults or children 1 to < 2 years old.

2. **Application site study in Tulare County, CA and ambient site study in Fresno County, CA[37].**

Application site monitoring for simazine was conducted from December 18 to December 22, 1998 in orange orchards in Tulare County to correspond with simazine use/applications. Ambient monitoring was conducted to coincide with the use of simazine on grapes in Fresno County from February 18 to April 1, 1998. Low level background contamination of simazine was observed in almost all laboratory solvents and resin blanks. This contamination was at a level just above the method detection limit (MDL) but below the estimated quantitation limit (EQL). The contamination most likely came from the simazine-Cl3 isotope dilution standard (99% pure).

All four of the application background samples had results above the EQL for simazine. The highest simazine concentration, 190 ng/m^3 (23 pptv), was observed at the east sampling site

[36] Available at: http://www.cdpr.ca.gov/docs/emon/pubs/tac/studies/lmpc_links.htm
[37] Available at: http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/simazine.pdf

during the 2nd sampling period (1 hour). The air temperature during the study was cold with freezing at night and so these test results do not represent worst case conditions (i.e., hot days). The highest ambient simazine concentration, 18 ng/m^3 (2.2 pptv), was observed at the Fremont Middle School sampling site in Fowler on March 2, 1998. The average of all ambient samples was 5.35 ng/m^3.

Tables 8.1 and 8.2 summarizes the risk estimates for non-occupational bystanders using the highest air concentration data available. There are no risk estimates of concern for adults and children (MOE≥30) using the maximum air concentration data from all application site monitoring, and no risk estimates of concern for adults and children (MOEs ≥ 30) using the average of all ambient air concentrations from all monitoring sites.

3. Ambient studies by the CDPR Air Monitoring Network (AMN) in 2011 in Salinas (Monterey County), Shafter (Kern County), and Ripon (San Joaquin County), CA. Simazine was monitored in 2011, 2012, 2013, 2014, 2015, and 2016.

CDPR monitored a total of 34 pesticides and 5 pesticide breakdown products. Pesticides included in AMN monitoring were selected based primarily on potential health risk.

Simazine was mostly reported as trace amounts in the CDPR AMN studies. Trace concentrations were reported as a value halfway between the MDL and LOQ. Therefore, as a conservative estimate of exposure, the residential bystander assessment was conducted using both the maximum air concentration and the average air concentration reported from all three sites, whether or not the amount was reported as "trace".

Tables 8.1 and 8.2 summarizes the risk estimates for non-occupational bystanders using the highest air concentration data available. There are no risk estimates of concern for adults and children (MOE≥30) using the maximum air concentration data from all application site monitoring, and no average risk estimates of concern for adults and children (MOEs ≥ 30) using the average of all ambient air concentrations from all monitoring sites.

Table 8.1. Simazine Preliminary Volatilization MOE Analysis for Non-Occupational Bystanders – Adults.

Study	Year of Study	Maximum Air Concentration (ng/m^3)	Average Air Concentration (ng/m^3)	MOE Using Maximum Air Concentration[1] (LOC = 30)	MOE Using Average Air Concentration[1] (LOC = 30)
CDPR Air Resources Board Application Site Monitoring Study in Tulare County, CA	2000	190	NA	49,000	NA
CDPR Air Resources Board Ambient Monitoring Study in Fresno County, CA		NA	5.35	NA	1,700,000
CDPR Air Monitoring Network Ambient Monitoring Study	2011	Trace (4.1)[2]	Trace (0.7)[2,3]	2,300,000	13,000,000
	2012	Trace (5.3)[2]	1.0[3]	1,800,000	9,300,000
	2013	ND (0.6)[4]	0.6[3]	16,000,000	16,000,000
	2014	Trace (5.3)[2]	0.7[3]	1,800,000	13,000,000
	2015	Trace (5.3)[2]	0.7[3]	1,800,000	13,000,000
	2016[4]	Trace (5.3)[2]	0.7[3]	1,800,000	13,000,000

1 MOE = POD (9.34 mg/m^3) ÷ [Maximum or Average Air Concentration (ng/m^3) × (1 mg/1,000,000 ng)].
2 Number in parenthesis for trace samples is the value halfway between the MDL and the LOQ.

3 Average of all monitoring sites.
4 Number in parenthesis for Non Detects (ND) is ½ the MDL.
5 2016 Report is labeled "draft." http://www.cdpr.ca.gov/docs/emon/airinit/amn_2016_report_draft.pdf.

Table 8.2. Simazine Preliminary Volatilization MOE Analysis for Non-Occupational Bystanders - Children.					
Study	**Year of Study**	**Maximum Air Concentration (ng/m^3)**	**Average Air Concentration (ng/m^3)**	**MOE Using Maximum Air Concentration[1] (LOC = 30)**	**MOE Using Average Air Concentration[1] (LOC = 30)**
CDPR Application Site Monitoring Study in Tulare County, CA	2000	190	NA	11,000	NA
CDPR Ambient Monitoring Study in Fresno County, CA		NA	5.35	NA	400,000
CDPR Air Monitoring Network Ambient Monitoring Study	2011	Trace (4.1)[1]	Trace (0.7)[1,2]	520,000	3,100,000
	2012	Trace (5.3)[1]	1.0[2]	400,000	2,100,000
	2013	ND (0.6)[3]	0.6[2]	3,600,000	3,600,000
	2014	Trace (5.3)[1]	0.7[2]	400,000	3,100,000
	2015	Trace (5.3)[1]	0.7[2]	400,000	3,100,000
	2016[4]	Trace (5.3)[1]	0.7[2]	400,000	3,100,000

1 MOE = POD (2.14 mg/m^3) ÷ [Maximum or Average Air Concentration (ng/m^3) × (1 mg/1,000,000 ng)].
2 Number in parenthesis for trace samples is the value halfway between the MDL and the LOQ.
3 Average of all monitoring sites.
4 Number in parenthesis for Non Detects (ND) is ½ the MDL.
5 2016 Report is labeled "draft." http://www.cdpr.ca.gov/docs/emon/airinit/amn_2016_report_draft.pdf.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

A quantitative spray drift assessment was conducted for simazine even though there are registered uses for direct treatment of residential turf, these uses resulted in some post-application risk estimates of concern for adults and children 1 to < 2 years old; therefore, they cannot be considered protective of potential spray drift exposures.

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[38]. 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

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

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 simazine. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at 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[39,40]. 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). Section 9.1 provides the screening level drift related risk estimates.
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. Simazine is registered on various agricultural crops using ground and aerial equipment. Aerial applications are prohibited on the and because simazine is a soil-directed herbicide, airblast applications are not expected. Therefore, the recommended drift scenario screening level options are listed below:

[39] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift
[40] Note that for many cases the scenarios outlined in the screening approach represent actual use practice so risk assessors should be aware and characterize these appropriately.

- **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.

A 4-day average turf transferrable residue were 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 TTR values used were adjusted for the maximum registered single application rates of simazine. 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 simazine at the field edge for children 1 to < 2 years old; except for applications to grapefruit and oranges at 8.0 lb ai/A (combined dermal + incidental oral MOE = 22, LOC = 30). Non-occupational spray drift exposure and risk estimates resulting from applications to grapefruit and oranges were not of concern for children 1 to < 2 years old 10 feet from the field edge (combined dermal + incidental oral MOE = 44, LOC = 30). There were no non-occupational spray drift risk estimates of concern for adults at the field edge; the dermal MOEs ranged from 35 to 280 (LOC = 30).

Using coarser sprays and lowering boom height for groundboom sprayers lowers risk concerns. Non-occupational spray drift risk estimates are provided in Table 9.1.

Table 9.1. Summary of Spray Drift Risk Estimates Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Simazine[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
Grapefruit, Oranges	8.0	0		35			**22**	
		10		N/A			44	
Christmas Tree Farms & Shelterbelts, Lowbush Blueberries, Cranberries, Grapefruit, Oranges, Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts, Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts, Sod, Tree Plantations	4.0	0	N/A	69	N/A	N/A	44	N/A
Corn	2.5	0		110			71	

Table 9.1. Summary of Spray Drift Risk Estimates Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Simazine[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
Corn, Almonds, Peaches, Nectarines	2.0	0		140			88	
Corn, Strawberries	1.0	0		280			180	

1. Risk estimates presented assuming screening-level droplet sizes (fine to medium for aerial applications; very fine to fine for groundboom 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 D428623 (K. Rickard, 06/12/2018). "N/A" provided when equipment not applicable based on the use pattern or when MOEs are not of concern at distances closer to the field edge (i.e., if risk estimates are not of concern at the field edge, additional risk estimates are not presented for 10 ft from the field edge).

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 as 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)[41] and conducting cumulative risk assessments (CRA)[42]. 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

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

the potential for food and drinking water exposures from the currently registered domestic use on sorghum.

11.0 Occupational Exposure/Risk Characterization

11.1 Occupational Handler Exposure and Risk Estimates – Proposed and Existing Uses

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 and existing uses of simazine. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios listed in Tables 11.1.1 and 11.1.2.

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 proposed and registered application rates are in Tables 3.3.1 and 3.3.2.

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[43]", 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[44].

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,

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

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

For simazine, based on the proposed and registered uses, both short- and intermediate-term exposures are expected for occupational handlers. Currently available toxicity data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats. Therefore, for the purposes of the occupational risk assessments, only the 4-day steady-state duration will be assessed since it is 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: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Both proposed product labels require occupational handlers to wear baseline attire and chemical resistant gloves; EPA Reg. No. 100-603 (DF/WDG) requires mixer/loaders and others supporting groundboom applications to wear baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, socks, chemical resistant apron, and a NIOSH dust/mist respirator. The registered labels vary with respect to PPE requirements. All of the DF/WDG labels require mixer/loaders for groundboom applications; and/or mixer/loaders, cleaners of equipment or spills, or other handlers otherwise exposed to the concentrate to wear: baseline attire (long sleeved shirts, long pants, shoes, and socks), chemical resistant gloves, and a dust/mist respirator. Some labels also require mixer/loaders to wear a double layer of clothing or coveralls. All other handlers of DF/WDG products must wear baseline attire and chemical resistant gloves. All of the registered liquid labels require handlers to wear baseline attire and waterproof or chemical resistant gloves. Therefore, results are presented for "baseline attire," (long sleeved shirt, long pants, shoes plus socks), protective gloves, and no respirator; as well as baseline, gloves, and various levels of 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 D428623.

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 – *Proposed Uses*
There were combined (dermal + inhalation) occupational handler exposure and risk estimates of concern (MOE > 30) with baseline attire and chemical resistant gloves (lowest level of PPE on the proposed labels) for some of the proposed uses of simazine. Dermal exposures were the highest contributors to the combined (dermal + inhalation) risk estimates. The following scenarios are of concern with baseline attire and chemical resistant gloves:

- Mixing/loading/applying DF/WDG and liquid formulations using backpack spray equipment to grapefruit and oranges (0.4 lb ai/gal).
    - *These scenarios were not of concern with the addition of a double layer of clothing.*
- Mixing/loading/applying DF/WDG and liquid formulations using mechanically pressurized handgun spray equipment to grapefruit and oranges (0.4 lb ai/gal); lemon, pome fruit, stone fruit, filberts, macadamia nuts, pecans, and walnuts (0.2 lb ai/gal); and almonds (0.1 lb ai/gal).
    - *These scenarios are **still of concern** with the addition of a double layer of clothing and a PF10 respirator (maximum available PPE).*

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Proposed Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
Mixer/Loader						
DF/WDG for Groundboom Application	Grapefruit, Oranges	8.0 lb ai/A	40 A	150	50	38
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	290	100	74
	Almonds	2.0 lb ai/A	40 A	580	200	150
Liquids for Groundboom Application	Grapefruit, Oranges	8.0 lb ai/A	40 A	200	2,100	180
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	400	4,100	360
	Almonds	2.0 lb ai/A	40 A	800	8,300	730
Applicator						
Applying Sprays via Groundboom	Grapefruit, Oranges	8.0 lb ai/A	40 A	470	1,300	350
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	930	2,700	690
	Almonds	2.0 lb ai/A	40 A	1,900	5,300	1,400
Mixer/Loader/Applicator						
DF/WDG Formulations for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	**18** 36 [DL/G]	3,500	**18** 36 [DL/G, No R]
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	40 gals	36	7,000	36
	Almonds	0.1 lb ai/gal	40 gals	73	14,000	73
DF/WDG for Mechanically Pressurized Handgun	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**2.9** **4.4 [DL/G]**	42 210 [PF5]	**2.7** **4.0 [DL/G, No R]**

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Proposed Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
Applications					420 [PF10]	**2.9 [SL/G, PF5]** **4.3 [DL/G, PF5]** **2.9 [SL/G, PF10]** **4.4 [DL/G, PF10]**
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**5.9** **8.8 [DL/G]**	83 420 [PF5] 830 [PF10]	**5.5** **8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]** **8.7 [DL/G, PF10]**
	Almonds	0.1 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**
Liquids for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	**18** 36 [DL/G]	3,500 18,000 [PF5] 35,000 [PF10]	**18** 36 [DL/G, No R]
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	40 gals	36	7,000 35,000 [PF5] 70,000 [PF10]	36
	Almonds	0.1 lb ai/gal	40 gals	73	14,000	73
Liquids for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**2.9** **4.4 [DL/G]**	42 210 [PF5] 420 [PF10]	**2.7** **4.0 [DL/G, No R]** **2.9 [SL/G, PF5]** **4.3 [DL/G, PF5]**

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Proposed Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
						2.9 [SL/G, PF10] **4.4 [DL/G, PF10]**
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**5.9** **8.8 [DL/G]**	83 420 [PF5] 830 [PF10]	**5.5** **8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]** **8.7 [DL/G, PF10]**
	Almonds	0.1 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**

1 Risk estimates of concern are in bold.
2 Based on Table 3.3.1.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (34.8 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). SL = Single Layer of Clothing, G = Gloves, DL = Double Layer.
5 Inhalation MOE = Inhalation POD (2.1 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). No R = No Respirator, PF5 = Respirator with Protection Factor of 5, PF10 = Respirator with a Protection Factor of 10.
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates - *Existing Uses*
There were no occupational handler risk estimates of concern for the existing uses of simazine except for some of the mixing/loading/applying using handheld spray equipment scenarios. In all cases, dermal exposures were the highest contributors to the combined (dermal + inhalation) risk estimates.

The following crop/application rate combinations are of concern assuming baseline attire and label-specified PPE (gloves), but are not of concern assuming a double layer of clothing:

- Mixing/loading/applying DF/WDG and liquid formulations for backpack sprayer application to grapefruit and oranges (0.4 lb ai/gal).
- Mixing/loading/applying DF/WDG and liquid formulations for mechanically pressurized handgun applications to strawberries (0.05 lb ai/gal).

The following crop/application rate combinations are ***still of concern*** assuming baseline attire, label-specified PPE (gloves), a double layer of clothing, and a PF10 respirator (maximum available PPE):

- Mixing/loading/applying DF/WDG and liquid formulations for broadcast backpack sprayer applications to landscape turf (0.13 lb ai/gal) (spot applications do not result in risk estimates of concern with label-specified PPE).
- Mixing/loading/applying DF/WDG and liquid formulations for mechanically pressurized handgun applications to grapefruit and oranges (0.4 lb ai/gal); lemons, apples, pears, tart cherries, avocadoes, filberts, grapes, olives, peaches, plums, sweet cherries, pecans, walnuts (0.2 lb ai/gal); almonds, peaches, nectarines, macadamia nuts, blueberries, blackberries, loganberries, raspberries (0.1 lb ai/gal); nursery ornamentals (0.15 lb ai/gal); lowbush blueberries (0.1 lb ai/gal); cranberries (0.2 lb ai/gal); and sweet corn (0.13 lb ai/gal).

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
Mixer/Loader						
DF/WDG for Chemigation Application	Sweet Corn, Field Corn	1.0 lb ai/A	350 A	130	46	34
Liquids for Chemigation Application	Grapefruit, Oranges	4.0 lb ai/A	350 A	46	470	42
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	4.0 lb ai/A	350 A	46	470	42
	Almonds, Peaches, Nectarines	2.0 lb ai/A	350 A	91	950	83
	Sod	4.0 lb ai/A	350 A	46	470	42
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	350 A	46	470	42
	Field Corn	2.0 lb ai/A	350 A	91	950	83
	Nursery Ornamentals	3.0 lb ai/A	60 A	350	3,700	320
	Sweet Corn	2.0 lb ai/A	350 A	91	950	83
	Strawberries	1.0 lb ai/A	350 A	180	1,900	160
DF/WDG for Groundboom Application	Golf Course	2.0 lb ai/A	40 A	580	200	150
	Nursery Ornamentals	3.0 lb ai/A	60 A	260	90	67
	Sod	4.0 lb ai/A	80 A	150	50	38
	Grapefruit, Oranges	8.0 lb ai/A	40 A	150	50	38
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts	4.0 lb ai/A	40 A	290	100	74
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	580	200	150
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	150	50	38
	Sweet Corn	2.0 lb ai/A	80 A	290	100	74
	Strawberries	1.0 lb ai/A	80 A	580	200	150
	Field Corn	2.0 lb ai/A	200 A	120	40	30

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
Liquids for Groundboom Application	Golf Course	2.0 lb ai/A	40 A	800	8,300	730
	Nursery Ornamentals	3.0 lb ai/A	60 A	350	3,700	320
	Sod	4.0 lb ai/A	80 A	200	2,100	180
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts	4.0 lb ai/A	40 A	400	4,100	360
	Field Corn	2.5 lb ai/A	200 A	130	1,300	120
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	800	8,300	730
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	200	2,100	180
	Grapefruit, Oranges	8.0 lb ai/A	40 A	200	2,100	180
	Strawberries	1.0 lb ai/A	80 A	800	8,300	730
	Sweet Corn	2.5 lb ai/A	80 A	320	3,300	290
Applicator						
Applying Sprays via Groundboom	Golf Course	2.0 lb ai/A	40 A	1,900	5,300	1,400
	Nursery Ornamentals	3.0 lb ai/A	60 A	830	2,400	620
	Sod	4.0 lb ai/A	80 A	470	1,300	350
	Grapefruit, Oranges	8.0 lb ai/A	40 A	470	1,300	350
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	470	1,300	350
	Sweet Corn	2.5 lb ai/A	80 A	750	2,100	550
	Strawberries	1.0 lb ai/A	80 A	1,900	5,300	1,400
	Field Corn	2.5 lb ai/A	200 A	300	850	220
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Raspberries,	4.0 lb ai/A	40 A	930	2,700	690

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
	Loganberries, Macadamia Nuts					
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	1,900	5,300	1,400
Mixer/Loader/Applicator						
DF/WDG Formulations for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	**18** 36 [DL/G]	3,500	**18** 36 [DL/G, No R]
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	40 gals	36	7,000	36
	Almonds, Peaches, Nectarines	0.1 lb ai/gal	40 gals	73	14,000	73
	Christmas Tree Farm	0.2 lb ai/gal	40 gals	36	7,000	36
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	48	9,300	48
	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	**15** **27 [DL/G]**	400 2,000 [PF5] 4,000 [PF10]	**14** **25 [DL/G, No R]** **15 [SL/G, PF5]** **15 [SL/G, PF10]** **27 [DL/G, PF10]**
	Landscape Turf [Spot]	0.13 lb ai/gal	40 gals	56	11,000	56
	Forestry	0.2 lb ai/gal	40 gals	36	7,000	36
DF/WDG for Manually Pressurized Handwand Applications	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	1,100	930	500
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	930	800	430
DF/WDG for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**2.9** **4.4 [DL/G]**	42 210 [PF5] 420 [PF10]	**2.7** **4.0 [DL/G, No R]** **2.9 [SL/G, PF5]** **4.3 [DL/G, PF5]** **2.9 [SL/G, PF10]** **4.43 [DL/G, PF10]**
	Lemons, Apples, Pears, Tart Cherries, Avocadoes,	0.2 lb ai/gal	1000 gals	**5.9**	83	**5.5**

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
	Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts			**8.8 [DL/G]**	420 [PF5] 830 [PF10]	**8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]** **8.7 [DL/G, PF10]**
	Almonds, Peaches, Nectarines, Macadamia Nuts, Blueberries, Blackberries, Loganberries, Raspberries	0.1 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**
	Golf Course	2.0 lb ai/A	5 A	170	340	110
	Nursery Ornamentals	0.15 lb ai/gal	1000 gals	**7.8** **12 [DL/G]**	110 560 [PF5] 1,100 [PF10]	**7.3** **11 [DL/G, No R]** **7.7 [SL/G, PF5]** **12 [DL/G, PF5]** **7.7 [SL/G, PF10]** **12 [DL/G, PF10]**
	Landscape Turf	2.0 lb ai/A	5 A	170	340	110
	Lowbush Blueberries	0.1 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**
	Cranberries	0.2 lb ai/gal	1000 gals	**5.9** **8.8 [DL/G]**	83 420 [PF5] 830 [PF10]	**5.5** **8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]**

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
						8.7 [DL/G, PF10]
	Strawberries	0.05	1000 gals	**23** 35 [DL/G]	330 1,700 [PF5] 3,300 [PF10]	**22** 32 [DL/G, No R]
	Sweet Corn	0.13	1000 gals	**9.0** **14 [DL/G]**	130 640 [PF5] 1,300 [PF10]	**8.4** **13 [DL/G, No R]** **8.9 [SL/G, PF5]** **14 [DL/G, PF5]** **8.9 [SL/G, PF10]** **14 [DL/G, PF10]**
Liquids for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	**18** 36 [DL/G]	3,500 18,000 [PF5] 35,000 [PF10]	**18** **36 [DL/G, No R]**
	Christmas Tree Farm	0.2 lb ai/gal	40 gals	36	7,000 35,000 [PF5] 70,000 [PF10]	36
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	48	9,300	48
	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	**15** **270 [DL/G]**	390 2,000 [PF5] 3,900 [PF10]	**14** **25 [DL/G, No R]** **15 [SL/G, PF5]** **27 [DL/G, PF5]** **15 [SL/G, PF10]** **270 [DL/G, PF10]**
	Landscape Turf [Spot]	0.13 lb ai/gal	40 gals	55	11,000 53,000 [PF5] 110,000 [PF10]	55
	Aquatic areas (ponds, lakes, fountains)	0.19 lb ai/A	5 A	310	59,000	310
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet	0.2 lb ai/gal	40 gals	36	7,000	36

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
	Cherries, Pecans, Walnuts					
	Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts; Almonds, Nectarines, Peaches	0.1 lb ai/gal	40 gals	73	14,000	73
Liquids for Manually Pressurized Handwand Applications	Nursery Ornamentals	0.15 lb ai/gal	40 gals	930	800	430
	Landscape Turf	0.13 lb ai/gal	40 gals	1,000	910	480
Liquids for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**2.9** **4.4 [DL/G]**	42 210 [PF5] 420 [PF10]	**2.7** **4.0 [DL/G, No R]** **2.9 [SL/G, PF5]** **4.3 [DL/G, PF5]** **2.9 [SL/G, PF10]** **4.4 [DL/G, PF10]**
	Golf Course	2 lb ai/A	5 A	270	7,600	260
	Nursery Ornamentals	0.15 lb ai/gal	1000 gals	**7.8** **12 [DL/G]**	110 560 [PF5] 1,100 [PF10]	**7.3** **11 [DL/G, No R]** **7.7 [SL/G, PF5]** **12 [DL/G, PF5]** **7.7 [SL/G, PF10]** **12 [DL/G, PF10]**
	Landscape Turf	2.0 lb ai/A	5 A	270	7,600	260
	Aquatic Areas (fountains, ponds)	0.19 lb ai/A	5 A	1,200	18,000	1,00
	Cranberries	0.2 lb ai/gal	1000 gals	**5.9** **8.8 [DL/G]**	83 420 [PF5] 830 [PF10]	**5.5** **8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]** **8.7 [DL/G, PF10]**
	Sweet Corn	0.13 lb ai/gal	1000 gals	**9.0** **14 [DL/G]**	130 640 [PF5]	**8.4** **13 [DL/G, No R]**

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
					1,300 [PF10]	**8.9 [SL/G, PF5]** **14 [DL/G, PF5]** **8.9 [SL/G, PF10]** **14 [DL/G, PF10]**
	Lowbush Blueberries	0.10 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**
	Strawberries	0.05 lb ai/gal	1000 gals	**23** 35 [DL/G]	330	**22** 32 [DL/G, No R]
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**5.9** **8.8 [DL/G]**	83 420 [PF5] 830 [PF10]	**5.5** **8.0 [DL/G, No R]** **5.8 [SL/G, PF5]** **8.6 [DL/G, PF5]** **5.9 [SL/G, PF10]** **8.7 [DL/G, PF10]**
	Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts; Almonds, Nectarines, Peaches	0.1 lb ai/gal	1000 gals	**12** **18 [DL/G]**	170 830 [PF5] 1,700 [PF10]	**11** **16 [DL/G, No R]** **12 [SL/G, PF5]** **18 [DL/G, PF5]** **12 [SL/G, PF10]** **18 [DL/G, PF10]**

1 Risk estimates of concern are in bold.
2 Based on Table 3.3.2.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (34.8 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). SL = Single Layer of Clothing, G = Gloves, DL = Double Layer.
5 Inhalation MOE = Inhalation POD (2.1 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). No R = No Respirator, PF5 = Respirator with Protection Factor of 5, PF10 = Respirator with a Protection Factor of 10.

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

11.2 Post-Application Exposure and Risk Estimates – Proposed and Existing Uses

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

Most of the registered and the proposed uses for simazine are soil-directed preplant or pre-emergent uses where no crop foliage is present. Currently, HED has no transfer coefficients or other data to assess post-application dermal exposures to soil by occupational workers. In general, such exposures are considered to be negligible. Therefore, for the soil-directed uses, post-application exposures and risks to occupational workers were not assessed.

The registered uses on turf (golf courses and sod farms) are not specifically soil-directed and, therefore, could result in potential post-application exposures and have been assessed assuming high "crop" height and full foliage density.

Since simazine is mostly applied as an early season herbicide and is a ground/soil directed application for most agricultural crops, the dermal post-application exposure assessment assumed low crop height and minimum foliage density for the rest of the registered agricultural crops. Therefore, only the following activities were assessed: frost control, grafting, irrigation, propagating, scouting, transplanting, and weeding. This is expected to be a conservative assessment of potential post-application dermal exposures as most simazine applications are expected to be directed towards weeds, not growing crops.

<u>Occupational Post-Application Dermal Exposure Data and Assumptions</u>

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 simazine, both short- and intermediate-term post-application exposure could occur for the proposed and registered agricultural uses. However, for the chlorotriazine herbicides, only 4-day exposure durations are assessed since they will be protective for longer durations of exposure.

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[45]" which, along with additional information about the ARTF data, can be found at the Agency website[46]. Table 11.2.2.2 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

Application Rate: The proposed application rates are provided in Table 3.3.1 and the registered application rates are provided in 3.3.2.

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 simazine; 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 plants treated with atrazine (K. Rickard, D442405, 09/26/2017).

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

Study Summary: The available 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 a 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 2.636 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 11.2.2.1. The predicted DAT0 residue value of 4.147 µg/cm^2 derived from the DF formulation was used to estimate dermal risk from contact with treated crops because it provided a more conservative value than that generated using the liquid formulation (2.486 µg/cm^2). This residue value was adjusted for any difference between the study application rate and the registered agricultural crop application rates.

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

Table 11.2.2.1. Summary Statistics for "Dislodgeable Foliar Residues of Atrazine on Field Corn" (D442405).		
Corn DFR MRID # 44883601		
Statistic	**Atrazine 4L (Missouri)**	**Atrazine 90 DF (Missouri)**
Application Rate (lb ai/A), Target Application Rate = 2.5 lb ai/A	2	2.5
Measured Average Day 0 Residue (µg/cm^2)	2.636	4.2063
Predicted Day 0 Residue (µg/cm^2)	2.486	**4.147**
Slope	-0.449	-0.586
Half-Life (days)	1.5	1.2
R^2	0.95	0.87

Turf Transferrable Residues: See Section 6.2 and Table 11.2.2.2 for a summary of the available TTR data for simazine.

Table 11.2.2.2. Summary Statistics for "Turf Transferrable Residues for Simazine Applied to Turf" (D261345).				
Statistic	**Florida**		**California**	
	Non-Irrigated	**Irrigated**	**Non-Irrigated**	**Irrigated**
Application Rate (lb ai/A)	2.0	2.0	2.0	2.0
Measured Average Day 0 Residue (µg/cm^2)	0.3187	0.1753	0.2698	0.0885
Predicted Day 0 Residue (µg/cm^2)	0.313	0.146	**0.385**	0.065
Slope	-0.084	-0.098	-0.068	-0.039
Half-Life (days)	8.2	7.1	10.2	17.9
R^2	0.8423	0.8495	0.8515	0.5572

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 Appendix A.

Occupational Post-Application Non-Cancer Dermal Risk Estimates

Using atrazine DFR and simazine TTR data, there are no occupational post-application MOEs are of concern for the registered and proposed uses of simazine on the day of application, except for hand-set irrigation for highbush and lowbush blueberries; this scenario is not of concern 1 day after application. The occupational post-application MOEs range from 24 to 1,000 (LOC = 30). All dermal post-application risk estimates are presented in Table 11.2.2.3.

Table 11.2.2.3. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Proposed and Existing Uses of Simazine[1].							
Crop/Site	**Activities**	**Application Rate (lb ai/A)**	**Transfer Coefficient (cm^2/hr)**	**DFR/TTR[2]**	**Dermal Dose (mg/kg/day)[3]**	**Day 0 MOE[4]**	**DAT for MOE > LOC[5]**
Almond	Transplanting	2.0	230	3.32	0.088	390	N/A
Apple, Avocado, Blackberry, Highbush Blueberry, Lowbush Blueberry, Cherry, Cranberry, Grape (Wine), Grape (Juice), Grape (Table), Grape (Raisin), Hazelnuts (Filberts), Lemon, Macadamia Nuts, Olive, Peach, Pear, Pecan, Plum, Raspberry, Walnut	Transplanting	4.0	230	6.64	0.177	200	N/A
Blackberry, Highbush Blueberry, Grape (Wine), Grape (Juice), Raspberry	Scouting	4.0	640	6.64	0.492	71	N/A

Table 11.2.2.3. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Proposed and Existing Uses of Simazine[1].							
Crop/Site	**Activities**	**Application Rate (lb ai/A)**	**Transfer Coefficient (cm^2/hr)**	**DFR/TTR[2]**	**Dermal Dose (mg/kg/day)[3]**	**Day 0 MOE[4]**	**DAT for MOE > LOC[5]**
Highbush Blueberry, Lowbush Blueberry	Handset Irrigation	4.0	1,900	6.64	1.46	**24**	1 (MOE = 43)
Cherry, Pear	Scouting	4.0	580	6.64	0.446	78	N/A
Field Corn, Sweet Corn (Grain), Sweet Corn (Processing)	Scouting	2.5	210	4.15	0.101	340	N/A
	Handset Irrigation	2.5	1,900	4.15	0.914	38	N/A
	Hand Weeding	2.5	70	4.15	0.034	1,000	N/A
Grape (Wine), Grape (Juice)	Propagating	4.0	640	6.64	0.492	71	N/A
Grapefruit, Orange	Transplanting	8.0	230	13.27	0.354	98	N/A
Nectarine	Transplanting	2.0	230	3.32	0.088	390	N/A
Nursery Ornamentals	Grafting, Propagating, Transplanting	3.0	230	4.98	0.133	260	N/A
Strawberry	Scouting	1.0	210	1.66	0.040	860	N/A
	Hand Weeding	1.0	70	1.66	0.013	2,600	N/A
	Transplanting	1.0	230	1.66	0.044	790	N/A
Golf Course Turf	Maintenance	2.0	3,700	0.385	0.165	210	N/A
Sod	Maintenance, Slab Harvesting, Transplanting/Planting	4.0	6,700	0.770	0.598	58	N/A

1 The registered uses on turf (golf courses and sod farms) are not specifically soil-directed and, therefore, could result in potential post-application exposures and have been assessed assuming full high "crop" height and full foliage density. Since atrazine is mostly applied as an early season herbicide and is a ground/soil directed application, the dermal post-application exposure assessment assumed low crop height and minimum foliage density for the rest of the registered agricultural crops.

2 DFR Data Source: Field Corn – MRID 44883601: Day 0 residue = 4.147 ug/cm^2, study application rate = 2.5 lb ai/A. Turf – MRID 44958701: Day 0 residue: 0.385 ug/cm^2, study application rate = 2.0 lb ai/A.

3 Daily Dermal Dose = [DFR/TTR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

4 MOE = POD (34.8 mg/kg/day) / Daily Dermal Dose.

5 DAT = Day after Treatment/Application for MOE to be greater than the LOC (30).

Restricted Entry Interval

Simazine is classified as Toxicity Category III for acute dermal toxicity and Toxicity Category IV for eye irritation, and skin irritation potential. It is not a skin sensitizer. One occupational post-application scenario (handset irrigation for highbush and lowbush blueberries) resulted in a risk estimate of concern on the day of application. This scenario is not of concern 1 day after application. The REIs on the existing simazine labels ranged from 12 to 24 hours; therefore, the REIs on the registered labels may need to be revised to address those concerns.

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 simazine.

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.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

12.0 Incident Data Review

The OPP Incident Data System (IDS), National Pesticide Information Center (NPIC), California Pesticide Illness Surveillance Program (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 were consulted for pesticide incident data on the active ingredient simazine (S. Recore *et al.,* D444041, 11/01/2017). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to atrazine, propazine, and simazine exposure. In the current IDS analysis, from January 1, 2012 to January 12, 2017, four incidents were reported involving simazine. These incidents were classified as minor severity. A query of NPIC incidents from 2012 to 2017, found one incident involving simazine. NPIC classified this incident as minor in severity. A query of CA PISP incidents from 2010 to 2014, found one incident involving simazine. A query of SENSOR-Pesticides from 2010-2013 identified three cases involving simazine. Two cases were moderate in severity and one case was low in severity. All three cases were occupational exposures. The details regarding the reported incidents from the various sources can be found in the 11/01/2017 document (S. Recore *et. al*., D444041 11/01/2017). The Agricultural Health Study (AHS) findings and epidemiological investigations for simazine are reviewed in separate documents (A. Aldridge, D447697, 07/09/2018 and A. Aldridge, D447696, 07/09/2018).

Based on the low frequency and severity of simazine incidents reported to IDS, NPIC, CA PISP and SENSOR-Pesticides, 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 analyses will be conducted.

13.0 References

Disciplinary Human Health References

Aldridge, A. D447696, 07/09/2018. Atrazine: Tier II Epidemiology Report.

Aldridge, A. D447697, 07/09/2018. Simazine: Tier II Epidemiology Report.

Donovan, W. D442825, 07/10/2018. Simazine. Abbreviated Residue Chemistry Review of Studies Submitted in Response to Data Call-In (DCI) Request.

Donovan, W. D442822, 06/12/2018. Simazine. Acute, 4-Day, Background, and Chronic Dietary (Food Only) Exposure Assessments for Registration Review.

Donovan, W. D409212, 06/26/2013. Simazine. Section 3 Registration for Citrus, Pome, and Stone Fruits; and Tree Nuts. Summary of Analytical Chemistry and Residue Data.

Eiden, C. D270177, 11/15/2000. Atrazine. HED Metabolism Assessment Review Committee: Residues to be Regulated and Residues of Concern for Dietary Assessment.

Kidwell, J. TXR 0052664, 04/14/2002. Simazine: Third Report of the Cancer Assessment Review Committee.

Liccione, J. D444631. 02/01/2018. Chlorotriazines. Toxicology Systematic Literature Review – Atrazine, Simazine and Propazine.

Recore, S. D444041, 11/01/2017. Atrazine, Propazine, and Simazine: Tier I Update Incident Report.

Rinde, E. TXR 0052670, 07/31/1989. Peer Review of Simazine.

Rickard, K. D442405, 09/26/2017. Atrazine: Review of Dissipation of Dislodgeable Foliar Residues of Atrazine on Field Corn (MRID No. 44883601)

Rickard, K. D428623, 06/12/2018. Simazine. Occupational and Residential Exposure and Risk Assessment for Registration Review and to Support the Registration of Proposed Uses on Citrus Fruit (Crop Group 10), Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Tree Nuts (Crop Group 14), and Tolerance Amendment for Almond Hulls.

Rickard, K., Drew, D., Donovan, W., Liccione, J., D418316, 07/10/2018. Atrazine. Draft Human Health Risk Assessment for Registration Review.

Rickard, K., Drew, D., Liccione, J., Donovan, W. D447476. 07/10/2018. Chlorotriazines: Cumulative Risk Assessment – Atrazine, Propazine, and Simazine

Rury, K. TXR 0056587, 04/16/2013. **Triazines:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 14, 2013: Recommendations on the Requirement for Acute and Subchronic Neurotoxicity, Dermal, and Inhalation.

Soderberg, D. D325433, 01/12/2006. Simazine: Revised HED Chapter of the Reregistration Eligibility Decision Document (RED); Revised for Public Comments and to Correct DWLOC Values.

Spencer, H. TXR 0052671, 05/24/1990. Peer Review Meeting on Simazine Following SAP Review.

Travaglini, R. D261346, 08/15/2001. Simazine: Secondary Review of "Turf Transferrable Residues for Simazine Applied to Turf MRID 44958701.

External References

Some of these references were considered by the 2010 SAP.

Adami, H. e. (2002). Textbook of Cancer Epidemiology. New York NY: Oxford University Press. Alavanja, M. C., Dosemeci, M., Samanic, C., Lubin, J., Lynch, C. F., Knott, C., Blair, A. (2004). Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol, 160(9), 876-885. doi: 160/9/876 [pii] 10.1093/aje/kwh290

Agopian AJ., et al (2013). Maternal residential atrazine exposure and risk for choanal atresia and stenosis in offspring. J.Pediatr. 2013 Mar; 162(3): 581-586. (Full Text). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105141/

Agopian AJ1, Langlois PH, Cai Y, Canfield MA, Lupo PJ. (2013). Maternal residential atrazine exposure and gastroschisis by maternal age. Matern Child Health J. 2013 Dec;17(10):1768-75. doi: 10.1007/s10995-012-1196-3.

Agopian AJ1, Lupo PJ, Canfield MA, Langlois PH. (2013). Case-control study of maternal residential atrazine exposure and male genital malformations. Am J Med Genet A. 2013 May;161A(5):977-82. doi: 10.1002/ajmg.a.35815.

Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F . Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol, 157(9), 800-814

Alavanja, M. C., Sandler, D. P., Lynch, C. F., Knott, C., Lubin, J. H., Tarone, R. Blair, A. (2005). Cancer incidence in the agricultural health study. Scand J Work Environ Health, 31 Suppl 1, 39-45; discussion 35-37.

Alavanja M.C.R, Ross M.K. Jan 15, 2013. Increased cancer burden among pesticide applicators and others due to pesticide exposure. http://onlinelibrary.wiley.com/doi/10.3322/caac.21170/full.

Albanito, L., Madeo, A., Lappano, R., Vivacqua, A., Rago, V., Carpino, A., Oprea, T., Prossnitz, E., Musti, A.M., Andò, S., & Maggiolini, M. (2007). G Protein–Coupled Receptor 30 (GPR30) Mediates Gene Expression Changes and Growth Response to 17ß-Estradiol and Selective GPR30 Ligand G-1 in Ovarian Cancer Cells. Cancer Res, Feb 15; 67(4): 1859-66.

Amory JK (2004) Testosterone/progestin regimens: A realistic option for male contraception? Curr Opin Invest Drugs 5:1025-1030

Andreotti, G., Freeman, L. E., Hou, L., Coble, J., Rusiecki, J., Hoppin, J. A. Alavanja, M. C. (2009). Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. Int J Cancer, 124(10), 2495-2500. doi: 10.1002/ijc.24185

Ankley GT,_ Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, Serrano JA, Tietge JE, Villeneuve DL. (2010). Adverse Outcome Pathways: A Conceptual Framework to Support Ecotoxicology Research and Risk Assessment. Environ Toxicol Pharmacol 29(3):730-741

Arbuckle, T. E., Lin, Z. Q., & Mery, L. S. (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environmental Health Perspectives, 109(8), 851-857.

Baetcke, K. P., & Dellarco, V. (2000). Atrazine: Evaluation of Carcinogenic Potential HED TXR 0014431: U.S. EPA.

Bakke B., De Roos A.J., Barr D.B., Stewart P.A., Blair A., Freeman L.B., Lynch C.F., Allen R.H., Alavanja M.C., Vermeulen R. (2009). Exposure to atrazine and selected non-persistent pesticides among corn farmers during the growing season. J Expo Sci Environ Epidemiol, Sep; 19(6): 544-54.

Banks J. A. and Freeman M. E. The Temporal Requirement of Progesterone on Proestrus for Extinction of the Estrogen-Induced Daily Signal Controlling Luteinizing Hormone Release in the Rat. Endocrinology 102 (2): 426-432

Barr DB, Panuwet P, Nguyen JV, Udunka S, Needham LL. Assessing exposure to atrazine and its metabolites using biomonitoring. Environ Health Perspect. 2007 Oct, 115(10):1474-8. PubMed PMID: 17938738; PubMed Central PMCID: PMC2022667.

Barraclough CA, Camp P, Weiland N, Akabori A. (1986). Stimulatory versus Inhibitory Effects of Progesterone on Estrogen-Induced Phasic LH and Prolactin Secretion Correlated with Estrogen Nuclear and Progestin Cytosol Receptor Concentrations in Brain and Pituitary Gland. Neuroendocrinology 42:6-14

Bassil, K. L., Vakil, C., Sanborn, M., Cole, D. C., Kaur, J. S., & Kerr, K. J. (2007). Cancer health effects of pesticides - Systematic review. Canadian Family Physician, 53, 1705-1711.

Beane Freeman, L. E., Rusiecki, J. A., Hoppin, J. A., Lubin, J. H., Koutros, S., Andreotti, G Alavanja, M. C. (2011). Atrazine and Cancer Incidence Among Pesticide Applicators in the Agricultural Health Study (1994-2007). Environ Health Perspect. doi: 10.1289/ehp.1103561

Bergendahl M, Evans WS, Veldhuis JD. (1996). Current Concepts in Ultradian Rythms of Luteininzing Hormone Secretion in the Human. Hum Reprod. Upate 2:507-518.

Blair, A. (1996). The Agricultural Health Study. Environ Health Perspect, 104(4), 362-369.
Albanito, L., Lappano, R., Madeo, A., Chimento, A., Prossnitz, E.R., Cappello, A.R., Dolce, V., Abonante, S., Pezzi, V., & Maggiolini, M. (2008). G-protein-coupled receptor 30 and estrogen receptor-alpha are involved in the proliferative effects induced by atrazine in ovarian cancer cells. Environ Health Perspect, 116(12): 1648-55.

Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, Steen WC, Samanic C, Dosemeci M, Alavanja MC. (2002) Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. Jan;13(1):94-9. PubMed PMID: 11805592.

Blair, A., Tarone, R., Sandler, D., Lynch, C. F., Rowland, A., Wintersteen, W. Alavanja, M. C. (2002). Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology, 13(1), 94-99.

Blair, A., Thomas, K., Coble, J., Sandler, D. P., Hines, C. J., Lynch, C. F., . . . Lubin, J. H. (2011).
Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. Occup Environ Med. doi: oem.2010.059469 [pii] 10.1136/oem.2010.059469

Blondell, J., & Dellcarco, V. (October, 28, 2003). Review of Atrazine Cancer Epidemiology (DP Barcode 295200).

Boffetta P., Hans-Olov, Adami, et al. August 2012. Atrazine and cancer: a review of the epidemiologic evidence. Eur J Cancer Prev. 2013 Mar;22(2):169-80. PMID: 2914097. http://www.researchgate.net/publication/230721982_Atrazine_and_cancer_a_review_of_the_epidemiologic_evidence

Boobis, A. R., Cohen, S. M., Dellarco, V., McGregor, D., Meek, M. E., Vickers, C., et al. (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol, 36(10), 781-792.

Boobis, A.R., J.E. Doe, B. Heinrich-Hirsch et al. 2008. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol, 38(2):87-96.

Brown-Grant K. and F. Naftolin (1972). Facilitation of Luteinizing Hormone Secretion in the Female Rat by Progesterone. J. Endocrinol.53:37-46

Brown TJ, Clark AS, MacLusky NJ. (1987). Regional Sex Differences in Progestin Receptor Induction in the Rat Hypothalamus: Effects of Various Doses of Estradiol Benzoate. J Neurosci 7(8):2529-2536

Brown, L. M., Blair, A., Gibson, R., Everett, G. D., Cantor, K. P., Schuman, L. M. Dick, F. (1990). Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res, 50(20), 6585-6591.

Brown, L. M., Burmeister, L. F., Everett, G. D., & Blair, A. (1993). Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control, 4(2), 153-156.
Burmeister, L. F. (1990). Cancer in Iowa farmers: recent results. Am J Ind Med, 18(3), 295-301

Caligaris L, Astrada JJ, Taleisnik S. (1968). Stimulating and Inhibiting Effects of Progesterone on the Release of Luteinizing Hormone. Acta Endocrinol 59:177-185

Caligaris L, Astrada JJ, Taleisnik, S. (1971). Biphasic Effect of Progesterone on the Release of Gonadotropin in Rats. Endocrinology 89:331-337.

Canfield MA, Honein MA, Yuskiv N, Xing J, Mai CT, Collins JS, et al. (2006) National estimates and race/ethnic-specific variation of selected birth defects in theUnited States, 1999-2001. BirthDefects Res A Clin Mol Teratol, 76:747-56.

Canfield MA, Ramadhani TA, Langlois PH, Waller DK. (2006) Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. J Expo Sci Environ Epidemiol., Nov;16(6):538-43. Epub 2006 May 31. PubMed PMID: 16736057.

Cantor, K. P., Blair, A., Everett, G., Gibson, R., Burmeister, L. F., Brown, L. M. Dick, F. R. (1992). Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res, 52(9), 2447-2455.

Carreon, T., Butler, M. A., Ruder, A. M., Waters, M. A., Davis-King, K. E., Calvert, G. M.Brain Canc Collaborative Study, G. (2005). Gliomas and farm pesticide exposure in women: The Upper Midwest Health Study. Environmental Health Perspectives, 113(5), 546-551. doi: 10.1289/ehp.7456

Chevirier C., Limon G., Monfort C., et al., (2011). Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. Environ Health Perspect. 2011 Jul; 119(7):1034-41. doi: 10.1289/ehp.1002775. Epub 2011 Mar 2. (Full Text). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222984/

Clavel, J., Hemon, D., Mandereau, L., Delemotte, B., Severin, F., & Flandrin, G. (1996). Farming, pesticide use and hairy-cell leukemia. Scandinavian Journal of Work Environment & Health, 22(4), 285-293.

Coder, P. (2010). Atrazine: An Oral (Gavage) Immunotoxicity and Hormone Evaluation Study for the Effects of Atrazine on Male Rats. Final Report. Unpublished data from Syngenta Crop Protection, Inc. Report Number WIL-639072. Study Completion Date July 13, 2010.
Coder, P. (2010). Atrazine: An Oral (Gavage) Study of the Effects of Atrazine on the Estrous Cycle and the Estrogen-Induced Luteinizing Hormone Surge in Female Rats. Final Interim Report. Unpublished data from Syngenta Crop Protection, Inc. Report Number WIL-639062. Study Completion Date July 14, 2010.

Coder, P. (2010). Atrazine: An Oral (Gavage) Study to Assess the Potential for Detecting the Estrogen-Induced Luteinizing Hormone Surge in Female Rats. Final Report. Unpublished data from Syngenta Crop Protection, Inc. Report Number WIL-639062. Study Completion Date July 2, 2010.

Coder, P. (2010). Atrazine: An Oral Developmental Toxicity Study of Atrazine in the Rat, Including Cross-Fostering and Pair-Feeding. Final Report. January 28, 2010. Project Number: WIL/639025, T007794/08, 140/107. Unpublished study prepared by WIL Research Laboratories, Inc. 2827 p. MRID 47972801.

Coder, Prägati Sawhney. (2011) An Oral (Gavage and Dietary) Study Evaluating the Pharmacokinetics of Atrazine in Female Sprague-Dawley Rats, WIL Research Laboratories, LLC Project ID 639081; Sponsor: Syngenta Crop Protection, LLC.

Cooper, R. L., Stoker, T. E., Tyrey, L., Goldman, J. M., and McElroy, W. K. (2000) Atrazine disrupts the hypothalamic control of pituitary-ovarian function, Toxicol Sci 53, 297-307.

Cooper, R.L., Stoker, T.E., Goldman, J.M., Parrish, M.B, & Tyrey, L. (1996). Effect of atrazine on ovarian function in the rat. Reprod Toxicol, Jul-Aug; 10(4): 257-64.

Cooper, R, Buckalew, A. Fraites, M., et al. (2010). Internal Report: Evaluation of Effects of the Chlorotriazine Herbicide Atrazine on the Amplitude of the Pre-ovulatory LH Surge in the Long Evans Rat. Memorandum dated July 8, 2010 from Ralph Cooper, NHEERL/ORD to Elizabeth Mendez, HED.

Cooper, R, Buckalew, A. Fraites, M., et al. (2010). Internal Report: Evaluation of Effects of the Chlorotriazine Herbicide Atrazine on the Amplitude of the Pre-ovulatory LH Surge in the Long Evans Rat. Memorandum dated July 8, 2010 from Ralph Cooper, NHEERL/ORD to Elizabeth Mendez, HED. *Corrected Report.*

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.

Dabrowski, S., Hanke, W., Polańska, K., Makowiec-Dabrowska, T., & Sobala, W. (2003). Pesticide exposure and birthweight: an epidemiological study in Central Poland. Int J Occup Med Environ Health, 16(1), 31-39.

Das PC, McElroy WK, Cooper RL (2000) Differential Modulation of Catecholamines by Chlorotriazine Herbicides in Pheochromocytoma (PC12) Cells in Vitro. Tox Sci. 56:324-331

Das, P.C., McElroy, W.K. & Cooper, R.L. (2001). Alteration of Catecholamines in Pheochromocytoma (PC12) Cells *in vitro* by the Metabolites of Chlorotriazine Herbicide. Toxicol Sci, Jan; 59(1): 127-37.

De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., & Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occupational and Environmental Medicine, 60(9). doi: e11

Dennis, L. K., Lynch, C. F., Sandler, D. P., & Alavanja, M. C. (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environ Health Perspect,
118(6), 812-817. doi: 10.1289/ehp.0901518

Devos S., Van Den Heuvel R., et al. (2004). Limited effect of selected organic pollutants on cytokine production by peripheral blood leukocytes. Euro Cytokine Netw, Apr-Jun; 15(2): 145-51.

Devos, S., Hooghe, R., Hooghe-Peters, E.L., De Bosscher, K., Vanden Berghe, W., Haegeman, G., Staels, B., Bauer, E., Roels, F., & Hooghe, R. (2003). Inhibition of cytokine production by the herbicide atrazine: Search for nuclear receptor targets. Biochem Pharmacol, Jan 15; 65(2): 303-8.

Donna, A., Betta, P. G., Robutti, F., Crosignani, P., Berrino, F., & Bellingeri, D. (1984). Ovarian mesothelial tumors and herbicides: a case-control study. Carcinogenesis, 5(7), 941-942.

Donna, A., Crosignani, P., Robutti, F., Betta, P. G., Bocca, R., Mariani, N. Berrino, F. (1989). Triazine herbicides and ovarian epithelial neoplasms. Scand J Work Environ Health, 15(1), 47-53.

Ebling, F.J.P. (2005) The Neuroendocrine Timing of Puberty. Reproduction 129:675-683

Engel, L. S., Hill, D. A., Hoppin, J. A., Lubin, J. H., Lynch, C. F., Pierce, J. Alavanja, M. C. (2005). Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. Am J Epidemiol, 161(2), 121-135. doi: 161/2/121 [pii] 10.1093/aje/kwi022

EPA Atrazine updates (2013)
http://archive.epa.gov/pesticides/reregistration/web/html/atrazine_update.html#_ga=1.255334600.1914500597.1443449563

EPA, U. S. (2000). FIFRA Scientific Advisory Panel (SAP) Meeting Final Report (June 27-29, 2000). Arlington, VA: Retrieved from http://archive.epa.gov/scipoly/sap/meetings/web/html/062700_mtg.html.

Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. (2008) Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J., Feb; 22(2):338-42. Epub 2007 Sep 20. PubMed PMID: 17884971.

Fan, W., Yanase, T., Morinaga, H., Gonda, S., Okabe, T., Nomura, M., Hayes, T., Takayanagi, R., & Nawata, H. (2007a). Herbicide atrazine activates SF-1 by direct affinity and concomitant co-activators recruitments to induce aromatase expression via promoter II. Biochemical and Biophysical Research Communications, 355(4): 1012-8.

Fan, W., Yanase, T., Morinaga, H., Gondo, S., Okabe, T., Normura, M., Komatsu, T., Moroashi, K., Hayes, T.B., Takayanagi, R., & Nawata, H. (2007b). Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. Environ Health Perspect, May, 115(5): 720-7.

Farr, S., Cai, J., Savitz, D., Sandler, D., Hoppin, J., & Cooper, G. (2006). Pesticide exposure and timing of menopause: the Agricultural Health Study. Am J Epidemiol, 163(8), 731-742 doi: kwj099 [pii] 10.1093/aje/kwj099.

Farr, S., Cooper, G., Cai, J., Savitz, D., & Sandler, D. (2004). Pesticide use and menstrual cycle characteristics among premenopausal women in the Agricultural Health Study. Am J Epidemiol, 160(12), 1194-1204. doi: 160/12/1194 [pii] 10.1093/aje/.

Fauser, B.C., de Jong, D., Olivennes, F. et al. (2002). Endocrine Profiles after 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.

Feldkamp ML, Carey JC, Sadler TW. Development of gastroschisis: review of hypotheses, a novel hypothesis, and implications for research. (2007) Am J Med Genet A., Apr 1; 143 (7):639-52. Review. PubMed PMID: 17230493.

Fenton, S.E. (2006). Endocrine-disrupting compounds and mammary gland development: Early exposure and later life consequences. Endocrinology, 147: S18-24.

FIFRA SAP. (2000b). "Atrazine:Hazard and Dose-Response Assessment and Characterization." Report from the FIFRA Scientific Advisory Panel Meeting of June 27-29, 2000. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. SAP Report 2000-05. Available: http://archive.epa.gov/scipoly/sap/meetings/web/pdf/finalatrazine.pdf

FIFRA Scientific Advisory Panel (SAP). (2003). "Characterization of Epidemiology Data Relating to Prostate Cancer and Exposure to Atrazine." Report from the FIFRA Scientific

Advisory Panel Meeting of July, 2003. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: http://www2.epa.gov/ingredients-used-pesticide-products/atrazine-background-and-updates

FIFRA Scientific Advisory Panel (FIFRA SAP). (2009). A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: The Ecological Significance of Atrazine Effects on Primary Producers in Surface Water Streams in the Corn and Sorghum Growing Region of the United States (Part II). SAP Minutes No. 2009-06. May 12 – 14, 2009 FIFRA Scientific Advisory Panel. Document available at http://archive.epa.gov/scipoly/sap/meetings/web/html/index-14.html

FIFRA Scientific Advisory Panel (FIFRA SAP). (2010a). A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency, FIFRA Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Available at: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

FIFRA Scientific Advisory Panel (FIFRA SAP). (2010b). A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health
Effects of Atrazine: Review of Non-cancer Effects and Drinking Water Monitoring Frequency, FIFRA Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Available at: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

FIFRA Scientific Advisory Panel (FIFRA SAP). 2009. A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: The Ecological Significance of Atrazine Effects on Primary Producers in Surface Water Streams in the Corn and Sorghum Growing Region of the United States (Part II). SAP Minutes No. 2010-04. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available at http://archive.epa.gov/scipoly/sap/meetings/web/html/index-14.html

FIFRA Scientific Advisory Panel (FIFRA SAP). 2010. Transmittal of Meeting of the FIFRA Scientific Advisory Panel Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data in Human Health Risk Assessment. SAP Minutes No. 2010-03. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html

FIFRA Scientific Advisory Panel (FIFRA SAP). 2010. A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking

Water Monitoring Frequency. SAP Minutes No. 2010-04. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html

FIFRA Scientific Advisory Panel (SAP). (1988). "A set of issues being considered by the Agency in connection with the peer review classification of atrazine a class C carcinogen." Report from the FIFRA Scientific Advisory Panel Meeting of September 14, 1988. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: https://www.epa.gov/sap/1988

FIFRA Scientific Advisory Panel (SAP). (2000a). "Atrazine: Hazard and Dose-Response Assessment and Characterization." Report from the FIFRA Scientific Advisory Panel Meeting of June 27-29, 2000. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: http://archive.epa.gov/scipoly/sap/meetings/web/pdf/finalatrazine.pdf

FIFRA Scientific Advisory Panel (SAP). (2003). "Characterization of Epidemiology Data Relating to Prostate Cancer and Exposure to Atrazine." Report from the FIFRA Scientific Advisory Panel Meeting of July, 2003. FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/071703_mtg.html

Flower, K. B., Hoppin, J. A., Lynch, C. F., Blair, A., Knott, C., Shore, D. L., & Sandler, D. P. (2004). Cancer risk and parental pesticide application in children of agricultural health study participants. Environmental Health Perspectives, 112(5), 631-635.

Follicle-Stimulating Hormone Surge in Postmenopausal Women: A Simulated Ovulatory Peak. PNAS 61:529-536

Foradori, C., Hinds, L., Hanneman, W., & Handa, R. (2009a). Effects of atrazine and its withdrawal on gonadotropin-releasing hormone neuroendocrine function in the adult female Wistar rat. Biol Reprod, Dec, 81(6): 1099-105.

Foradori, C., Hinds, L., Hanneman, W., Legare, M., Clay, C., & Handa, R. (2009b). Atrazine inhibits pulsatile luteinizing hormone release without altering pituitary sensitivity to a gonadotropin- releasing hormone receptor agonist in female Wistar rats. Biol Reprod, Jul; 81(1): 40-5.

Fox SR, Smith MS. (1986). Changes in the Pulsatile Pattern of Luteininzing Hormone Secretion During the Rat Extrous Cycle. Endocrinology 116:1485-1492

Frydman, R., Cornel, C., de Ziegler D. et al. (1992) Spontaneous luteininzing 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

Fukamachi, K., Han, B.S., Kim, C.K., Takasuka, N., Matsuoka, Y., Matsuda, E., Yamasaki, T., and Tsuda, H. (2004). Possible enhancing effects of atrazine and nonylphenol on 7,2-dimethylbenz[a]anthracene-induced mammary tumor development in human c-Ha-ras proto-oncogene transgenic rats. Cancer Sci., May; 95(5): 404-10.

Gao H.B., Shan L.X., Monder C., Hardy M.P. (1996). Suppression of endogenous corticosterone levels *in vivo* increases the steroidogenic capacity of purified rat Leydig cells *in vitro*. Endocrinology, May; 137(5):1714-8.

Goldfein A, Monroe SE. (1994) Ovaries. In: Greenspan FS, Baxter JD, editors.Basic and clinical endocrinology 4th ed. Norwalk, CT: Appleton and Lange, pp. 419-70.
Goldner, W. S., Sandler, D. P., Yu, F., Hoppin, J. A., Kamel, F., & Levan, T. D. (2010). Pesticide use and thyroid disease among women in the Agricultural Health Study. Am J Epidemiol, 171(4), 455-464. doi: kwp404 [pii] 10.1093/aje/kwp404

Goldman J, Davis L, Murr A, Cooper R. 2011. The influence of 1, 2, and 4 days of atrazine treatment on the LH surge of ovariectomized/estradiol-primed rats: Preliminary report to the Office of Chemical Safety and Pollution Prevention. Internal Report Submitted 28 April 2011. National Health and Environmental Effects Research Laboratory, EPA Office of Research and Development.

Goodman M., Mandel J.S., DeSesso J.M., Scialli A.R. (2014). Atrazine and Pregnancy Outcomes: A Systematic Review of Epidemiologic Evidence. Birth Defects Res B Dev Reprod Toxicol. 2014 Jun; 101(3):215-236. Full Text.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265844/

Grumbach, M.M. (2002) The Neuroendocrinology of Human Puberty Revisited. Horm. Res. 57(supp 2):2-14

Guillaume AJ, Benjamin F, Sicuranza B, Deutsch S, Spitzer M. (1995). Luteal phase defects and ectopic pregnancy. Fertility and Sterility 63(1): 30-33

Henderson KD, Bernstein L, Henderson B, Kolonel L, Pike MC. (2008) Predictors of the timing of natural menopause in the Multiethnic Cohort Study. Am J Epidemiol. 2008 Jun 1;167(11):1287-94. Epub Mar 21. PubMed PMID: 18359953.

Henderson, B. E., Ponder, B., & Ross, R. K. (2003). Hormones, Genes and Cancer. new York, NY: Oxford University Press.

Hertig AT, and Adams EC. (1967). Studies on the Human Oocyte and its Follicle. JCB 34(2): 647-675

Hertig AT, Sheldon WH. (1943). Minimum Criteria Required to Prove Prima Facie Case of Traumatic Abortion or Miscarriage. Ann Surg 117:596-606

Hessel, P. A., Kalmes, R., Smith, T. J., Lau, E., Mink, P. J., & Mandel, J. (2004). A nested case-control study of prostate cancer and atrazine exposure. Journal of Occupational and Environmental Medicine, 46(4), 379-385. doi: 10.1097/01.jom.0000121128.73921.a1

Hessel, P., Kalmes, R., Smith, T., Lau, E., Mink, P., & Mandel, J. (2004). A nested case-control study of prostate cancer and atrazine exposure. J Occup Environ Med, 46(4), 379-385. doi: 00043764-200404000-00011 [pii]

Hoar Zahm, S., Weisenburger, D., Cantor, K., Holmes, F., & Blair, A. (1993). Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. Scand J Work Environ Health, 19(2), 108-114.

Hoar, S. K., Blair, A., Holmes, F. F., Boysen, C. D., Robel, R. J., Hoover, R., & Fraumeni, J. F. (1986). Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA, 256(9), 1141-1147.

Hoar, S. K., Blair, A., Holmes, F. F., Boysen, C., & Robel, R. J. (1985). Herbicides and colon cancer. Lancet, 1(8440), 1277-1278.

Hocking, B. (2009). Melamine-contaminated powdered formula and urolithiasis. N Engl J Med., June 18; 360(25): 2676-7.

Hoehn K., Salmon A., Hohnen-Behrens C., Turner N., Hoy A., Maghzal G., Socker R., Van Remmen H., Kraegen E., Cooney G., Richardson A., James D. (2009). Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci U S A, Oct 20 106(42):17787-92.

Hopenhayn-Rich, C., Stump, M. L., & Browning, S. R. (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Archives of Environmental Contamination and Toxicology, 42(1), 127-136.

Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Coble J, Alavanja MC, Beane Freeman LE, Sandler DP. (2009) Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. Eur Respir J., Dec;34(6):1296-303. Epub 2009 Jun 18. PubMed PMID: 19541724; PubMed Central PMCID: PMC2822385.

Hoppin JA, Yucel F, Dosemeci M, Sandler DP. (2002) Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol, Sep;12(5):313-8. PubMed PMID: 12198579.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C. R., & Sandler, D. P. (2002). Chemical predictors of wheeze among farmer pesticide applicators in the agricultural health study. American Journal of Respiratory and Critical Care Medicine, 165(5), 683-689. doi:

10.1164/rccm.2106074.

Hoppin, J. A., Yucel, F., Dosemeci, M., & Sandler, D. P. (2002). Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol, 12(5), 313-318. doi: 10.1038/sj.jea.7500232

Hornemann et al. "Seasonality of omphalocele in Northern Germany," (2008) [Ultraschall in Med.
29:591-595.].

Hornemann, A., Weichert, J., Thill, M., Altgassen, C., Luedders, D., & Bohlmann, M. K. (2009). Seasonality of Omphalocele in Northern Germany. Ultraschall in Der Medizin, 30(6), 591-595. doi: 10.1055/s-2008-1027896. [German]

Hyun Joo, K. C., Ernest Hodgson. (2010) Human metabolism of atrazine, Pesticide Biochemistry and Physiology 98, 73-79.

Iffy L, Wingate MB. (1970). Risks of Rhythm Method of Birth Control. J Reprod Med 5:96-102

Iffy l. (1961). Contribution to the Aetiology of Ectopic Pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology 68(3):441-450

International Life Sciences Institute (ILSI). (1999). A Framework for Estimating Pesticide Concentrations in Drinking Water for Aggregate Exposure Assessments. International Life Sciences Institute Risk Science Institute Working Group Report, Washington, D.C., 61 pp. Available at http://www.ilsi.org/ResearchFoundation/Publications/Estimating%20Pesticide%20Concentrations.pdf

Jakobovits AA, Iffy L. (1988). Disorders of Follicular Ripening and Ovulation in Human. Acta Med Hungar 45:179-190

Jerry Campbell, M. A., Harvey Clewell. (2011) PBPK model for atrazine and chlorinated metabolites, Sponsor: Syngenta Crop Protection, LLC.

Judson R.S., Houck K.A., Kavlock R.J., Knudsen T.B., Martin M.T., et al. (2009). In vitro Screening of Environmental Chemicals for Targeted Testing Prioritization - The Tox Cast Project. Environ Health Perspect, doi:10.1289/ehp.0901392

Kalra, S.P., & Kalra, P.S.(1983). Neural regulation of luteinizing hormone secretion in the rat. Endocr Rev., Fall; 4(4): 311-51.

Kettles, M. A., Browning, S. R., Prince, T. S., & Horstman, S. W. (1997). Triazine herbicide exposure and breast cancer incidence: An ecologic study of Kentucky counties. Environmental Health Perspectives, 105(11), 1222-1227.

Kettles, M., Browning, S., Prince, T., & Horstman, S. (1997). Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. Environ Health Perspect, 105(11), 1222-1227.

Kim, D., Breckenridge, C. (Syngenta) (2010). Atrazine - Derivation of the short-term inhalation NOAEL using a physiologically-based pharmacokinetic model. Unpublished data from Syngenta

Kłuciński, P., Kossmann, S., Tustanowski, J., Friedek, D., & Kamińska-Kołodziej, B. (2001). Humoral and cellular immunity rates in chemical plant workers producing dust pesticides. Med Sci Monit, 7(6), 1270-1274. doi: 1270 [pii].

Kossmann, S., Konieczny, B., & Hoffmann, A. (1997). The role of respiratory muscles in the impairment of the respiratory system function in the workers of a chemical plant division producing pesticides. Przegl Lek, 54(10), 702-706.

Koutros, S., Alavanja, M. C., Lubin, J. H., Sandler, D. P., Hoppin, J. A., Lynch, C. F., Freeman, L. E. (2010). An update of cancer incidence in the Agricultural Health Study. J Occup Environ Med, 52(11), 1098-1105. doi: 00043764-201011000-00006 [pii] 10.1097/JOM.0b013e3181f72b7c

Laville, N., Balaguer, P., Brion, F., Hinfray, N., Casellas, C., Porcher, J.M., & Ait-Aissa, S. (2006). Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line. Toxicology, Nov 10; 228(1): 98-108.

Laws, S. C., Ferrell, J. M., Stoker, T. E., Schmid, J. & Cooper, R. L. (2000). The Effects of Atrazine on Female Wistar Rats: An Evaluation of the Protocol for Assessing Pubertal Development and Thyroid Function. Toxicol Sci, 58: 366-76.

Laws, S.C., Ferrell, J.M., Stoker, T.E., & Cooper, R.L. (2003). Pubertal development in female Wistar rats following exposure to propazine and atrazine biotransformation by-products, diamino-S-chlorotriazine and hydroxyatrazine. Toxicol Sci, Nov; 76(1): 190-200.

Laws, S.C., Hotchkiss, M., Ferrell, J., Jayaraman, S., Mills, L., Modic, W., Tinfo, N., Fraites, M., Stoker, T., & Cooper, R. (2009). Chlorotriazine Herbicides and Metabolites Activate an ACTH-Dependent Release of Corticosterone in Male Wistar Rats. Tox. Sci., 112(1): 78-87.

Laws, S.C., Stoker, T.E., Ferrell, J.M., Hotchkiss, M.G., & Cooper R.L. (2007). Effects of Altered Food Intake During Pubertal Development in Male and Female Wistar Rats. Toxicol. Sci., Nov; 100(1): 194-202.

LeBlanc Andre, Lekha Sleno. (2011) Atrazine Metabolite Screening in Human Microsomes: Detection of Novel Reactive Metabolites and Glutathione Adducts by LC-MS, Chemical Research in Toxicology 24, 329-339.

Lee, W. J., Sandler, D. P., Blair, A., Samanic, C., Cross, A. J., & Alavanja, M. C. R. (2007).

Pesticide use and colorectal cancer risk in the Agricultural Health Study. International Journal of Cancer, 121(2), 339-346. doi: 10.1002/ijc.22635

Lim, S., Ahn, S.Y., Song, I.C., Chung, M.H., Jang, H.C., Park, K.S., Lee, K., Pak, Y.K., & Lee, H.K. (2009). Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. PLOS One, 4(4): 1-11.

MacLennan, P. A., Delzell, E., Sathiakumar, N., & Myers, S. L. (2003). Mortality among triazine herbicide manufacturing workers. Journal of Toxicology and Environmental Health-Part a-Current Issues, 66(6), 501-517. doi: 10.1080/15287390390156254

MacLennan, P. A., Delzell, E., Sathiakumar, N., Myers, S. L., Cheng, H., Grizzle, W. Wu, X. C. (2002). Cancer incidence among triazine herbicide manufacturing workers. Journal of Occupational and Environmental Medicine, 44(11), 1048-1058. doi: 10.1097/01.jom.0000038322.36316.59

MacLennan, P., Delzell, E., Sathiakumar, N., & Myers, S. (2003). Mortality among triazine herbicide manufacturing workers. J Toxicol Environ Health A, 66(6), 501-517.

MacLennan, P., Delzell, E., Sathiakumar, N., Myers, S., Cheng, H., Grizzle, W. Wu, X. (2002). Cancer incidence among triazine herbicide manufacturing workers. J Occup Environ Med, 44(11), 1048-1058.

Malik, S.I., Terzoudi, G.I., & Pantelias, G.E. (2004). SCE analysis in G2 lymphocyte prematurely condensed chromosomes after exposure to atrazine: the non-dose-dependent increase in homologous recombinational events does not support its genotoxic mode of action. Cytogenet and Genome Research, 104(1-4): 315-9.

Manske, M., Beltz, L, and Dhanwada, K. (2004). Low-Level Atrazine Exposure Decreases Cell Proliferation in Human Fibroblasts. Arch. Environ. Contam. Toxicol. 46: 438-44.

Marshall, F. (1966) Marshall's Physiology of Reproduction. Longmans, Green and Co. LTD

Mattix, K., Winchester, P., & Scherer, L. (2007). Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. J Pediatr Surg, 42(6), 947-949. doi: S0022-3468(07)00056-5 [pii] 10.1016/j.jpedsurg.2007.01.027.

McElroy, J. A., Gangnon, R. E., Newcomb, P. A., Kanarek, M. S., Anderson, H. A., Brook, J. V., Remington, P. L. (2007). Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. Journal of Exposure Science and Environmental Epidemiology, 17(2), 207-214. doi: 10.1038/sj.jes.7500511

McElroy, J., Gangnon, R., Newcomb, P., Kanarek, M., Anderson, H., Brook, J. Remington, P. (2007). Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. J Expo Sci Environ Epidemiol, 17(2), 207-214. doi: 7500511 [pii] 10.1038/sj.jes.7500511

McMullin T.S. (2003). Pharmacokinetic modeling of disposition and time-course studies with [14C]- atrazine. J. Toxicol. Environ. Health, May 23;66(10):941-64.

McMullin TS, Andersen ME, Nagahara A, Lund TD, Pak T, Handa RJ, Hanneman, WH. (2004) Evidence That Atrazine and Diaminochlorotriazine Inhibit the Estrogen/Progesterone Induced Surge of Luteinizing Hormone in Female Sprague-Dawley Rats Without Changing Estrogen Receptor Action Tox Sci. 79:278-286

McMullin, T. S., Hanneman, W. H., Cranmer, B. K., Tessari, J. D., and Andersen, M. E. (2007) Oral absorption and oxidative metabolism of atrazine in rats evaluated by physiological modeling approaches, Toxicology 240, 1-14.

Meczekalski b, Podfigurna-Stopa A, Warenik-Szymankiewicz Al. Riccardo Genazzani A (2008). Functional hypothalamic amenorrhea: Current view on neuroendocrine aberrations. Gyn Endocr. 24(1):4-11

Meek, M.E., J.R. Bucher, S.M. Cohen et al. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol, 33(6): 591-653.

Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 2014 Jan;34(1):1-18.

Melvin M. Grumbach (2002). The Neuroendocrinology of Human Puberty Revisited. Horm Res;57(suppl 2):2–14

Merritt, A. 2011. Summary of Site Selection and Monitoring Plan for Atrazine Daily Monitoring in Selected Community Water Systems: Study Plan. Report Number: T001301-03. Task Number: T001301-03.

Mikamo K (1968) Mechanism of Non-dysjunction of Meiotic Chromosomes and of Degeneration of Maturation Spindles in Eggs Affected by Intrafollicular Overripeness. Experientia 24: 75-78

Miller, P.S., Northcott, W.J., Andrus, J. M., Zwilling, L.F., Cheplick, J. M., Harbourt, C.M., and Hendley, P. (2011). Atrazine - Development of the PRZM-Hybrid Watershed Exposure Modeling System, Unpublished study from Syngenta Crop Protection, Inc. MRID 48470007

Mills, P. (1998). Correlation analysis of pesticide use data and cancer incidence rates in California counties. Arch Environ Health, 53(6), 410-413.

Mills, P. K., & Yang, R. (2003). Prostate cancer risk in California farm workers. Journal of Occupational and Environmental Medicine, 45(3), 249-258. doi: 10.1097/01.jom.0000058339.05741.0c

Mills, P., & Yang, R. (2006). Regression analysis of pesticide use and breast cancer incidence in California Latinas. J Environ Health, 68(6), 15-22; quiz 43-14.

Minnema, D. (2001). "Special Study (non-guideline). Comparison of the LH surge in female rats administered atrazine, simazine, or diaminochlorotriazine (DACT) via gavage for one month." Covance Laboratories Inc. Vienna, VA Laboratory report number 6117-398(MRID # 45471002).

Minnema, D.J. (2002). 52-Week toxicity study of simazine, atrazine, and DACT administered in the diet to female rats. Covance Laboratories Inc., 9200 Leesburg Pike, Vienna, VA. Laboratory Identification Number 6117-399. February 21, 2002. MRID 45622309. Unpublished

Molcrani M.C., Duval F., Crocq M.A., Bailey P., Macher J.P. (1997). HPA axis dysfunction in depression: Correlation with monoamine system abnormalities. Psychoneuroendocrinology, 22, Suppl 1: S63-8

Morseth, S. (1996a). "Evaluation of the lutenizing hormone (LH) surge in atrazine expose female Sprague Dawley rats." Covance Laboratories Inc. Vienna, VA Laboratory report # CHV 2386-111(MRID # 43934406).

Morseth, S. (1996b). "Evaluation of the lutenizing hormone (LH) surge in atrazine exposed female Sprague Dawley rats - 6 month report." Covance Laboratories Inc. Vienna, VA Laboratory study no. CHV 2386-108(MRID # 44152102).

Muir, K., Rattanamongkolgul, S., Smallman-Raynor, M., Thomas, M., Downer, S., & Jenkinson, C. (2004). Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. Public Health, 118(7), 513-520. doi: 10.1016/j.puhe.2003.12.019

Munger, R., Isacson, P., Hu, S., Burns, T., Hanson, J., Lynch, C. F., et al. (1997). Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. Environmental Health Perspectives, 105(3), 308-314.

Narotsky, M. G., D. S. Best, et al. (2001). "Strain comparisons of atrazine-induced pregnancy loss in the rat." Reprod Toxicol 15(1): 61-69.

Ochoa-Acuña, H., & Carbajo, C. (2009). Risk of limb birth defects and mother's home proximity to cornfields. Sci Total Environ, 407(15), 4447-4451. doi: S0048-9697(09)00373-8 [pii] 10.1016/j.scitotenv.2009.04.028.

Ochoa-Acuña, H., Frankenberger, J., Hahn, L., & Carbajo, C. (2009). Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. Environ Health Perspect, 117(10), 1619-1624. doi: 10.1289/ehp.0900784.

Odell WD, Swerdloff RS. (1968). Progestogen-Induced Luteinizing and Prilusky J, Vermouth NT, Deis RP. (1984). A Dual Modulatory Effect of Progesterone on the LHRH-Induced LH Release. J Steroid Biochem 21(1):107-110

Ojeda, S.R., and Urbanski, H.F. (1994). Puberty in the rat. In E. Knobil and J.D. Neill (Eds.): The Physiology of Reproduction, 2nd ed. New York, Raven Press. 363-409

Olivennes, F., Alvarez, S., Bouchard, P. et al. (1998). The use of GnRH antagonist (Cetrorelix®) in a single dose protocol in IVF-embryo transfer: a dose finding study of 3 versus 2 mg. Human Reproduction 13(9):2411-2413

Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P. Clavel, J. (2009). Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occupational and Environmental Medicine, 66(5), 291-298. doi: 10.1136/oem.2008.040972

Philippe E, Ritter J, Lefakis P, Laedlein-Greilsammer D, Itten S, Foussereau S (1970). Tubal Pregnancy, Delayed Ovulation and Anomaly of Nidation. Gynecol Obstet. 69:Suppl 5:617+.

Plant, T.M.; Barker-Gibb, L.M. (2004). Neurobiological mechanisms of puberty in higher primates. Human Reproduction Upda t e 10(1): 67-77

Pogrmic, K., Fa, S., Dakic, V., Kaisarevic, S. & Kovacevic, R. (2009). Atrazine oral exposure of peripubertal male rats downregulates steroidogenesis gene expression in Leydig cells. Toxicol. Sci., 111(1): 189-97.

Pryor JL, Hughes C, Foster W, Hales BF, Robaire B. (2000) Critical windows of exposure for children's health: the reproductive system in animals and humans. Environ Health Perspect. Jun;108 Suppl 3:491-503. Review. PubMed PMID: 10852849; PubMed Central PMCID: PMC1637840.

Pulkkinen MO, Jaakkola UM. (1989). Low serum progesterone levels and tubal dysfunction--a possible cause of ectopic pregnancy. Am J Obstet Gynecol. 161(4):934-7

Ralph Cooper, A. B., Melanie Fraites, Jerome Goldman, Susan Laws, Michael Narotsky, and Tammy Stoker. (2010) Evaluating the effect of the chlorotriazine herbicide atrazine on the amplitude of the pre-ovulatory LH surge in the Long-Evans Rat, In Unpublished internal report.

Rhomberg, L.R., and Lewandowski, T.A. (2006). Methods for identifying a default cross-species scaling factor. Hum Ecol Risk Assess 12, 1094-1127.

Rinsky JL1, Hopenhayn C, Golla V, Browning S, Bush HM. (2012). **Atrazine exposure in public drinking water and preterm birth**. Public Health Rep. 2012 Jan-Feb;127(1):72-80. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234399/

Rivest, .S & Rivier, C. (1995). The role of corticotropin-releasing factor and interleukin-1 in the regulation of neurons controlling reproductive functions. Endocr Rev, 16(2): 177-99.

Rivier, C. & Rivest, S. (1991). Effect of stress on the activity of the hypothalamic-pituitary-gondal axis: peripheral and central mechanisms. Biol Reprod., October 1; 45 (4): 523-532

Rivier, C., Rivier, J., & Vale, W. (1986). Stress-induced inhibition of reproductive functions: role of endogenous corticotropin-releasing factor. Science, 231(4738): 607-9.

Rosenberg, B.G., Chen, H., Folmer, J., Liu, J., Papadopoulos, V., & Zirkin, B.R. (2008). Gestational exposure to atrazine: effects on the postnatal development of male offspring. J Androl. May-June; 29(3): 304-11.

Ruder, A. M., Waters, M. A., Butler, M. A., Carreón, T., Calvert, G. M., Davis-King, K. E. Group, B. C. C. S. (2004). Gliomas and farm pesticide exposure in men: the upper midwest health study. Arch Environ Health, 59(12), 650-657.

Rull, R. P., Gunier, R., Von Behren, J., Hertz, A., Crouse, V., Buffler, P. A., & Reynolds, P. (2009). Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. Environmental Research, 109(7), 891-899. doi: 10.1016/j.envres.2009.07.014

Rull, R., Gunier, R., Von Behren, J., Hertz, A., Crouse, V., Buffler, P., & Reynolds, P. (2009). Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. Environ Res, 109(7), 891-899. doi: S0013-9351(09)00139-X [pii] 10.1016/j.envres.2009.07.014

Rusiecki, J. A., De Roos, A., Lee, W. J., Dosemeci, M., Lubin, J. H., Hoppin, J. A. Alavanja, M. C. R. (2004). Cancer incidence among pesticide applicators exposed to atrazine in the agricultural health study. Journal of the National Cancer Institute, 96(18), 1375-1382.

Rusiecki, J., De Roos, A., Lee, W., Dosemeci, M., Lubin, J., Hoppin, J. Alavanja, M. (2004). Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst, 96(18), 1375-1382. doi: 96/18/1375 [pii] 10.1093/jnci/djh264

Rusiecki, J.A., De Roos, A., Lee, W.J., Dosemci, M., Lubin J.H., Hoppin, J.A., Blair, A., & Alavanja, M.C. (2004). Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst, Sept 15; 96(18): 1375-82.

Safranski TJ, Lamberson WR, Keisler DH.(1993). Correlations among Three Measures of Puberty in Mice and Relationships with Estradiol Concentration and Ovulation. Biol Repro 48:669- 673

Saldana, T. M., Basso, O., Hoppin, J. A., Baird, D. D., Knott, C., Blair, A., et al. (2007). Pesticide exposure and self-reported gestational diabetes mellitus in the agricultural health study. Diabetes Care, 30(3), 529-534. doi: 10.2337/dc06-1832.

Sathiakumar N, MacLennan PA, Mandel J, Delzell E. (2011). **A review of epidemiologic studies of triazine herbicides and cancer.** Crit Rev Toxicol. 2011 Apr;41 Suppl 1:1-34. doi: 10.3109/10408444.2011.554793. Review. PMID: 21425949.

Sanderson J.T., Letcher R.J., Heneweer M., Giesy J.P., van den Berg M. (2001). Effects of chloro- s-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. Environ health Perspect, Ovt; 109(10): 1027-31.

Sanderson J.T., Seinen W., Giesy J.P., van den Berg M. (2000). 2-Chloro-s-triazine herbicides induce aromatase (CYP19) activity in H295R human adrenocortical carcinoma cells: a novel mechanisms for estrogenicity? Toxicol Sci, Mar; 54(1): 121-27.

Sanderson, J.T., Boerma, J., Gideon, W.A., Lansbergen, G.W. & van den Berg, M. (2002). Induction and inhibition of aromatase (CYP19) activity by various classes of pesticides in H295R human adrenocortical carcinoma cells. Toxicol Appl Pharmacol. Jul 1; 182: 44-54.

Santen R.J., Brodie H., Simpson E.R., Siiteri P.K., Brodie A. (2009). History of Aromatase: saga of an important biological mediator and therapeutic target. Endocr Rev, Jun; 30(4): 343-75.

SAP. (2010a) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency, FIFRA Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

SAP. (2010b) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health Effects of Atrazine: Review of Non-cancer Effects and Drinking Water Monitoring Frequency, FIFRA Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

Sathiakumar, N., & Delzell, E. (1997). A review of epidemiologic studies of triazine herbicides and cancer. Critical Reviews in Toxicology, 27(6), 599-612.

Sathiakumar, N., Delzell, E., & Cole, P. (1996). Mortality among workers at two triazine herbicide manufacturing plants. Am J Ind Med, 29(2), 143-151 doi: 10.1002/(SICI)1097-0274(199602)29:2<143::AID-AJIM4>3.0.CO;2-T [pii] 10.1002/(SICI)1097-0274(199602)29:2<143::AID-AJIM4>3.0.CO;2-T

Sathiakumar, N., Delzell, E., & Cole, P. (1996). Mortality among workers at two triazine herbicide manufacturing plants. American Journal of Industrial Medicine, 29(2), 143-151.

Sathyanarayana S, Basso O, Karr CJ, Lozano P, Alavanja M, Sandler DP, Hoppin JA. 2010. Maternal pesticide use and birth weight in the agricultural health study. J Agromedicine. 2010 Apr;15(2):127-36.

Savitz, D., Arbuckle, T., Kaczor, D., & Curtis, K. (1997). Male pesticide exposure and pregnancy outcome. Am J Epidemiol, 146(12), 1025-1036.
Schultz TW. (2010). Adverse Outcome Pathways: A Way of Linking Chemical Structure to In Vivo Toxicological Hazards. In: Cronin MTD, Madden JC, eds. In silico Toxicology: Principles and Applications. Cambridge, UK: Royal Society of Chemistry.

Scientific Advisory Panel. (2010a) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency, FIFRA Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Available: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

Seed, J., E.W. Carney, R.A. Corley et al. (2005). Overview: Using mode of action and lifestage information to evaluate the human relevance of animal toxicity data. Crit. Rev. Toxicol., Oct-Nov; 35(8-9):664-72.

Siega-Riz AM, Herring AH, Olshan AF, Smith J, Moore C; National Birth Defects Prevention Study. (2009) The joint effects of maternal prepregnancy body mass index and age on the risk of gastroschisis. Paediatr Perinat Epidemiol., Jan;23(1):51-7. Review. PubMed PMID: 19228314.

Simpson, E.R., & Davis, S.R. (2001). Minireview: aromatase and the regulation of estrogen biosynthesis – some new perspectives. Endocrinology, Nov; 142(11): 4589-94.
Simpson, E.R., Clyne, C.D., Rubin, G., Boon, W.C., Robertson, K., Britt, K., Speed, C., & Jones, M.E. (2002). Aromatase: a brief review. Annu Rev Physiol, 64: 93-127.

Simpkins JW, Swenberg JA, Weiss N, Brusick D, Eldridge JC, Stevens JT, Handa RJ, et al., (2011). **Atrazine and breast cancer: a framework assessment of the toxicological and epidemiological evidence.** Toxicol Sci. 2011 Oct;123(2):441-59. doi: 10.1093/toxsci/kfr176. Epub 2011 Jul 18. PMID: 21768606. Free PMC Article.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179673/

Sliwiński, Z., Hermanowicz, A., Kossmann, S., & Hrycek, A. (1991). Neutrophil function in chemical plant workers employed in the production of dust pesticides. Pol J Occup Med Environ Health, 4(3), 241-247.

Smits LJ, Jongbloet PH, Zielhuis GA. (1995). Preovulatory Overripeness of the Oocyte as a Cause of Ovarian Dysfunction in the Human Female. Med Hypotheses 45:441-448

Sonich-Mullin, C., R. Fielder, J. Wiltse et al. (2001). IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. Regul Toxicol Pharmacol, Oct; 34(2):146-52.

Stoker T.E & Cooper R.L. (2007). Distribution of 14C-atrazine following an acute lactational exposure in the Wistar rat. Reprod Toxicol, Jun; 23(4):607-10.

Stoker T.E., Robinette, C.L. & Cooper, R.L. (1999). Maternal exposure to atrazine during lactation suppresses suckling- induced prolactin release and results in prostatitis in the adult offspring. Toxicol Sci, 52: 68-79

Stoker, T., Zorilla, L., Strader, L. Et al. 2010. Internal Report: The Distribution of Atrazine in the Wistar Rat Following Gestational/Lactational Exposures. Memorandum dated July 14, 2010 from Tammy Stoker, NHEERL/ORD to Elizabeth Mendez, HED/OPP.

Stoker, T.E., Guidici, D.L., Laws, S.C. & Cooper, R.L. (2002). The Effects of Atrazine Metabolites on Puberty and Thyroid Function in the Male Wistar Rat: An Evaluation in the Male Pubertal Protocol. Toxicol. Sci., 67(2): 198-206.

Stoker, T.E., Laws, S.C., Guidici, D., & Cooper, R.L. (2000). The effects of atrazine on puberty and thryroid function in the male wistar rat: An evaluation of a protocol for the assessment of pubertal development and thyroid function. Toxicol. Sci., 58: 50-9.

Stoker, T.E., Parks, L.G., Gray, L.E., and Cooper, R.L. (2000) Effects of endocrine disrupting chemicals on puberty in the male rat: A review of the EDSTAC recommendations.Critical Reviews in Toxicology 30: 197-252, 2000.

Swan SH. Semen quality in fertile US men in relation to geographical area and pesticide exposure. Int J Androl. 2006 Feb;29(1):62-8; discussion 105-8. PubMed PMID: 16466525.

Swan, S. H., Kruse, R. L., Liu, F., Barr, D. B., Drobnis, E. Z., Redmon, J. B., et al. (2003). Semen quality in relation to biomarkers of pesticide exposure. Environmental Health Perspectives, 111(12), 1478-1484. doi: 10.1289/ehp.6417.

Terasawa El, Yeoman RR, Schultz NJ. (1984). Factors Influencing the Progesterone-Induced Luteinizing Hormone Surge in Rhesus Monkeys: Diurnal Influence and Time Interval After Estrogen Biol Reprod 31:732-741

Terasawa, E., and C.L. Nyberg. 1997. LHRH pulse generation in the monkey: *in vivo* and *in vitro* studies. In: Neural control of reproduction: physiology and behavior, K. Maeda, H. Tsukamura, and E. Yokoyama, eds., pp. 57-70. JSS Press, Tokyo.

Timchalk, C., Dryzga, M. D., Langvardt, P. W., Kastl, P. E., and Osborne, D. W. (1990) Determination of the effect of tridiphane on the pharmacokinetics of [14C]-atrazine following oral administration to male Fischer 344 rats, Toxicology 61, 27-40.

Tinfo, N., & Laws, S.C. (2009). Understanding the Effects of Atrazine on Steroidogenesis in Wistar rats. Society of Toxicology, Itinerary Planner, Baltimore, MD.

Trentacoste, S.V., Friedmann, A.S., Youker, R.T., Breckenridge, C.B. & Zirkin, B.R. (2001). Atrazine effects on testosterone levels and androgen-dependent reproductive organs in peripubertal male rats. J. Androl, Jan-Feb; 22(1): 142-8.

Turgeon JL and Waring DW. (2000). Progesterone Regulation of the Progesterone Receptor in Rat Gonadotropes. Endocrinology 141:3422-3429.

U.S. Environmental Protection Agency (USEPA). (2010a). Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. Prepared for the April 26-29, 2010 FIFRA Scientific Advisory Panel. Document available at: http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

U.S. Environmental Protection Agency (USEPA). (2010b). Re-evaluation of the Human Health Effects of Atrazine: Review of Non-Cancer Effects and Drinking Water Monitoring Frequency. Prepared for the September 14 – 17, 2010 FIFRA Scientific Advisory Panel. Document available at http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html.

U.S. Environmental Protection Agency (USEPA). 2000. Atrazine: Hazard and Dose-Response Assessment and Characterization.

U.S. Environmental Protection Agency (USEPA). 2010. Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency. Prepared for the April 26-29, 2010 FIFRA Scientific Advisory Panel. Document available at http://archive.epa.gov/scipoly/sap/meetings/web/html/index-16.html

U.S. Environmental Protection Agency. (2010). DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Draft dated January 7, 2010). Presented to the FIFRA Scientific Advisory Panel, February 2-4, 2010. https://www.regulations.gov (Docket EPA-HQ-OPP-2009-0851).

U.S. EPA, U. (2010). FIFRA SAP Final Report (February 2-4, 2010).

U.S. EPA, U. S. (2003a). Atrazine Interim Reregistration Eligibility Document (IRED). Washington D.C.

U.S. EPA, U. S. (2003b). FIFRA Scientific Advisory Panel Final Meeting Report (July 17, 2003 Meeting). Retrieved from http://archive.epa.gov/scipoly/sap/meetings/web/html/071703_mtg.html.

U.S. EPA. (2010). FIFRA SAP Final Report "Re- Evaluation of Human Health Effects of Atrazine: Review of Experimental Animal and In Vitro Studies and Drinking Water Monitoring Frequency." (April 26-29, 2010)

U.S. EPA. (1999). Guidelines for carcinogen risk assessment. Risk Assessment Forum. SAB review draft. Washington, DC: U.S. Environmental Protection Agency. www.epa.gov/ncea/raf/crasab.htm.*

U.S. EPA. (2003). Interim Re-registration Eligibility Decision
U.S. EPA. (2005). Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Federal Register 70(66):17765-17817. Available at http://www2.epa.gov/risk/guidelines-carcinogen-risk-assessment

U.S. EPA. (2006). Decision Documents for Atrazine. Atrazine IREDs (January and October 31, 2003) and Atrazine RED (April 6, 2006). EPA-HQ-OPP-2003-0367.

U.S. EPA (2006). Harmonization in interspecies extrapolation: use of body weight3/4 as the default method in derivation of the oral reference dose. External Review Draft. Office of the Science Advisor.

U.S. EPA. (2000). "Benchmark Dose Technical Guidance Document." Draft report. Risk Assessment Forum, Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/630/R-00/001.

U.S. EPA. (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment, National Center for Environmental Assessment, Office of Research and Development.

Van Leeuwen, J., Waltner-Toews, D., Abernathy, T., Smit, B., & Shoukri, M. (1999). Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. Int J Epidemiol, 28(5), 836-840.

Veldhuis JD, Keenan DM, Pincus SM. (2008). Motivations and Methods for Analyzing Pulsatile Hormone Secretion. Endocr. Rev. 29:823-864

Villanueva, C., Durand, G., Coutté, M., Chevrier, C., & Cordier, S. (2005). Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. Occup Environ Med, 62(6), 400-405. doi: 62/6/400 [pii] 10.1136/oem.2004.016469.

Waggoner, J. K., Kullman, G. J., Henneberger, P. K., Umbach, D. M., Blair, A., Alavanja, M. C., Hoppin, J. A. (2011). Mortality in the agricultural health study, 1993-2007. Am J Epidemiol, 173(1), 71-83. doi: kwq323 [pii] 10.1093/aje/kwq323

Walford TL (1871). Retrospective Address of the Pathological Society of Reading. Br Med J 2:634

Waller, S. A., Paul, K., Peterson, S. E., & Hitti, J. E. (2010). Agricultural-related chemical exposures, season of conception, and risk of gastroschisis in Washington State. American Journal of Obstetrics and Gynecology, 202(3). doi: 10.1016/j.ajog.2010.01.023.

Watkins ML, Edmonds L, McClearn A, Mullins L, Mulinare J, Khoury M. (1996) The surveillance of birth defects: the usefulness of the revised US standard birth certificate. Am J Public Health, May;86(5):731-4. PubMed PMID: 8629729; PubMed Central PMCID: PMC1380486.

Weichenthal S., Moase C., Chan P., (Jan 2012**). A review of pesticide exposure and cancer incidence in the agricultural health study cohort.**
http://www.scielo.br/scielo.php?pid=S1413-81232012000100028&script=sci_arttext

Weisenburger, D. (1990). Environmental epidemiology of non-Hodgkin's lymphoma in eastern Nebraska. Am J Ind Med, 18(3), 303-305.

Weselak M, Arbuckle TE, Walker MC, Krewski D. The influence of the environment and other exogenous agents on spontaneous abortion risk. (2008) J Toxicol Environ Health B Crit Rev., Mar;11(3-4):221-41. Review. PubMed PMID: 18368554

Wetzel L.T., Luempert L.G., III Breckenridge C.B., Tisdel M.O., Stevens J.T. (1994). Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fisher 344 rats. J Toxicol. Environ. Health, Oct; 43(2):169-82.

Williams LJ,Kucik JE,Alverson CH, Olney RS, Correa A. (2005) Epidemiology of gastroschisis in metropolitan Atlanta, 1968 through 2000. Birth Defects Res Part A Clin Mol Teratol, 73:177-83.

Winchester, P., Huskins, J., & Ying, J. (2009). Agrichemicals in surface water and birth defects in the United States. Acta Paediatr, 98(4), 664-669. doi: APA1207 [pii] 10.1111/j.1651-2227.2008.01207.x.

Wingate MB, Arrata WSM, Iffy L. (1973). Delayed Ovulation Ill Med J 144:44-47

Witschi E. (1952). Overripeness of the Egg as a Cause of Twinning and Teratogenesis. Cancer Res 12:763-797

Xiaoying Hui, R. C. W. a. H. I. M. (2011) Pharmacokinetics of [14C]-atrazine in rhesus monkeys, single-dose intravenous and oral administration, Toxicological and Enviromental Chemistry
93, 370-382.

Young, H. A., Mills, P. K., Riordan, D. G., & Cress, R. D. (2005). Triazine herbicides and epithelial ovarian cancer risk in central California. Journal of Occupational and Environmental Medicine, 47(11), 1148-1156. doi: 10.1097/01.jom.0000177044.43959.e8

Zahm, S. H., Weisenburger, D. D., Saal, R. C., Vaught, J. B., Babbitt, P. A., & Blair, A. (1993). The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. Arch Environ Health, 48(5), 353-358.

Zorrilla, L.M., Gibson, E.K., Stoker (2009) Effect of Chlorotriazine Pesticides on Gonadotrophin Releasing Hormone in the Neuronal GT1-7 Cell Line and Hypothalamic Explants. Annual Meeting of the Society for Study of Reproduction, Pittsburgh, PA. Biol Reprod, 81: 638.

Appendix A. Toxicology Profile and Executive Summaries

A.1. Toxicology Data Requirements - Simazine

The requirements (40 CFR 180.213) for food uses of simazine are in Table A.1. Use of the new guideline numbers does not imply that the new guideline protocols were used.

Table A.1.3. Summary of Toxicological Data Requirements for Simazine.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	waived[1]
870.3250	90-Day Dermal	yes	waived[1]
870.3465	90-Day Inhalation*	yes	waived[1]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5385	Mutagenicity—Mammalian Bone Marrow	yes	yes
	Chromosome Aberration 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	General Metabolism	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

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

A.2. Toxicity Profiles – Simazine

Table A.2.1 Acute Toxicity Profile – Simazine.				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.11	Acute Oral	00148897	LD_{50} > 5 g/kg (M&F combined)	IV
870.12	Acute Dermal	00148898	LD_{50} > 2 g/kg (M&F combined)	III
870.13	Acute Inhalation	00148899	LC_{50} > 1.71 mg/L	III
870.24	Primary Eye Irritation	00148900	Slight irritant	IV
870.25	Primary Dermal Irritation	00148901	PIS = 0.2	IV
870.26	Dermal Sensitization	41184501	Negative	N/A

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Simazine.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	00143265 (1985) 0, 14.25, 142, or 276 mg/kg/day	NOAEL = not identified. LOAEL = 14.25 mg/kg/day, based on decreased body weight gain, decreased food consumption and hematological changes.
870.3150 13-Week dietary toxicity (dog)	00146655 M: 6.9, 65.2, 133.6 F: 8.2, 64.3, 136.7	NOAEL = 6.9 mg/kg/day (M); 8.2 mg/kg/day (F) LOAEL = 65.2 mg/kg/day (M); 64.3 mg/kg/day (F) based on decreased body weight/body weight gain, decreased food consumption, organ weight changes, decreased serum glutamate oxaloacetate (SGOT) and reduced alkaline phosphatase activities (females).
870.3200 21/28-Day [illegible] (rat)	[illegible]	[illegible]
870.3700a Prenatal developmental in Rat	40614403 (1986) 0, 30, 300 or 600 mg/kg/day	Maternal NOAEL = 30 mg/kg/day LOAEL = 300 mg/kg/day based on decreased body weight/body weight gain, and decreased food utilization. Developmental NOAEL = 30 mg/kg/day LOAEL = 300 mg/kg/day based on skeletal variations.
870.3700b Prenatal developmental in Rabbit	00161407 (1984) 0, 5, 75 or 200 mg/kg/day	Maternal NOAEL = 5 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain, decreased food consumption, increased tremors, and stool alterations. Developmental NOAEL = 75 mg/kg/day LOAEL = 200 mg/kg/day based decreased fetal weight and increased skeletal variations.
870.3800 Reproduction and fertility effects (Rat)	41803601 (1991) 0, 10, 100, or 500 ppm M: 0, 0.56, 5.61, 28.9 mg/kg/day F: 0, 0.7, 7.04, 34.96 mg/kg/day	Parental/Systemic NOAEL = 0.56 mg/kg/day (M); 0.7 (F) LOAEL = 5.61 mg/kg/day (M); 7.04 mg/kg/day (F), based on decreased body weight/body weight gain. Offspring NOAEL = 31.93 mg/kg/day

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Simazine.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		LOAEL = not identified
870.4100b Chronic toxicity (dog)	40614402 Acceptable-guideline M: 0, 0.68, 3.41, 42.9 mg/kg/day F: 0, 0.76, 3.64, 44.9 mg/kg/day	NOAEL = 3.41 mg/kg/day (M); 0.76 mg/kg/day (F) LOAEL = 42.9 mg/kg/day (M) based on decreased body weight gains, increased platelet counts, and increased adrenal/brain weight ratio; 3.64 mg/kg/day (F), based on decreased body weight gain, hematological effects (decreased levels of red blood cell counts, hemoglobin and hematocrit) and increased adrenal weight, adrenal/brain weight ratio, and adrenal/body weight ratio.
870.4200 Carcinogenicity (rat)	40614405 Acceptable-guideline 0, 10, 100, or 1000 ppm M: 0, 0.4, 4.2, or 45.8 mg/kg/day F: 0, 0.5, 5.3, or 63.1 mg/kg/day	NOAEL = 0.4 mg/kg/day (M); 0.5 mg/kg/day (F) LOAEL = 4.2 mg/kg/day (M) based on decreased leukocyte counts; 5.3 mg/kg/day (F), based on hematological changes and decreased body weight gain. Carcinogenicity -treatment-related increase in mammary carcinomas and fibroadenomas tumor incidence.
870.4300 Carcinogenicity (mouse)	40614404 (1988) Acceptable-guideline 0, 40, 1000 or 4000 ppm M: 0, 5.3, 131.5, 542 mg/kg/day F: 0, 6.2, 160, 652.1 mg/kg/day	NOAEL = 5.3 mg/kg/day (M); 6.2 mg/kg/day (F) LOAEL = 131.5 mg/kg/day (M), 160 mg/kg/day (F) based on decreased body weight/body weight gain. No evidence of carcinogenicity.
Gene Mutation: In vitro Bacterial Gene Mutation (Bacterial system, Salmonella typhimurium) gene mutation assay 870.5100	40614406 (1987) Acceptable-guideline 0, 10, 25, 50, 100, or 250 µg/plate in the in the presence and absence of mammalian metabolic activation (S9-mix)	There was no evidence of induced mutant colonies over background.
Cytogenetics: In vivo Mammalian Cytogenetics - Micronucleus Assay 870.5395	41442901 (1988) Acceptable-guideline 1250, 2500 or 5000 mg/kg	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow.
Unscheduled DNA Synthesis in Rat Hepatocytes/Mammalian Cells 870.5550	41441902 (1989) Acceptable-guideline 1.57, 4.72, 14.17, 42.5, 85 or 170 µg/ml	There was no evidence that UDS was induced by exposure to simazine.
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)	00143266 (1986) Acceptable-guideline	At the low dose (0.5 mg/kg) of radiolabeled simazine, the principal route of excretion was via the urine, however, at the higher dose (200 mg/kg) the principal route of excretion was via the feces. Significant radioactive residues

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Simazine.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		remained in the tissues of the rat for extended periods of time. Results indicate that 94 to 99% of the elimination of radioactive material occurred within 48 to 72 hours with a half-life of 9 to 15 hours. Elimination of the remaining radioactivity exhibited 21- to 32-hour half-life values. Heart, lung, spleen, kidney, and liver appear to be principal sites of retention of radioactivity. However, erythrocytes concentrated radioactivity to higher levels than did other tissues, perhaps due to high affinity of the triazine ring for cysteine residues of hemoglobin, a phenomenon apparently unique to rodent species.
Dermal Absorption - rat.	40614409 (1988) Acceptable-guideline	Male rats were received doses of 0.1 or 0.5 mg/cm^2 radiolabeled simazine for 2, 4, 10 or 24 hours. Dermal absorption was less than 1% at both doses and all time points. However, 11-20% of the low dose and 31-41% of the high dose remained on skin, and potentially absorbable.
Special Study - *in vivo* endocrine effects in rats. Acceptable-Non-guideline	43598614	In a special study (MRID 43598614) on *in vivo* endocrine effects, atrazine and simazine (>96 % a.i.) were administered to11 female rats/dose/strain (both Sprague-Dawley and Fischer 344 rats were used) by oral gavage at dose levels of 0, 100, and 300 mg/kg/day for 14 to 23 days depending on time to achieve proestrus. The LOAEL for systemic toxicity is 100 mg/kg/day for both atrazine and simazine, based on body weight effects and reproductive organ weight effects for atrazine. The NOAEL for toxicity cannot be determined. The LOAEL for endocrine effects of atrazine is 100 mg/kg/day based on organ weight effects, plasma hormone changes (estradiol), estrus cycle lengthening, and vaginal cytology. The NOAEL for endocrine effects of atrazine cannot be determined. The LOAEL for endocrine effects of simazine is 300 mg/kg/day based on organ weight effects and vaginal cytology. The NOAEL for endocrine effects of simazine is 100 mg/kg/day.
Special Study - LH surge in rats Acceptable-Nonguideline	45471002	In a special study (MRID 45471002) on the effects of chlorotriazines on luteinizing hormone (LH) surge, simazine (100%, batch no. SG202028GB10), diaminochlorotriazine (DACT) (96.8%, batch no. GP720301) and atrazine (97.1%, batch no. SG8029BA10) were administered to 20 Sprague-Dawley Crl:CD BR female rats/dose/group by oral gavage at dose levels of 0, 2.5, 5, 40, 200 mg/kg bw/day (equivalent to 12.4, 24.8, 198.3, and 991.6 µmol//kg/day for simazine; for 17.2, 34.4, 274.9, 1374.6 µmol//kg/day for DACT; and 11.6, 23.2,

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Simazine.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		185.4, 927.2 µmol//kg/day for atrazine) once daily for at least 4 weeks. The LOAEL for systemic toxicity is 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects. The NOAEL for all three compounds is 5 mg/kg/day. The LOAEL for endocrine effects for simazine, atrazine, and DACT is 40 mg/kg/day, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels). The NOAEL for endocrine effects for simazine atrazine, and DACT is 5.0 mg/kg/day.

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).

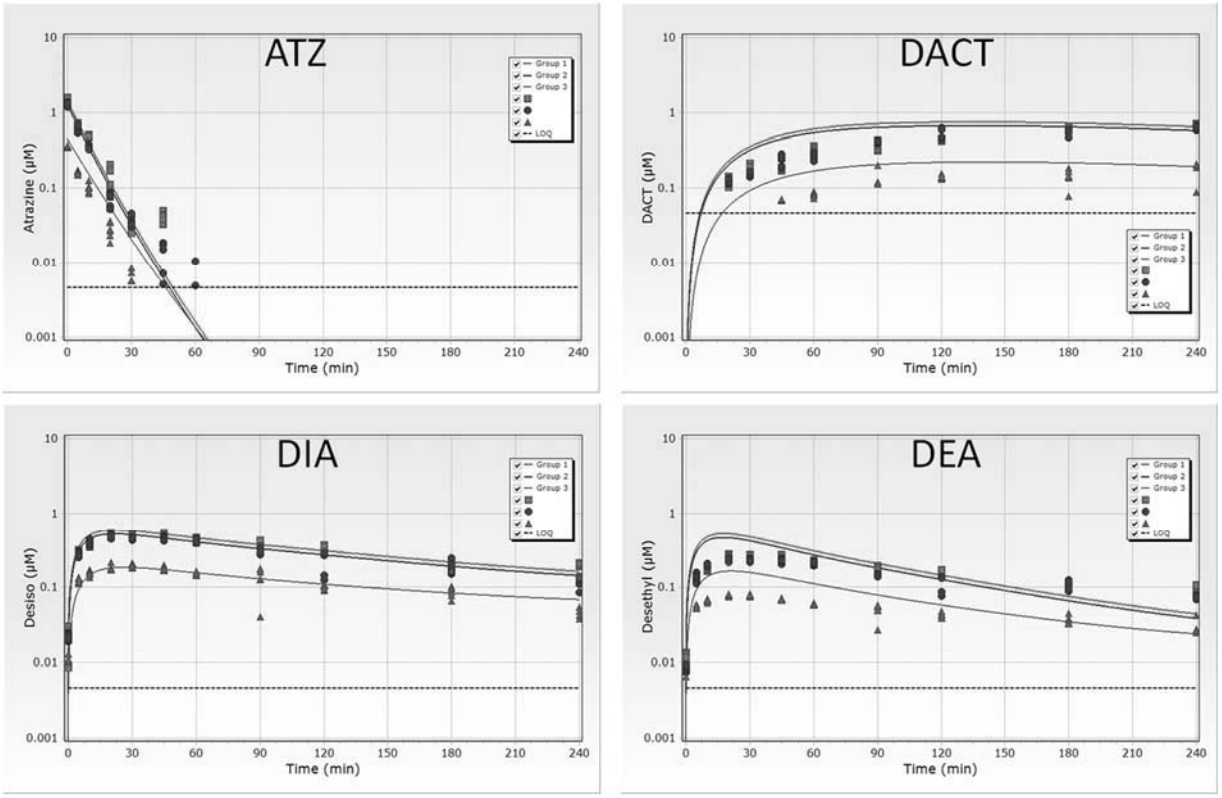


Figure A.3.1. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.26 µM – Group 2, and 0.45 µM – Group 3).

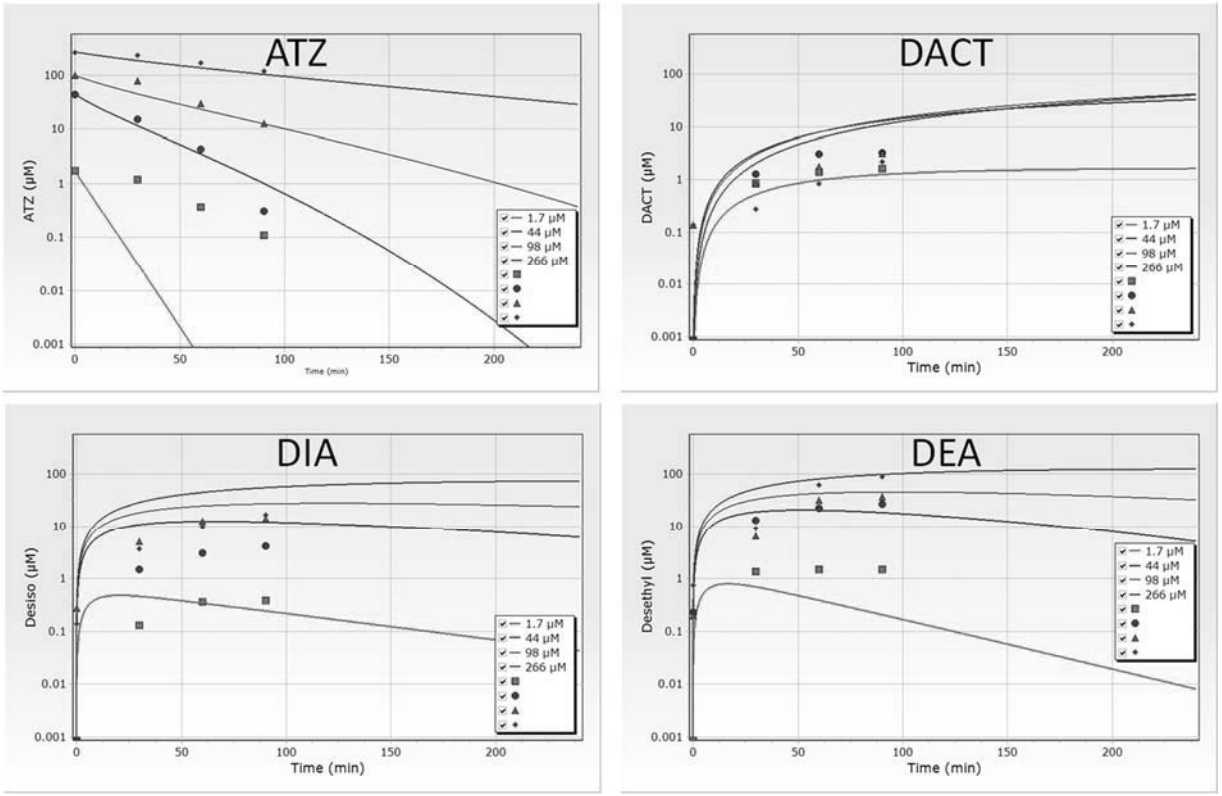


Figure A.3.2. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (McMullin et al., 2007).

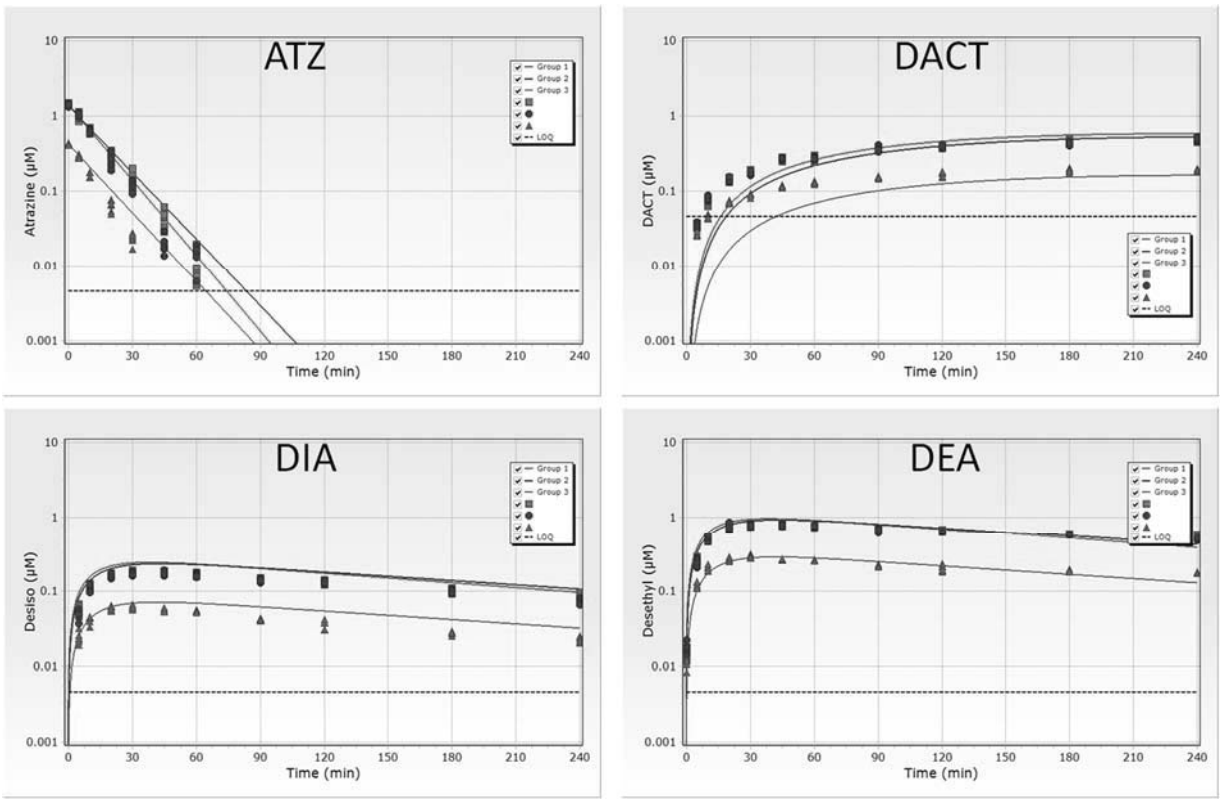


Figure A.3.3. Model prediction of intact human hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.38 µM – Group 2, and 0.42 µM – Group 3).

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).

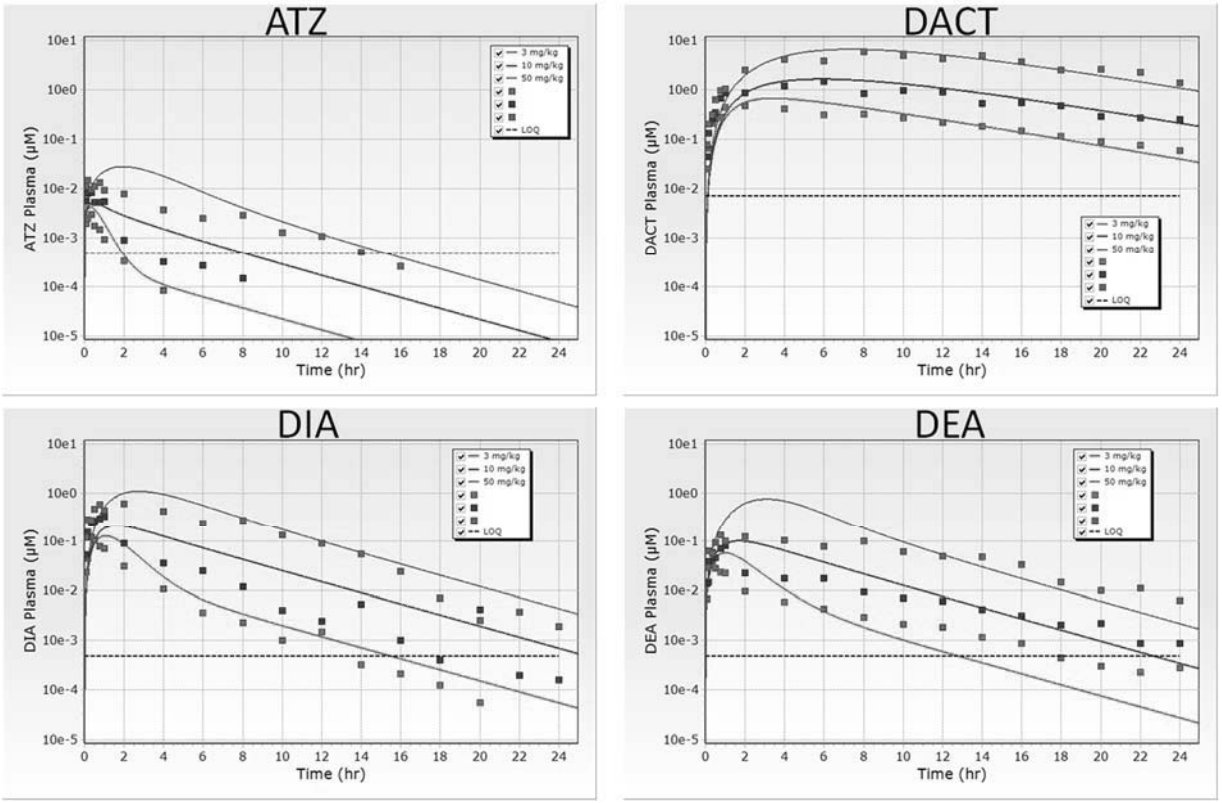


Figure A.3.4. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats after a single gavage dose of atrazine at 3, 10 and 50 mg/kg.

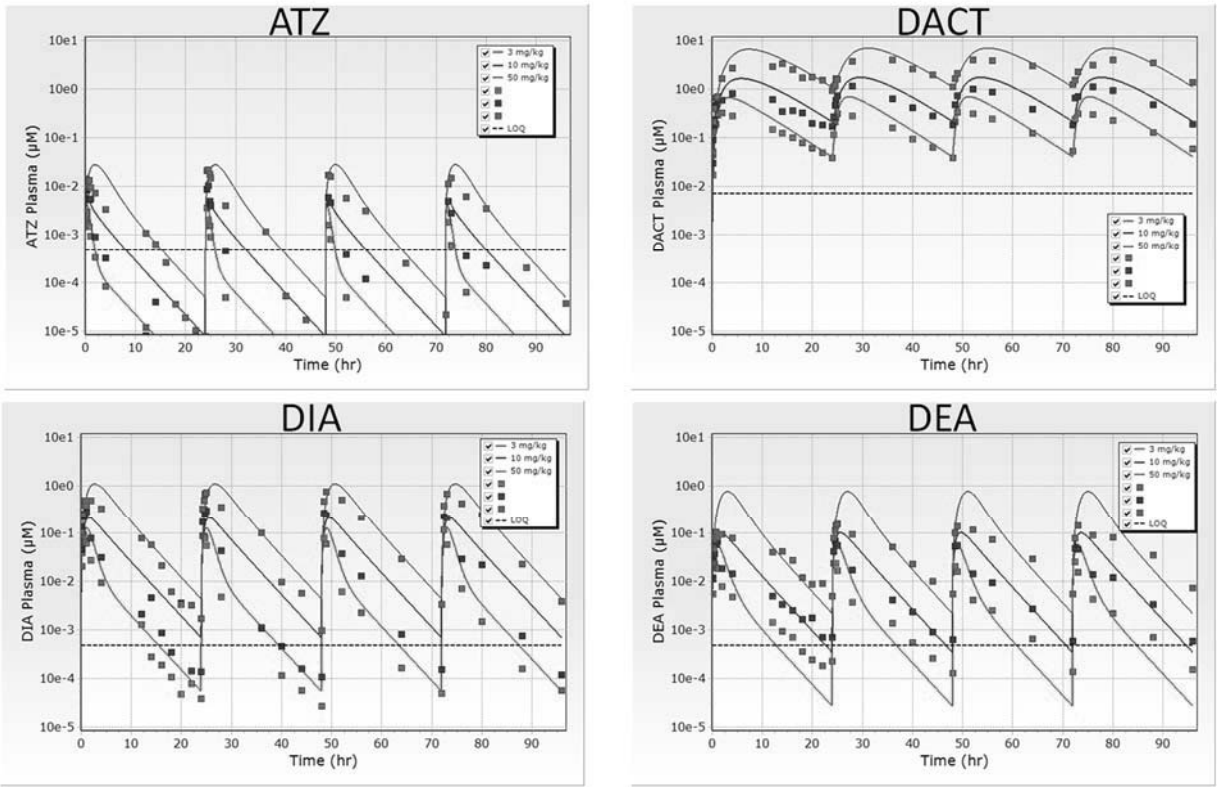


Figure A.3.5. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated daily gavage doses of atrazine at 3, 10 and 50 mg/kg.

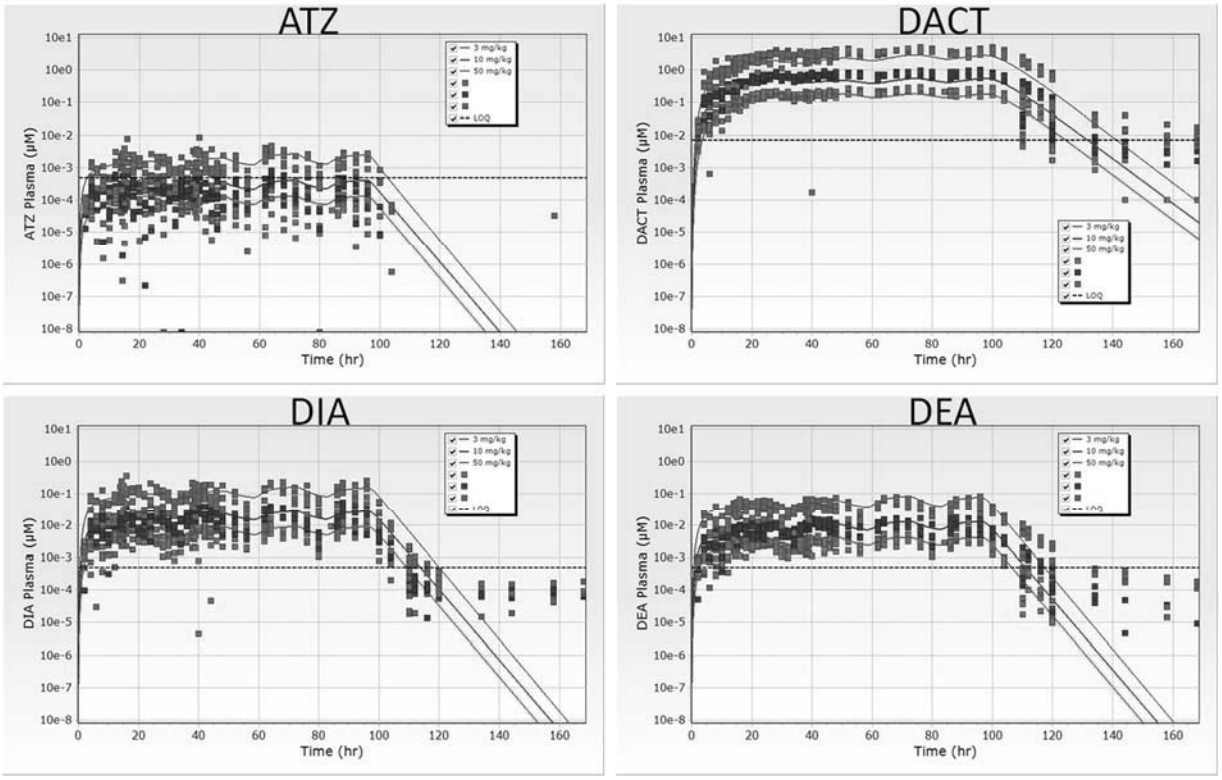


Figure A.3.6. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated dietary exposure to atrazine at 3, 10 and 50 mg/kg.

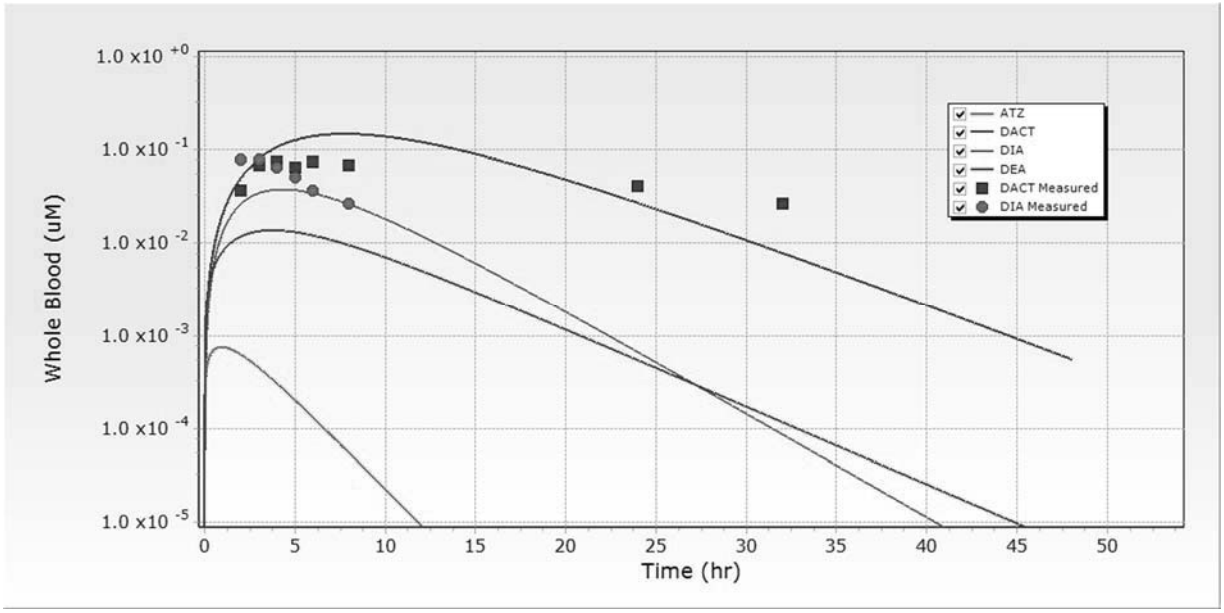


Figure A.3.7. Model simulations of atrazine, DIA, DEA, and DACT concentrations in the plasma of humans exposed to a single oral dose of 100 µg/kg atrazine.

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. New Epidemiology Literature on Simazine

The Agency conducted a formalized literature review to collect, evaluate, and integrate evidence from relevant epidemiological literature on the potential association between atrazine, simazine, and/or propazine (chlorotriazines) exposure and human health outcomes in order to evaluate whether chronic, subacute exposure to these chemicals is associated with an increased (or decreased) risk of various cancer and non-cancer health effects.

This epidemiology literature review identified 93 publications from 1990 – 2017 for inclusion. Of particular interest to the current weight of evidence for the risk assessment of simazine were the 3 epidemiology publications identified in the literature that generally met 1 or more of the following criteria: reported a statistically significant estimate of effect for simazine; originated from a prospective cohort and/or were otherwise of a moderate or high quality study design[47]; or were often referenced in the epidemiology literature and were unavailable at the time of the recent SAPs.

This appendix to the simazine risk assessment briefly describes the methods and results from the epidemiology literature review of atrazine, simazine, and/or propazine, and describes the 3 studies of particular interest to the simazine risk assessment in detail.

Eligibility Criteria

Specific inclusion criteria were identified prior to collecting potentially relevant publications for the epidemiology literature review of atrazine, simazine, and/or propazine. Inclusion criteria required studies to include information on the population, exposure, comparator, and outcome of interest (PECO)[48]. The population of interest was humans with no restrictions, including no restrictions on age, life stage, sex, country of residence/origin, race/ethnicity, lifestyle, or occupation. Exposure was to atrazine, simazine, and/or propazine (chlorotriazines) in any application via any route of exposure. The exposed or case population must have been compared to a population with low/no exposure or to non-cases to arrive at a risk/effect size estimate of a health outcome associated with atrazine, simazine, and/or propazine (chlorotriazine) exposure. The outcome of interest were any reported human health effects, with no restrictions on human system affected. Additionally, study publications must have been full text articles from observational studies published in English language peer reviewed journals, and publications must have reported on original data.

Exclusion criteria were also identified prior to collecting potentially relevant publications. Articles were excluded for the following reasons: not full text (*e.g.*, abstracts); not peer-reviewed (*e.g.*, letters, editorials, presentations); not in English; non-human study subjects; in-vitro studies; fate and transport studies; outcome other than human health effects (*e.g.*, environmental measures); experimental model system studies; no specific atrazine, simazine, and/or propazine

[47] 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

[48] Woodruff, T. J., & Sutton, P. (2014). The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental Health Perspectives (Online)*, *122*(10), 1007.

(chlorotriazines) investigation (*e.g.*, general herbicide or triazine studies); no risk/effect estimate reported (*e.g.*, case studies/series); no original data (*e.g.*, review publications).

The specificity of the chemical inclusion/exclusion criteria of this epidemiology literature review should be noted: Only studies that investigated exposures to atrazine, simazine, and/or propazine (chlorotriazines) were considered; studies that reported only on "triazines" were not retained for review in this epidemiology literature review. This inclusion/exclusion criterion may differ from other systematic literature reviews of the epidemiology evidence and from previous reports from the Agency.

A key element of the inclusion/exclusion criteria hinged on the definition of "human health effect" outcomes. For the purposes of the epidemiology literature review, the Agency considered human health effects via the toxicological paradigm presented by the NRC as pathologies or health impairments subsequent to altered structure/function[49]. Thus, studies with outcomes of altered structure (e.g., DNA alteration, sister chromatid exchange, cell proliferation), biomarker or other exposure outcomes (e.g., in breast milk, urine, cord blood, or plasma) that did not also include an associated health pathology (e.g., cancer, asthma, birthweight) failed to meet the inclusion criteria for "human health effects" for the purposes of the epidemiology literature review.

Open Literature Search

To complete a thorough search of the published literature in peer-reviewed journals, the Agency searched the established literature databases PubMed, Web of Science, and ScienceDirect (Table 1). Publications underwent a series of reviews to determine eligibility for inclusion in the epidemiology literature review. To be retained in the epidemiology literature review, study publications had to meet the specific inclusion criteria and avoid the exclusion criteria described above.

Table B-1: Literature databases, search strategies, search dates, and articles returned[50,51].

[49] Henderson, R., Hobbie, J., Landrigan, P., Mattisoti, D., Perera, F., Pfttaer, E., ... & Wogan, G. (1987). Biological markers in environmental health research. Environmental Health Perspectives, 7, 3-9.

[50] Chemical synonyms were utilized in the PubMed and the Web of Science literature search to capture articles utilizing only these terms in the citation material and the abstract; since ScienceDirect searches full text, only the generic chemical names were searched in ScienceDirect to reduce false hits. Chemical synonyms obtained from the following manual: Roberts, James R., and John Routt Reigart. *Recognition and management of pesticide poisonings.* 6th edition. National Pesticide Telecommunications Network, 2013.

[51] The number of articles reported reflects a net return and does not consider duplicates (the same article returned in multiple databases and/or multiple times in one database).

Database	Search strategy	Search date	Articles returned
Web of Science	TS=((atrazine OR simazine OR propazine OR chlorotriazine* OR aatrex OR atranex OR crisazina OR milo-pro OR prozinex OR gesatop OR princep) AND human AND (health OR epidemiologic stud* OR epidemiol* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR ecological stud*))	1/11/2017	246
PubMed	(atrazine[MeSH Major Topic] OR simazine[MeSH Major Topic] OR atrazine OR aatrex OR atranex OR crisazina OR simazine OR gesatop OR propazine OR milo-pro OR prozinex OR princep OR chlorotriazine* AND (health OR epidemiologic stud* OR epidemiol* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*)) AND "humans"[MeSH Terms]	1/11/2017	239
ScienceDirect	(atrazine OR simazine OR propazine OR chlorotriazine*) and (health OR epidemiol* OR cohort* OR "case control*" OR case-control* OR "cross section*" OR cross-section* OR cluster* OR occupational exposure* OR ecologic stud* OR aggregate stud*) and not TITLE(mouse OR mice OR biodegradation OR rice OR immunoassay OR vitro OR fish OR zebrafish OR bovine OR turtle OR crab OR crayfish OR ring OR carp OR alfalfa OR swine OR pig OR fate OR transport OR salamander OR trout OR polymer OR titanium OR catfish OR rodent OR dam OR dams OR diamond OR clay OR pathway OR production OR expression OR sorption OR review OR larva* OR chromatograph* OR spectrometr* OR nanopart* OR bioremed* OR animal* OR mussel* OR quail* OR rat* OR validat* OR cytomet* OR biopurificat* OR immunosens* OR alga* OR microalg* OR degrad* OR biodegrade* OR gravimeter* OR effluent* OR tadpole* OR imputat* OR adsorpt* OR transformat* OR oxidat* OR kinetic* OR photoactive* OR snail* OR electrod* OR pharmacokinet* OR spectra* OR microsom* OR biosens* OR model* OR immunobiosens*)	1/11/2017	841

Supplemental Literature Search

To supplement the open literature search conducted via PubMed, Web of Science, and ScienceDirect, the Agency reviewed publications resulting from the Agricultural Health Study (AHS) for articles that satisfied the inclusion/exclusion criteria (see https://aghealth.nih.gov/news/publications.html). The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. The AHS participant cohort includes more than 89,000 licensed commercial and private pesticide applicators and their spouses from Iowa and North Carolina. Enrollment occurred from 1993 – 1997, and data collection is ongoing.

Additionally, a citation review of the publications identified in both the open literature search and the AHS publication review identified additional studies for inclusion in the epidemiology literature review of atrazine, simazine, and/or propazine. Citations were examined to identify relevant publications that were not captured in either the open literature search or the AHS publication search. Resulting articles from this citation review that satisfied inclusion/exclusion criteria were selected for inclusion in the epidemiology literature review.

Study Selection

A total of 93 articles were selected for inclusion in the literature review (Figure 1) (References, Appendix B). These publications investigated carcinogenic and noncarcinogenic effects (43% and 58%, respectively; not mutually exclusive). Most (88%) reported an estimate of effect for atrazine, 14% reported an estimate of effect for simazine (not mutually exclusive: some articles reported estimates for both chemicals, while other articles reported estimates for only one). No publications reported an estimate of effect for propazine. Various study designs, including cohort, case-control, cross-sectional, and ecologic, were represented in the epidemiology

material. Included publications were restricted to English language articles that reported estimates of effect (*ex.*, odds ratio, p-trend, regression or correlation coefficients) for atrazine and/or simazine specifically, and included study populations from the USA, France, England, Canada, and Spain.

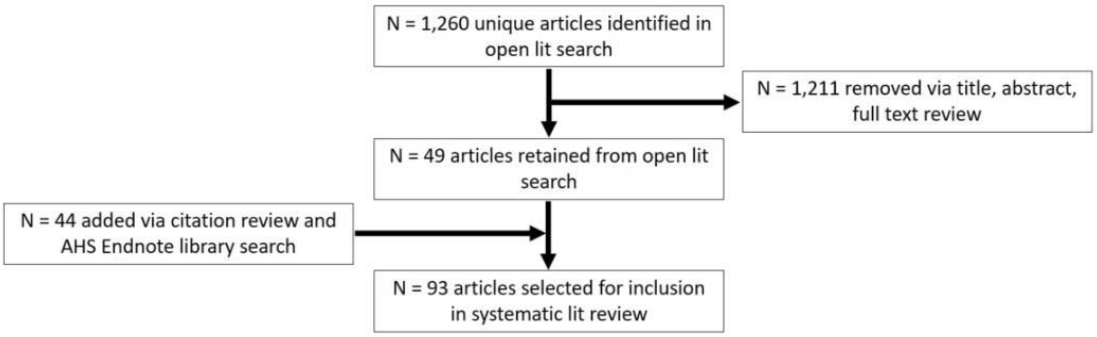


Figure B-1: Selection of studies for literature review of atrazine, simazine, and/or propazine (chlorotriazines) and carcinogenic and noncarcinogenic epidemiological effects.

Data Evaluation and Critical Review

Data evaluation included a concise summary of the publications found to be fit for purpose and thus included in the literature review of epidemiology investigations of atrazine, simazine, and/or propazine (chlorotriazines). Each publication was assessed for study quality[52]. Study quality assessment considered aspects of the study design, conduct, analysis, and interpretation of study results, including whether study publications adequately assessed exposure, used valid and reliable outcome ascertainment methods, employed appropriate statistical modeling techniques, considered potential confounders and critical health windows when appropriate, characterized potential systematic biases, and evaluated and reported statistical power.

Of the n = 93 publications from 1990 – 2017 identified for inclusion in the epidemiology literature review, n = 35 were not available for review at previous SAPs. Of particular interest to the current weight of evidence for the risk assessment of simazine were the 3 epidemiology publications that originated from the 13 epidemiology studies that were assessed in the current Atrazine DRA report (as mentioned above). These 3 studies are summarized and reviewed below:

[52] 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

Study 1. Chevrier, C., Limon, G., Monfort, C., Rouget, F., Garlantezec, R., Petit, C., Durand, Gael, & Cordier, S. (2011). Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. Environ Health Perspect, 119(7), 1034-1041. doi:10.1289/ehp.1002775

Chevrier *et al.* (2011) investigated the association between prenatal simazine exposure and risk of adverse birth outcomes through a nested case-cohort study of the PELAGIE (Perturbateurs endocriniens: Etude Longitudinale sur les Anomalies de la Grossesse, l'lnfertilite et l'Enfance) cohort in the Brittany region of France. The study subcohort included n = 579 women/child pairs (children included live-born, singleton offspring, and women were included if they submitted urine samples). The study subcohort was comprised of all PELAGIE cohort members with adverse birth outcomes of interest (congenital anomalies, fetal growth restriction (FGR), and small head circumference (SHC)), plus children randomly selected from the remaining cohort members. Birth information including birth weight, length, and head circumference was collected from hospital records. Gestational age was estimated based on maternal report of last menstrual period as well as ultrasound exams. Cases of FGR (n = 178 with accompanying maternal urine sample) were defined as births below the 5th percentile of the distribution of expected birth weight of the cohort modeled by gestational age, sex, parity, and maternal weight, height, and age (Mamelle et al. 2001). Cases of SHC (n = 103 with accompanying maternal urine sample) were defined as head circumference at birth below the 5th percentile of the birth head circumference distribution for a given gestational age and sex, using country-wide (French) reference curves (Mamelle et al. 1996). Cases of major congenital malformations (n = 88 with accompanying maternal urine sample) including male genital anomalies (hypospadias, undescended testis, and micropenis) were defined via diagnosis by pediatrician. Prenatal exposure to simazine was assessed through the maternal urine sample, provided before the 19th week of gestation. Urine samples were collected from 2002 to 2006, and levels of simazine and simazine metabolites were quantified through liquid chromatography/triple-quadrupole mass spectrometry (LC/MS-MS). Mothers and fetuses were considered exposed if simazine or at least one of its metabolites (simazine mercapturate or hydroxysimazine) was quantified in the maternal urine sample. Agricultural activity data (estimated by the proportion of a municipality's area used for corn crops as reported in the national agricultural census, conducted in 2000) was defined for each mother's municipality of residence at study enrollment. Multivariate logistic models were used to estimate ORs and 95% CIs for each adverse birth outcome, adjusting for selected covariates and using the unexposed group as the referent[53]. Additionally, linear models explored the associations between urinary biomarkers of exposure and birth weight, birth length, and head circumference as continuous outcomes. Backward selection process with a cut-off p = 0.20 was used to determine which of the large number of potential covariates were retained in the final models (at least 38 parameters for the initial list of covariates in the SHC analysis, at least 30 parameters for the initial list of covariate in the FGR analysis, and at least 44 parameters for the initial list of covariates in the congenital anomalies analysis).

Urinalysis results identified 6 women with simazine concentrations above the limit of quantification (LOQ) (median level = 1.00 µg/L; maximum = 4.40 µg/L), 44 with simazine mercapturate above the LOQ (median = 0.50 µg/L, max = 4.60 µg/L), and 50 with

[53] Case-control ORs were estimated without incorporating case-cohort sampling probabilities because the case-control ORs approximate case-cohort outcomes for rare outcomes per author's note.

hydroxysimazine above the LOQ (median = 0.80 µg/L, max = 1.60 µg/L), (urinalysis results not mutually exclusive; subjects could test positive for one or more markers of simazine exposure). Analyses of FGR did not suggest any evidence of significant positive association between simazine exposure and risk of FGR, adjusting for maternal smoking, blood pressure before and during pregnancy, thawing and refreezing of urine samples (OR = 1.10; 95% CI: 0.70, 1.80 with 28 cases exposed and 150 cases unexposed)[54]. Results also did not suggest a significant positive association between simazine exposure and risk of SHC for sex and gestational age, adjusting for residence district, alcohol consumption at enrollment, thawing and refreezing of urine samples, cesarean delivery, and parity (OR = 0.80; 95% CI: 0.40, 1.70 with 13 cases exposed and 90 cases unexposed). There was no evidence of a significant positive association between simazine exposure and major congenital anomalies, adjusting for year of enrollment, season at conception, maternal occupational exposure to solvents, and gestational age at birth (OR = 1.80; 95% CI:1.0, 3.50 with 17 cases exposed and 71 cases unexposed). Linear analyses did not suggest that simazine exposure was significantly associated with birth weight (simazine coefficient p-value = 0.45), birth length (simazine coefficient p-value = 0.48), or head circumference (simazine coefficient p-value = 0.11), controlling for year of enrollment, education level, smoking, high blood pressure before and during pregnancy, thawing and refreezing of urine samples, pre pregnancy BMI, child's sex, shellfish intake, gestational age at birth, alachlor exposure, season at conception, residence district, cesarean delivery, and/or parity[55]. In contrast, linear analyses looking at simazine and/or simazine mercapturate in maternal urine sample showed evidence of a positive statistically significant association between exposure and birthweight in grams (simazine β = (130), p-value = 0.04) as well as for birth length in cm (simazine β = (0.61), p-value = 0.03), thus suggesting that the presence of simazine and/or simazine mercapturate in maternal urine was associated with an ***increase*** in both infant birthweight and infant birth length of 130 grams and 0.61 centimeters, respectively, neither of which were considered adverse. Note, as above, that no statistically significant relationship was shown for these measures with simazine alone.

Strengths of Chevrier *et al.* (2011) included the nested case-cohort design, the use of biomarkers to assess exposure, the identification of cases based on hospital data and/or physician diagnosis, and the consideration of multiple potential confounders including exposure to other herbicides. The primary weakness of the study was that exposure was based on a single urine sample, and authors noted that this may not have adequately reflected chronic exposure and did not allow for intra-individual variability considerations. Women collected their own urine, transferred the samples to vials with nitric acid to inhibit bacterial growth, and mailed the samples to the study laboratory at ambient temperature. Urine delivery typically took 1 – 3 days. Upon receipt in the laboratory, the urine samples were frozen and stored at -20ºC. Authors acknowledged that this circuitous route from sample collection to freezer may have affected the sample concentrations. Destabilization of the urine samples may have led to exposure misclassification. Furthermore, the LC/MS-MS calibration standards were conducted using "fresh samples of pesticide-free human urine". The investigators did not discuss whether differences in handling methods

[54] In the publication, some results with lower bounds of CIs reported as 1.0 are marked significant while others are not (footnote, Table 4). For the purposes of this review, the CIs are reported as > or <1 to align with the authors declaration of significance.
[55] Confounders were selected for final models following backwards selection of all covariates considered and retaining only those with $p < 0.20$.

between the samples and the calibration standards may have impacted the results of the urinalyses.

Another major limitation of this study was potential statistical bias from the backward selection process used to select variables in their regression model. Backward selection is generally regarded as an unreliable variable selection method for regression models[56]. This is because the use of backward selection, particularly when it results in a large number of variables in a regression model, can result in biased parameter estimates with 95% confidence intervals that are too narrow due to underestimation of standard errors. As a result of this statistical issue, this study's findings are considered most appropriate for hypothesis generation[57].

EPA Evaluation of Chevrier et al. (2011)

Overall, the epidemiological evidence is insufficient at this time to conclude that there is a causal or clear associative relationship between maternal exposure to simazine and adverse birth outcomes in offspring. Chevrier *et al*. (2011) reported no evidence of a significant positive association between simazine exposure and adverse birth outcomes including FGR, SHC, and congenital malformations such as male genital anomalies. Several study limitations mentioned above including the use of the backward selection technique for the data analysis, and the lack of routine urine sampling from the study participants to assess chronic exposure (only a single urine sample was collected for the duration of the study), reduced the reliability of the study. These study limitations preclude the ability to determine a clear associative or causal association, between maternal exposure to simazine and adverse birth outcomes in offspring. Based on the study limitations, the overall quality of the study was ranked low.

Study 2. García-Pérez, J., López-Abente, G., Gómez-Barroso, D., Morales-Piga, A., Romaguera, E. P., Tamayo, I., Fernandez-Navarro, P., & Ramis, R. (2015). Childhood leukemia and residential proximity to industrial and urban sites. Environmental research, 140, 542-553.

Garcia-Perez *et al.* (2015) investigated potential associations between residential proximity to industrial and urban pollutants including atrazine, simazine, and other pesticides and risk of leukemia in children through a case-control study. The study population included children up to 14 years old, living in Catalonia, the Basque Country, Aragon, Navarre, and the Autonomous Region of Madrid, Spain (n = 13,826). Cases (n = 638) were identified from the Spanish Registry of Childhood Tumors and included leukemia diagnoses in children (aged 0 – 14 years) from 1996 to 2011. Controls (n = 13,188) were identified by simple random sampling of the Birth Registry of the Spanish National Statistics Institute and were matched to cases by sex, year of birth, and region of residence. Exposure was assessed by distance from the study subject's home to industrial and urban areas, and pollutant information for industrial and urban areas was determined through the 2009 European Pollutant Release and Transfer Register (E-PRTR), a database of industrial facilities locations and their pollution emissions (air and water releases).

[56] Flom, P. L., Cassell, D. L. (2007). Stopping stepwise: Why stepwise and similar selection methods are bad, and what you should use. Statistics and Data Analysis. NESUG 2007; Babyak, Michael A. (2004) What you see may not be what you get: a brief nontechnical introduction to overfitting in regression -type models. Psychosomatic Medicine 66:411-422.
[57] Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. EPA 2016

Urban areas were defined as towns or cities with ≥ 75,000 inhabitants. Mixed multiple logistic regression models (independent models for atrazine, simazine, and other pollutants investigated) calculated ORs and 95% CIs for distance categories to the pollutant source, adjusting for year of birth, sex, and autonomous region of residence.

Study results for simazine suggested a positive association between living within 2.5 km of a facility that released simazine and risk of childhood leukemia (OR = 1.66; 95% CI: 1.08, 2.54 with 29 cases and 423 controls living within 2.5 km of a facility; 22 facilities reported 8 kg simazine released into water and no facilities reporting simazine released into air).

Study strengths included the use of national registries to identify both cases and controls and the large number of controls[58]. Weaknesses of the study included the use of distance to a pollution source as a proxy of exposure which may have introduced misclassification bias. Personal exposures may be linked to a combination of locations, including home, work, school, and recreation locations; thus, using residential location alone introduced potential misclassification bias. Furthermore, residential locations were geocoded into latitude and longitude. However, geocoding was not successful for all study subjects (87% of cases and 98% of controls were successfully geocoded). Geocoding success varies across residential address type, with rural addresses and post office boxes typically returning lower success rates[59,60]. Removing participants whose addresses did not geocode introduced a potential for selection bias, particularly since cases had a lower geocoding success rate than controls. Another weakness that may have biased the results was the different methods for residential classification for cases and controls: cases were assigned residency based on address at time of diagnosis, while controls were assigned residency based on maternal address at time of birth. Furthermore, the study did not consider movement or migration over the study period. Finally, critical windows for exposure were not considered in this study of childhood leukemia.

EPA Evaluation of Garcia-Perez et al. (2015)

Overall, the epidemiological evidence is insufficient to conclude there is a causal or clear associative relationship between residential proximity to urban pollutants such as simazine and childhood leukemia. The study results reported by Garcia-Perez *et al.* (2015) suggested a positive association between living within 2.5 km of a facility that released simazine and risk of childhood leukemia; however, several limitations of the Garcia-Perez *et al.* (2015) study lead the Agency to place less emphasis on this finding. Study limitations mentioned above included the limited number of exposed cases observed (n = 30), the use of distance to a pollution source as a proxy of exposure, and the different methods for residential classification for cases and controls. These study limitations preclude the ability to determine a clear associative or causal association between residential proximity to urban pollutants including simazine and childhood leukemia. Based on the study limitations, the overall quality of the study was ranked low.

[58] With approximately 20 controls per case, this increased the statistical power of the study. However, power gains may drop off at a ratio of 1:4 cases: controls (See Gordis, Leon (2009). Epidemiology – 4th Edition. Philadelphia, Elsevier/Saunders; and Gregg, Michael B. (2002). Field Epidemiology. Oxford University Press.)

[59] Kravets, N., & Hadden, W. C. (2007). The accuracy of address coding and the effects of coding errors. *Health & place*, *13*(1), 293-298.

[60] Hurley, S. E., Saunders, T. M., Nivas, R., Hertz, A., & Reynolds, P. (2003). Post office box addresses: a challenge for geographic information system-based studies. *Epidemiology*, *14*(4), 386-391.

Study 3. Hoppin, J. A., Umbach, D. M., Long, S., London, S. J., Henneberger, P. K., Blair, A., Alavanja, M., Beane Freeman, L.E., & Sandler, D. P. (2016). Pesticides Are Associated with Allergic and Non-Allergic Wheeze among Male Farmers. Environ Health Perspect. doi:10.1289/ehp315

Hoppin *et al.* (2016)[61] investigated the association between allergic and non-allergic wheeze and atrazine, simazine, and other pesticide exposure among male farmers through a cross-sectional analysis of AHS data. The study population consisted of male participants in the AHS (n = 22,134) who completed a self-reported questionnaire at enrollment (1993 – 1997) detailing pesticide usage and symptoms of wheeze. Cases were subdivided into allergic wheeze (n = 1,310), defined as at least one episode of wheeze or whistling in the chest in the past year and a doctor diagnosis of hay fever, and nonallergic wheeze (n = 3,939), defined as at least one episode of wheeze or whistling in the chest in the past year without a diagnosis of hay fever. Survey information was used to assess specific pesticide exposure (current, past, or never use) and to assess frequency and duration of use. Among the 1,310 allergic wheeze cases, 3% (n ~ 40) reported current use of simazine[62]. Among the 3,939 non-allergic wheeze cases, 1% (n ~ 40) reported current use of simazine. Of the 16,885 non-case subjects, 1% (n ~ 169) reported current use of simazine. Polytomous logistic regression was used to determine the association between wheeze and ever exposure to each pesticide individually (compared to never exposed), and allergic and non-allergic wheeze were investigated separately. Models were adjusted for age, body mass index (BMI), state, smoking, and current asthma, as well as for days applying pesticides and days driving diesel tractors. Results suggested a positive association between current simazine use and allergic wheeze, and no evidence of a positive association between simazine use and nonallergic wheeze (allergic: OR = 1.71; 95% CI: 1.17, 2.50; nonallergic: OR = 0.94; 95% CI: 0.68, 1.28).

Hoppin *et al.* (2016) benefited from the large AHS participant cohort with data collected on specific pesticide usage, demographics, and lifestyle factors. Weaknesses of the Hoppin *et al.* (2016) study included the cross-sectional study design and thus lack of relative temporal information on exposure and outcome, the high percentage of white men compared to other demographic groups in the AHS cohort, potentially limiting the generalizability of results, the potential for the healthy worker effect confounding the results[63], and the reliance on self-reported exposure and lifestyle factors through questionnaires and thus the potential for recall bias and exposure misclassification. However, the AHS participant cohort has demonstrated high reliability for self-reported information for pesticide use, demographic, and lifestyle factors[64].

EPA Evaluation of Hoppin et al. (2016)

[61] Hoppin et al. 2016 is not a strict update to Hoppin et al. 2006a/2006b or 2002, which are also included in the epidemiology literature review (see References, Appendix B). We can assume overlap in participants, but publications do not summarize the overlap. All publications are summarized in the epidemiology literature review, but the consonant data sources should be recognized.

[62] Ns approximated via calculation and rounded to nearest whole number.

[63] Le Moual, N., Kauffmann, F., Eisen, E. A., & Kennedy, S. M. (2008). The healthy worker effect in asthma: work may cause asthma, but asthma may also influence work. American journal of respiratory and critical care medicine, 177(1), 4-10.

[64] Blair, A., Tarone, R., Sandler, D., Lynch, C. F., Rowland, A., Wintersteen, W., . . . Alavanja, M. C. (2002). Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology, 13(1), 94-99.

Overall, the epidemiological evidence is insufficient at this time to conclude that there is a causal or clear associative relationship between simazine exposure and wheeze. Hoppin *et al.* (2016) reported evidence of a significant positive association between simazine exposure and allergic wheeze, and no evidence of a positive association between simazine exposure and nonallergic wheeze among male pesticide applicators. Although this study benefited from the large AHS participant cohort with data collected on specific pesticide usage, the study was limited due to the small number of exposed cases observed for both allergic and nonallergic wheeze (n = ~ 40 exposed cases (or n = 1 - 3 % of cases) for both allergic and nonallergic wheeze). Furthermore, the cross-sectional study design was considered a study limitation, as temporality could not be determined. These study limitations limit the reliability of the study, and, the Agency is unable to conclude that a causal or clear associative relationship exists relative to simazine exposure at this time. Based on the above study limitations, the overall quality of the study was ranked low.

Publications (n = 93) retained in the atrazine, simazine, and/or propazine epidemiology literature review

1. Agopian, A. J., Cai, Y., Langlois, P. H., Canfield, M. A., & Lupo, P. J. (2013a). Maternal residential atrazine exposure and risk for choanal atresia and stenosis in offspring. *J Pediatr, 162*(3), 581-586. doi:10.1016/j.jpeds.2012.08.012
2. Agopian, A. J., Langlois, P. H., Cai, Y., Canfield, M. A., & Lupo, P. J. (2013b). Maternal residential atrazine exposure and gastroschisis by maternal age. *Matern Child Health J, 17*(10), 1768-1775. doi:10.1007/s10995-012-1196-3
3. Agopian, A. J., Lupo, P. J., Canfield, M. A., & Langlois, P. H. (2013c). Case-control study of maternal residential atrazine exposure and male genital malformations. *Am J Med Genet A, 161a* (5), 977-982. doi:10.1002/ajmg.a.35815
4. Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P., & Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol, 157*(9), 800-814.
5. Andreotti, G., Freeman, L. E., Hou, L., Coble, J., Rusiecki, J., Hoppin, J. A., Silverman, D.T., & Alavanja, M. C. (2009). Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. *Int J Cancer, 124*(10), 2495-2500. doi:10.1002/ijc.24185
6. Andreotti, G., Hou, L., Beane Freeman, L. E., Mahajan, R., Koutros, S., Coble, J., Lubin, J., Blair, A., Hoppin, J.A., & Alavanja, M. (2010). Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. *Cancer Causes Control, 21*(11), 1759-1775. doi:10.1007/s10552-010-9603-9
7. Andreotti, G., Koutros, S., Berndt, S. I., Hughes Barry, K., Hou, L., Hoppin, J. A., Sandler, D.P., Lubin, J.H., Burdette, L.A., Yuenger, J., Yeager, M., Beane Freeman, L.E., & Alavanja, M. C. (2012). The Interaction between Pesticide Use and Genetic Variants

Involved in Lipid Metabolism on Prostate Cancer Risk. *J Cancer Epidemiol, 2012*, 358076. doi:10.1155/2012/358076

8. Arbuckle, T. E., Lin, Z. Q., & Mery, L. S. (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect, 109*(8), 851-857. doi:10.2307/3454830
9. Band, P. R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R. P., & Le, N. D. (2011). Prostate cancer risk and exposure to pesticides in British Columbia farmers. *Prostate, 71*(2), 168-183. doi:10.1002/pros.21232
10. Beard, J. D., Hoppin, J. A., Richards, M., Alavanja, M. C. R., Blair, A., Sandler, D. P., & Kamel, F. (2013). Pesticide exposure and self-reported incident depression among wives in the Agricultural Health Study. *Environ Res, 126*, 31-42. doi:http://dx.doi.org/10.1016/j.envres.2013.06.001
11. Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D.P., & Kamel, F. (2011). Suicide and pesticide use among pesticide applicators and their spouses in the agricultural health study. *Environ Health Perspect, 119*(11), 1610-1615. doi:10.1289/ehp.1103413
12. Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D.P., & Kamel, F. (2014). Pesticide exposure and depression among male private pesticide applicators in the agricultural health study. *Environ Health Perspect, 122*(9), 984-991. doi:10.1289/ehp.1307450
13. Brown, L. M., Blair, A., Gibson, R., Everett, G. D., Cantor, K. P., Schuman, L. M., Burmeister, L.F., Van Lier, S.F., & Dick, F. (1990). Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Research, 50*(20), 6585-6591.
14. Brown, L. M., Burmeister, L. F., Everett, G. D., & Blair, A. (1993). Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes & Control, 4*(2), 153-156.
15. Cantor, K. P., Blair, A., Everett, G., Gibson, R., Burmeister, L. F., Brown, L. M., Schuman, L., & Dick, F. R. (1992). Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Research, 52*(9), 2447-2455.
16. Carreón, T., Butler, M. A., Ruder, A. M., Waters, M. A., Davis-King, K. E., Calvert, G. M., Heineman, E.F., Mandel, J.S., Morton, R.F., Reding, D.J., Rosenman, K.D., Talaska, G., Schulte, P.A., Connally, B., Ward, E.M., & Sanderson, W. T. (2005). Gliomas and farm pesticide exposure in women: the Upper Midwest Health Study. *Environ Health Perspect*, 546-551.
17. Chevrier, C., Limon, G., Monfort, C., Rouget, F., Garlantezec, R., Petit, C., Durand, Gael, & Cordier, S. (2011). Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. Environ Health Perspect, 119(7), 1034-1041. doi:10.1289/ehp.1002775
18. Cockburn, M., Mills, P., Zhang, X., Zadnick, J., Goldberg, D., & Ritz, B. (2011). Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. *Am J Epidemiol, 173*(11), 1280-1288. doi:10.1093/aje/kwr003
19. Cragin, L. A., Kesner, J. S., Bachand, A. M., Barr, D. B., Meadows, J. W., Krieg, E. F., & Reif, J. S. (2011). Menstrual cycle characteristics and reproductive hormone levels in women exposed to atrazine in drinking water. *Environ Res, 111*(8), 1293-1301. doi:10.1016/j.envres.2011.09.009

20. Crawford, J. M., Hoppin, J. A., Alavanja, M. C., Blair, A., Sandler, D. P., & Kamel, F. (2008). Hearing loss among licensed pesticide applicators in the agricultural health study. *J Occup Environ Med, 50*(7), 817-826. doi:10.1097/JOM.0b013e31816a8caf
21. Dayton, S. B., Sandler, D. P., Blair, A., Alavanja, M., Beane Freeman, L. E., & Hoppin, J. A. (2010). Pesticide use and myocardial infarction incidence among farm women in the agricultural health study. *J Occup Environ Med, 52*(7), 693-697. doi:10.1097/JOM.0b013e3181e66d25
22. De Roos, A. J., Cooper, G. S., Alavanja, M. C., & Sandler, D. P. (2005). Rheumatoid Arthritis among Women in the Agricultural Health Study: Risk Associated with Farming Activities and Exposures. *Ann Epidemiol, 15*(10), 762-770. doi:http://dx.doi.org/10.1016/j.annepidem.2005.08.001
23. De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., & Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med, 60*(9), E11.
24. Engel, L. S., Hill, D. A., Hoppin, J. A., Lubin, J. H., Lynch, C. F., Pierce, J., Samanic, C., Sandler, D.P., Blair, A., & Alavanja, M. C. (2005). Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. *Am J Epidemiol, 161*(2), 121-135. doi:10.1093/aje/kwi022
25. Farr, S. L., Cai, J., Savitz, D. A., Sandler, D. P., Hoppin, J. A., & Cooper, G. S. (2006). Pesticide exposure and timing of menopause: the Agricultural Health Study. *Am J Epidemiol, 163*(8), 731-742. doi:10.1093/aje/kwj099
26. Flower, K. B., Hoppin, J. A., Lynch, C. F., Blair, A., Knott, C., Shore, D. L., & Sandler, D. P. (2004). Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect, 112*(5), 631-635.
27. Freeman, L. E., Rusiecki, J. A., Hoppin, J. A., Lubin, J. H., Koutros, S., Andreotti, G., Zahm, S.H., Hines, C.J., Coble, J.B., Barone-Adesi, F., Sloan, J., Sandler, D.P., Blair, A., & Alavanja, M. C. (2011). Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994-2007). *Environ Health Perspect, 119*(9), 1253-1259. doi:10.1289/ehp.1103561
28. García-Pérez, J., Lope, V., López-Abente, G., González-Sánchez, M., & Fernández-Navarro, P. (2015). Ovarian cancer mortality and industrial pollution. *Environmental Pollution, 205*, 103-110. doi:http://dx.doi.org/10.1016/j.envpol.2015.05.024
29. García-Pérez, J., López-Abente, G., Gómez-Barroso, D., Morales-Piga, A., Romaguera, E. P., Tamayo, I., Fernandez-Navarro, P., & Ramis, R. (2015). Childhood leukemia and residential proximity to industrial and urban sites. Environmental research, 140, 542-553.
30. García-Pérez, J., Morales-Piga, A., Gómez-Barroso, D., Tamayo-Uria, I., Pardo Romaguera, E., López-Abente, G., & Ramis, R. (2017). Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study. *Science of the Total Environment, 579*, 1333-1342. doi:http://dx.doi.org/10.1016/j.scitotenv.2016.11.131
31. Goldner, W. S., Sandler, D. P., Yu, F., Hoppin, J. A., Kamel, F., & Levan, T. D. (2010). Pesticide use and thyroid disease among women in the Agricultural Health Study. *Am J Epidemiol, 171*(4), 455-464. doi:10.1093/aje/kwp404
32. Goldner, W. S., Sandler, D. P., Yu, F., Shostrom, V., Hoppin, J. A., Kamel, F., & LeVan, T. D. (2013). Hypothyroidism and pesticide use among male private pesticide applicators

in the agricultural health study. *J Occup Environ Med, 55*(10), 1171-1178. doi:10.1097/JOM.0b013e31829b290b
33. Henneberger, P. K., Liang, X., London, S. J., Umbach, D. M., Sandler, D. P., & Hoppin, J. A. (2014). Exacerbation of symptoms in agricultural pesticide applicators with asthma. *Int Arch Occup Environ Health, 87*(4), 423-432. doi:10.1007/s00420-013-0881-x
34. Hessel, P. A., Kalmes, R., Smith, T. J., Lau, E., Mink, P. J., & Mandel, J. (2004). A nested case-control study of prostate cancer and atrazine exposure. *J Occup Environ Med, 46*(4), 379-385.
35. Hoar Zahm, S., Weisenburger, D. D., Cantor, K. P., Holmes, F. F., & Blair, A. (1993). Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand J Work Environ Health, 19*(2), 108-114.
36. Hopenhayn-Rich, C., Stump, M. L., & Browning, S. R. (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Arch Environ Contam Toxicol, 42*(1), 127-136. doi:10.1007/s002440010300
37. Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C., & Sandler, D. P. (2002). Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. *Am J Respir Crit Care Med, 165*(5), 683-689. doi:10.1164/ajrccm.165.5.2106074
38. Hoppin, J. A., Umbach, D. M., London, S. J., Henneberger, P. K., Kullman, G. J., Alavanja, M. C., & Sandler, D. P. (2008). Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. *Am J Respir Crit Care Med, 177*(1), 11-18. doi:10.1164/rccm.200706-821OC
39. Hoppin, J. A., Umbach, D. M., London, S. J., Henneberger, P. K., Kullman, G. J., Coble, J., Alavanja, M.C.R., Beane Freeman, L.E., & Sandler, D. P. (2009). Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. *Eur Respir J, 34*(6), 1296-1303. doi:10.1183/09031936.00005509
40. Hoppin, J. A., Umbach, D. M., London, S. J., Lynch, C. F., Alavanja, M. C., & Sandler, D. P. (2006). Pesticides and adult respiratory outcomes in the agricultural health study. *Ann N Y Acad Sci, 1076*, 343-354. doi:10.1196/annals.1371.044
41. Hoppin, J. A., Umbach, D. M., London, S. J., Lynch, C. F., Alavanja, M. C., & Sandler, D. P. (2006). Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. *Am J Epidemiol, 163*(12), 1129-1137. doi:10.1093/aje/kwj138
42. Hoppin, J. A., Umbach, D. M., Long, S., London, S. J., Henneberger, P. K., Blair, A., Alavanja, M., Beane Freeman, L.E., & Sandler, D. P. (2016). Pesticides Are Associated with Allergic and Non-Allergic Wheeze among Male Farmers. Environ Health Perspect. doi:10.1289/ehp315
43. Hoppin, J. A., Valcin, M., Henneberger, P. K., Kullman, G. J., Umbach, D. M., London, S. J., Alavanja, M.C.R., & Sandler, D. P. (2007). Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study. *Am J Ind Med, 50*(12), 969-979. doi:10.1002/ajim.20523
44. James, K. A., & Hall, D. A. (2015). Groundwater pesticide levels and the association with Parkinson disease. *Int J Toxicol, 34*(3), 266-273. doi:10.1177/1091581815583561
45. Kamel, F., Tanner, C., Umbach, D., Hoppin, J., Alavanja, M., Blair, A., Comyns, K., Goldman, S.M., Korell, M., Langston, J.W., Ross, G.W., & Sandler, D. (2007). Pesticide

exposure and self-reported Parkinson's disease in the agricultural health study. *Am J Epidemiol, 165*(4), 364-374. doi:10.1093/aje/kwk024
46. Karami, S., Andreotti, G., Koutros, S., Barry, K. H., Moore, L. E., Han, S., Hoppin, J.A., Sandler, D.P., Lubin, J.H., Burdette, L., Yuenger, J., Yeager, M., Beane Freeman, L., Blair, A., & Alavanja, M. C. (2013). Pesticide exposure and inherited variants in vitamin d pathway genes in relation to prostate cancer. *Cancer Epidemiol Biomarkers Prev, 22*(9), 1557-1566. doi:10.1158/1055-9965.epi-12-1454
47. Kirrane, E. F., Hoppin, J. A., Kamel, F., Umbach, D. M., Boyes, W. K., Deroos, A. J., Alavanja, M., & Sandler, D. P. (2005). Retinal degeneration and other eye disorders in wives of farmer pesticide applicators enrolled in the agricultural health study. *Am J Epidemiol, 161*(11), 1020-1029. doi:10.1093/aje/kwi140
48. Koutros, S., Andreotti, G., Berndt, S. I., Hughes Barry, K., Lubin, J. H., Hoppin, J. A., Kamel, F., Sandler, D.P., Burdette, L.A., Yuenger, J., Yeager, M., Alavanja, M.C.R., & Freeman, L. E. (2011). Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer. *Pharmacogenet Genomics, 21*(10), 615-623. doi:10.1097/FPC.0b013e3283493a57
49. Koutros, S., Beane Freeman, L. E., Lubin, J. H., Heltshe, S. L., Andreotti, G., Barry, K. H., DellaValle, C.T., Hoppin, J.A., Sandler, D.P., Lynch, C.F., Blair, A., & Alavanja, M. C. (2013). Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. *Am J Epidemiol, 177*(1), 59-74. doi:10.1093/aje/kws225
50. Koutros, S., Silverman, D. T., Alavanja, M. C., Andreotti, G., Lerro, C. C., Heltshe, S., Lynch, C.F., Sandler, D.P., Blair, A., & Beane Freeman, L. E. (2016). Occupational exposure to pesticides and bladder cancer risk. *Int J Epidemiol, 45*(3), 792-805. doi:10.1093/ije/dyv195
51. Landgren, O., Kyle, R. A., Hoppin, J. A., Beane Freeman, L. E., Cerhan, J. R., Katzmann, J. A., Rajkumar, S.V., & Alavanja, M. C. (2009). Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood, 113*(25), 6386-6391. doi:10.1182/blood-2009-02-203471
52. LaVerda, N. L., Goldsmith, D. F., Alavanja, M. C., & Hunting, K. L. (2015). Pesticide Exposures and Body Mass Index (BMI) of Pesticide Applicators From the Agricultural Health Study. *J Toxicol Environ Health A, 78*(20), 1255-1276. doi:10.1080/15287394.2015.1074844
53. Lebov, J. F., Engel, L. S., Richardson, D., Hogan, S. L., Hoppin, J. A., & Sandler, D. P. (2016). Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study. *Occup Environ Med, 73*(1), 3-12. doi:10.1136/oemed-2014-102615
54. Lebov, J. F., Engel, L. S., Richardson, D., Hogan, S. L., Sandler, D. P., & Hoppin, J. A. (2015). Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study. *Environ Res, 143, Part A*, 198-210. doi:http://dx.doi.org/10.1016/j.envres.2015.10.002
55. Lee, W. J., Sandler, D. P., Blair, A., Samanic, C., Cross, A. J., & Alavanja, M. C. (2007). Pesticide use and colorectal cancer risk in the Agricultural Health Study. *Int J Cancer, 121*(2), 339-346. doi:10.1002/ijc.22635
56. Lerro, C. C., Koutros, S., Andreotti, G., Hines, C. J., Blair, A., Lubin, J., Ma, X., Zhang, Y., & Beane Freeman, L. E. (2015). Use of acetochlor and cancer incidence in the Agricultural Health Study. *Int J Cancer, 137*(5), 1167-1175. doi:10.1002/ijc.29416

57. Limousi, F., Albouy-Llaty, M., Carles, C., Dupuis, A., Rabouan, S., & Migeot, V. (2014). Does area deprivation modify the association between exposure to a nitrate and low-dose atrazine metabolite mixture in drinking water and small for gestational age? A historic cohort study. *Environ Sci Pollut Res Int, 21*(7), 4964-4973. doi:10.1007/s11356-013-1893-5
58. MacLennan, P. A., Delzell, E., Sathiakumar, N., & Myers, S. L. (2003). Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A, 66*(6), 501-517. doi:10.1080/15287390306356
59. MacLennan, P. A., Delzell, E., Sathiakumar, N., Myers, S. L., Cheng, H., Grizzle, W., Chen, V.W., & Wu, X. C. (2002). Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med, 44*(11), 1048-1058.
60. Mattix, K. D., Winchester, P. D., & Scherer, L. R. (2007). Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. *J Pediatr Surg, 42*(6), 947-949. doi:10.1016/j.jpedsurg.2007.01.027
61. McElroy, J. A., Gangnon, R. E., Newcomb, P. A., Kanarek, M. S., Anderson, H. A., Brook, J. V., Trentham-Dietz, AMY, & Remington, P. L. (2007). Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. *J Expo Sci Environ Epidemiol, 17*(2), 207-214. doi:10.1038/sj.jes.7500511
62. Metayer, C., Colt, J. S., Buffler, P. A., Reed, H. D., Selvin, S., Crouse, V., & Ward, M. H. (2013). Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. *J Expo Sci Environ Epidemiol, 23*(4), 363-370. doi:10.1038/jes.2012.115
63. Migeot, V., Albouy-Llaty, M., Carles, C., Limousi, F., Strezlec, S., Dupuis, A., & Rabouan, S. (2013). Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: a historic cohort study. *Environ Res, 122*, 58-64. doi:10.1016/j.envres.2012.12.007
64. Mills, K. T., Blair, A., Freeman, L. E., Sandler, D. P., & Hoppin, J. A. (2009). Pesticides and myocardial infarction incidence and mortality among male pesticide applicators in the Agricultural Health Study. *Am J Epidemiol, 170*(7), 892-900. doi:10.1093/aje/kwp214
65. Mills, P. K. (1998). Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Arch Environ Health, 53*(6), 410-413. doi:10.1080/00039899809605729
66. Mills, P. K., & Yang, R. (2003). Prostate cancer risk in California farm workers. *J Occup Environ Med, 45*(3), 249-258.
67. Mills, P. K., & Yang, R. (2006). Regression analysis of pesticide use and breast cancer incidence in California Latinas. *J Environ Health, 68*(6), 15-22; quiz 43-14.
68. Mills, P. K., & Yang, R. C. (2007). Agricultural exposures and gastric cancer risk in Hispanic farm workers in California. *Environ Res, 104*(2), 282-289. doi:http://dx.doi.org/10.1016/j.envres.2006.11.008
69. Montgomery, M. P., Kamel, F., Saldana, T. M., Alavanja, M. C., & Sandler, D. P. (2008). Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. *Am J Epidemiol, 167*(10), 1235-1246. doi:10.1093/aje/kwn028
70. Muir, K., Rattanamongkolgul, S., Smallman-Raynor, M., Thomas, M., Downer, S., & Jenkinson, C. (2004). Breast cancer incidence and its possible spatial association with

pesticide application in two counties of England. *Public Health, 118*(7), 513-520. doi:10.1016/j.puhe.2003.12.019
71. Munger, R., Isacson, P., Hu, S., Burns, T., Hanson, J., Lynch, C. F., Cherryholmes, K., Van Dorpe, P., & Hausler, W. J., Jr. (1997). Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. *Environ Health Perspect, 105*(3), 308-314.
72. Ochoa-Acuna, H., Frankenberger, J., Hahn, L., & Carbajo, C. (2009). Drinking-water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. *Environ Health Perspect, 117*(10), 1619-1624. doi:10.1289/ehp.0900784
73. Parks, C. G., Hoppin, J. A., DeRoos, A. J., Costenbader, K. H., Alavanja, M. C., & Sandler, D. P. (2016). Rheumatoid Arthritis in Agricultural Health Study Spouses: Associations with Pesticides and Other Farm Exposures. *Environ Health Perspect, 124*(11).
74. Reynolds, P., Hurley, S. E., Goldberg, D. E., Yerabati, S., Gunier, R. B., Hertz, A., Anton-Culver, H., Bernstein, L., Deapen, D., Horn-Ross, P.L., Peel, D., Pinder, R., Ross, R.K., West, D., Wright, W.E., & Ziogas, A. (2004). Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort. *Environ Res, 96*(2), 206-218. doi:http://dx.doi.org/10.1016/j.envres.2004.03.001
75. Rinsky, J. L., Hopenhayn, C., Golla, V., Browning, S., & Bush, H. M. (2012). Atrazine exposure in public drinking water and preterm birth. *Public Health Rep, 127*(1), 72-80.
76. Rinsky, J. L., Hoppin, J. A., Blair, A., He, K., Beane Freeman, L. E., & Chen, H. (2013). Agricultural exposures and stroke mortality in the Agricultural Health Study. *J Toxicol Environ Health A, 76*(13), 798-814. doi:10.1080/15287394.2013.819308
77. Rusiecki, J. A., De Roos, A., Lee, W. J., Dosemeci, M., Lubin, J. H., Hoppin, J. A., Blair, A., & Alavanja, M. C. (2004). Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. *J Natl Cancer Inst, 96*(18), 1375-1382. doi:10.1093/jnci/djh264
78. Saldana, T. M., Basso, O., Hoppin, J. A., Baird, D. D., Knott, C., Blair, A., Alavanja, M.C.R., & Sandler, D. P. (2007). Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. *Diabetes Care, 30*(3), 529-534. doi:10.2337/dc06-1832
79. Sathyanarayana, S., Basso, O., Karr, C. J., Lozano, P., Alavanja, M., Sandler, D. P., & Hoppin, J. A. (2010). Maternal pesticide use and birth weight in the agricultural health study. *J Agromedicine, 15*(2), 127-136. doi:10.1080/10599241003622699
80. Savitz, D. A., Arbuckle, T., Kaczor, D., & Curtis, K. M. (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol, 146*(12), 1025-1036.
81. Schroeder, J. C., Olshan, A. F., Baric, R., Dent, G. A., Weinberg, C. R., Yount, B., Cerhan, J.R., Lynch, C.F., Schuman, L.M., Tolbert, P.E., Rothman, N., Cantor, P, Kenneth, Blair, A. (2001). Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology, 12*(6), 701-709.
82. Slager, R. E., Poole, J. A., LeVan, T. D., Sandler, D. P., Alavanja, M. C., & Hoppin, J. A. (2009). Rhinitis associated with pesticide exposure among commercial pesticide applicators in the Agricultural Health Study. *Occup Environ Med, 66*(11), 718-724. doi:10.1136/oem.2008.041798

83. Starling, A. P., Umbach, D. M., Kamel, F., Long, S., Sandler, D. P., & Hoppin, J. A. (2014). Pesticide use and incident diabetes among wives of farmers in the Agricultural Health Study. *Occup Environ Med, 71*(9), 629-635. doi:10.1136/oemed-2013-101659
84. Stayner, L. T., Almberg, K., Jones, R., Graber, J., Pedersen, M., & Turyk, M. (2017). Atrazine and nitrate in drinking water and the risk of preterm delivery and low birth weight in four Midwestern states. *Environ Res, 152*, 294-303. doi:http://dx.doi.org/10.1016/j.envres.2016.10.022
85. Swan, S. H., Kruse, R. L., Liu, F., Barr, D. B., Drobnis, E. Z., Redmon, J. B., Wang, C., Brazil, C., & Overstreet, J. W. (2003). Semen quality in relation to biomarkers of pesticide exposure. *Environ Health Perspect, 111*(12), 1478-1484.
86. Thorpe, N., & Shirmohammadi, A. (2005). Herbicides and nitrates in groundwater of Maryland and childhood cancers: a geographic information systems approach. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 23*(2), 261-278. doi:10.1080/10590500500235001
87. Valcin, M., Henneberger, P. K., Kullman, G. J., Umbach, D. M., London, S. J., Alavanja, M. C., Sandler, D.P., & Hoppin, J. A. (2007). Chronic bronchitis among nonsmoking farm women in the agricultural health study. *J Occup Environ Med, 49*(5), 574-583. doi:10.1097/JOM.0b013e3180577768
88. Van Leeuwen, J. A., Waltner-Toews, D., Abernathy, T., Smit, B., & Shoukri, M. (1999). Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. *Int J Epidemiol, 28*(5), 836-840.
89. Villanueva, C. M., Durand, G., Coutte, M. B., Chevrier, C., & Cordier, S. (2005). Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. *Occup Environ Med, 62*(6), 400-405. doi:10.1136/oem.2004.016469
90. Waggoner, J. K., Henneberger, P. K., Kullman, G. J., Umbach, D. M., Kamel, F., Beane Freeman, L. E., Alavanja, M.C.R., Sandler, D.P., & Hoppin, J. A. (2013). Pesticide use and fatal injury among farmers in the Agricultural Health Study. *Int Arch Occup Environ Health, 86*(2), 177-187. doi:10.1007/s00420-012-0752-x
91. Waller, S. A., Paul, K., Peterson, S. E., & Hitti, J. E. (2010). Agricultural-related chemical exposures, season of conception, and risk of gastroschisis in Washington State. *Am J Obstet Gynecol, 202*(3), 241.e241-246. doi:10.1016/j.ajog.2010.01.023
92. Winchester, P. D., Huskins, J., & Ying, J. (2009). Agrichemicals in surface water and birth defects in the United States. *Acta Paediatr, 98*(4), 664-669. doi:10.1111/j.1651-2227.2008.01207.x
93. Young, H. A., Mills, P. K., Riordan, D. G., & Cress, R. D. (2005). Triazine herbicides and epithelial ovarian cancer risk in central California. *J Occup Environ Med, 47*(11), 1148-1156.

Appendix C. Physical/Chemical Properties

Table D. Physicochemical Properties of Simazine.		
Parameter	**Value**	**Reference[1]**
Molecular weight	201.7	D309943, D. Soderberg, 12/08/2004 (Simazine product chemistry review in support of the RED)
Molecular formula	$C_7H_{12}ClN_5$	
Melting point	225-227 °C	
pH	6 - 7	
Density (g/mL) (at 20°C)	0.436	
Water solubility	3.5 ppm at 20 °C	
Solvent solubility (at 20°C)	400 ppm in methanol 2 ppm in petroleum ether 300 ppm in diethyl ether 900 ppm in chloroform 1200 ppm in ethyl acetate	
Vapor pressure	6.1×10^{-9} mm Hg at 20 °C	
Octanol/water partition coefficient	P = 122 Log P = 2.09	
Acid dissociation constant (pK_a) [21°C]	1.70	A. Gunasakara, 4/2004, CDPR
Organic carbon partition coefficient K_{oc}	130	
Henry's Law Constant (atm-m^3/mole)	9.48×10^{-10}	

Appendix D. Tolerance/MRL Tables

Table D. Summary of US and International Tolerances and Maximum Residue Limits – Simazine.				
***Residue Definition*:**				
US		**Canada**	**Mexico[1]**	**Codex**
40 CFR § 180.213 (a) General: combined residues of the herbicide simazine, 6-chloro-N,N′-diethyl-1,3,5-triazine-2,4-diamine, and its metabolites 6-chloro-N-ethyl-1,3,5-triazine-2,4-diamine, and 6-chloro-1,3,5-triazine-2,4-diamine, calculated as the stoichiometric equivalent of simazine		6-chloro-N,N′-diethyl-1,3,5-triazine-2,4-diamine, including the metabolites 6-chloro-N-ethyl-1,3,5-triazine-2,4-diamine, and 6-chloro-1,3,5-triazine-2,4-diamine		None
Commodity	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[1]**	**Codex[2]**
Fruit, citrus, group 10-10	0.04			
Fruit, pome, group 11-10	0.03			
Fruit, stone, group 12-12	0.10			
Nut, tree, group 14-12	0.05	0.05		
Almond, hulls	3.0			
Corn, field, forage	0.20			
Corn, field, grain	0.20			
Corn, field, stover	0.25			
Corn, pop, grain	0.20			
Corn, pop, stover	0.25			
Corn, sweet, forage	0.20			
Corn, sweet, kernel plus cob with husks removed	0.20			
Corn, sweet, stover	0.25			
Cranberry	0.25			
Blueberry	0.20			
Blackberry	0.20			
Currant	0.25			
Grape	0.20			
Loganberry	0.20			
Olive	0.20			
Raspberry	0.20			
Strawberry	0.03			
Completed: W. Donovan; 07/10/2018				

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

Appendix E. 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 F-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 F.2. Based on the criteria to assess the best fit, the Log-logistic model resulted in the best fit of the data. Figures F.1 and F.2 present the BMDS outputs for male and female rats.

Table F.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 F.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 F.1. BMDS Output for the Log-Logistic model of fibrosis of the renal papillary interstitium incidence data for male rats administered atrazine 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

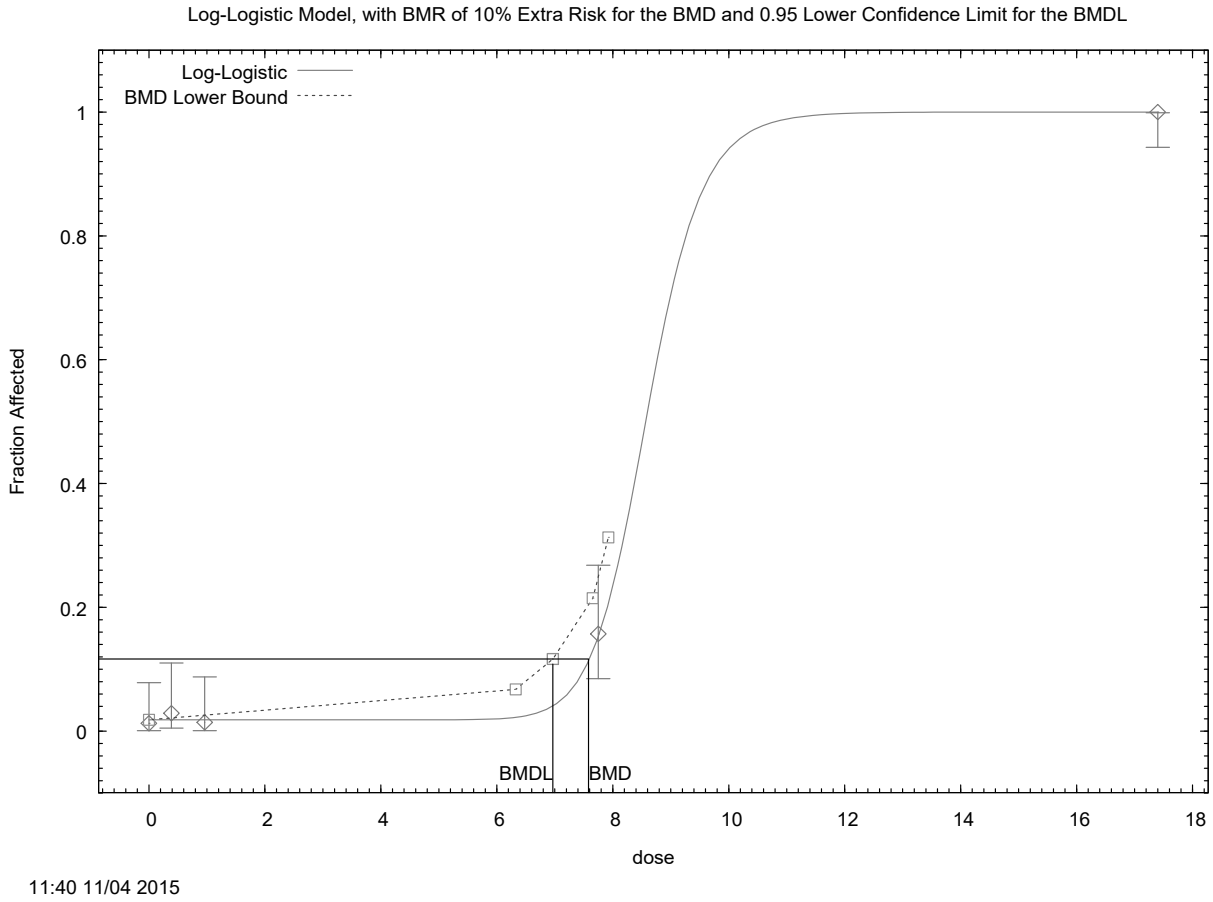
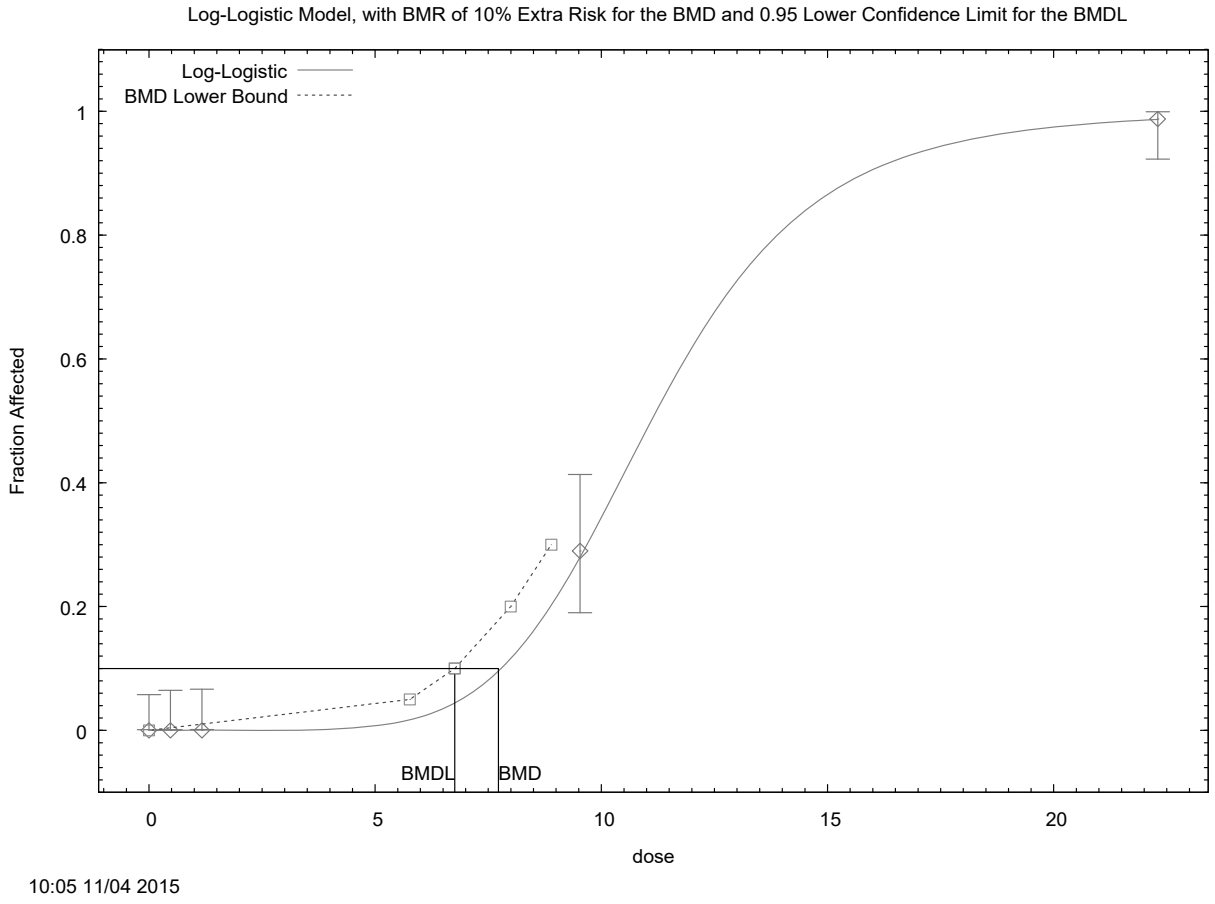


Figure F-2. BMDS Output for the Log-Logistic model of fibrosis of the renal papillary interstitium incidence data for female rats administered atrazine in the diet for 2 years

```
 ================================================================
        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 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 F. 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 ORETF database, the ARTF database; and the Residential SOPs (lawns/turf), and MRIDs 44339801 are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. Additionally, a human dermal absorption study was used to derive the scenario-specific dermal points of departure (MRID 44152114[65]). 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[66].

[65] Hui, X.; Gilman, S.; Simoneaux, B.; et al. (1996) In vivo Percutaneous Absorption of Atrazine in Man. 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.

[66] 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 G. Summary of Dermal Points of Departure Derived Assuming a Shower Occurs 8 hours After Initial Exposure and Risk Assessment Results

Table G.1. Simazine PBPK Modeled External Doses (PODs) Corresponding to 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)
Residential Handlers	Dermal (mg/kg/day)				106.58
Residential (Golfers)	Dermal (mg/kg/day)		118.22	106.75	105.15
Residential (Mowing)	Dermal (mg/kg/day)			108.22	105.58
Residential (Other Turf Scenarios)	Dermal (mg/kg/day)	151.36			106.24
Non-Occupational Spray Drift	Dermal (mg/kg/day)	151.36			106.24
	Oral (mg/kg/day)	3.34			
Occupational	Dermal (mg/kg/day)				104.32

Table G.2. Residential Handler Exposure and Risk Estimates for Simazine Using PODs that Assume a Shower Occurs 8 hours After Initial Exposure.										
Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[3]	MOE (LOC = 30)[4]	Dose (mg/kg/day)[5]	MOE (LOC = 30)[6]	MOE (LOC = 30)[7]
Mixer/Loader/Applicator										
Liquid formulations to Lawns/Turf with a Hose-End Sprayer	30	13.4	0.022	2.0 lb ai/A	0.5 A	0.19	550	0.00032	17,000	530
Liquid formulations to Lawns/Turf with a Manually Pressurized Handwand		63	0.018	0.0844 lb ai/gal	5 gals	0.39	280	0.00011	51,000	280
Liquid formulations to Lawns/Turf with a Sprinkler Can		13.4	0.022	0.00124 lb ai/ft^2	1,000 ft^2	0.24	440	0.0004	14,000	430
Liquid formulations to Lawns/Turf with a Backpack Sprayer		130	0.14	0.0844 lb ai/gal	5 gals	0.80	130	0.0086	6,500	130

1 See Table 3.3.2.
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (69 kg).
4 Dermal MOE = Dermal POD (106.58 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (69 kg).
6 Inhalation MOE = Inhalation POD (5.56 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
7 Total MOE = Total MOE = 1 ÷ [(1 / Dermal MOE) + (1 /Inhalation MOE)].

Table G.3. Residential Post-Application Exposure and Risk Estimates for Simazine Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure.

Lifestage	Use Site	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs (LOC = 30)[3]	Combined Routes (X indicates included in Combined MOE)	Combined MOEs (LOC = 30)[4]
		Activity	Route of Exposure					
Adult	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.107	980		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.028	3,800		
	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	1.37	78		
Children 11 to < 16 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.108	990		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.028	3,900		
Children 6 to < 11 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.127	930		
Children 1 to < 2 Years Old	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	2.33	65	X	34
			Hand-to-Mouth		0.048	70	X	
			Object-to-Mouth		0.0015	2,300		
			Soil Ingestion		0.0000677	49,000		
		High Contact Activities after Spray Application	Dermal	1.4 lb ai/A	1.632	93	X	48
			Hand-to-Mouth		0.0335	100	X	
			Object-to-Mouth		0.00102	3,300		
			Soil Ingestion		0.0000474	70,000		

1 See Table 3.3.2.
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day). Scenario-specific PODs provided in Table 4.6.2.4.2.2 and G.1..
4 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/incidental oral MOE)], where applicable.

Table G.4. Recommendations for the Residential Exposures for the Simazine Aggregate Assessment Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE (LOC = 30)[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adults	High Contact Activities after Spray Application	1.37	N/A	N/A	1.37	78	N/A	N/A	78
Children 11 to < 16 Years Old	Golfing after Spray Application	0.108			0.108	990			990
Children 6 to < 11 Years Old	Golfing after Spray Application	0.127			0.127	930			930
Children 1 to < 2 Years Old	High Contact Activities after Spray Application	2.33		0.048	2.37	65		70	34

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Incidental Oral MOE), where applicable.

Table G.5. Simazine 4-Day Aggregate Risk Calculations-Using PODs that Assume a Shower Occurred 8 Hours After Initial Exposure.

Lifestage	Turf Exposure Scenario	LOC for Aggregate Risk	MOE Food Exposure[1]	MOE Dermal Residential Exposure[2]	MOE Oral Residential Exposure[3]	MOE Inhalation Residential Exposure	Minimum Allowable MOE for Drinking Water Exposure[4]	4-Day DWLOC[5] (ppb)
All Infants (< 1 year old)	N/A	30	50,000	N/A	N/A	N/A	30	700
Children 1 to < 2 years old	High Contact Activities after Spray Application **(2.0 lb ai/A)**	30	23,000	65	70	N/A	280	**190**
	High Contact Activities after Spray Application **(1.4 lb ai/A)**	30	23,000	93	100	N/A	80	650
Children 6-12 years old	Golfing after Spray Application	30	60,000	930	N/A	N/A	31	3,800
Youth 13-19 years old	Golfing after Spray Application	30	102,000	990			49	2,500
Females 13-49 years old	High Contact Activities after Spray Application	30	93,000	78			30	1,900

1 **Food:** MOEfood = PODfood (mg/kg/day) (from Table 4.6.2.4.2.2)/ *Background* Food Exposure (mg/kg/day) (from Table 5.4.8.1).
2 **Dermal:** MOEdermal = PODdermal (mg/kg/day) (from Table G.2)/ Dermal Exposure (mg/kg/day) (from Table G.4).
3 **Oral:** MOEdermal = PODoral (mg/kg/day) (from Table 4.6.2.4.2.2)/ Oral Exposure (mg/kg/day) (from Table G.4).
4 **Water:** MOEwater = 1/ [(1/MOEagg) – ((1/MOEfood) + (1/MOEdermal) + (1/MOEoral) + (1/MOEinhalation))]; Where MOEagg =LOC.
5 **DWLOC:** DWLOC ppb= PODwater ppb; from Table 4.6.2.4.2.2) /MOEwater.

Table G.6. 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 Simazine – Using PODs That Assume a Shower Occurs 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)	Groundboom	Groundboom
Grapefruit, Oranges	8.0	0	100	45

1. Risk estimates presented assuming screening-level droplet sizes (very fine to fine), and high booms. 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 D428623. "N/A" provided when equipment not applicable based on the use pattern.

Table G.7. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Proposed Uses of Simazine Using PODs that Assume a Shower Occurs 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
Mixer/Loader						
DF/WDG for Groundboom Application	Grapefruit, Oranges	8.0 lb ai/A	40 A	440	50	45
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	870	100	90
	Almonds	2.0 lb ai/A	40 A	1,700	200	180
Liquids for Groundboom Application	Grapefruit, Oranges	8.0 lb ai/A	40 A	600	2,100	470
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	1,200	4,100	930
	Almonds	2.0 lb ai/A	40 A	2,400	8,300	1,900
Applicator						
Applying Sprays via Groundboom	Grapefruit, Oranges	8.0 lb ai/A	40 A	1,400	1,300	670
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	4.0 lb ai/A	40 A	2,800	2,700	1,400
	Almonds	2.0 lb ai/A	40 A	5,600	5,300	2,700
Mixer/Loader/Applicator						
DF/WDG Formulations for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	55	3,500	54
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	40 gals	110	7,000	110
	Almonds	0.1 lb ai/gal	40 gals	220	14,000	220
DF/WDG for Mechanically Pressurized Handgun	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**8.8** **13 [DL/G]**	42 210 [PF5]	**7.3 [SL/G]** **12 [DL/G, PF5]**

Table G.7. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Proposed Uses of Simazine Using PODs that Assume a Shower Occurs 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
Applications					420 [PF10]	**13 [DL/G, PF10]**
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15 [SL/G]** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Almonds	0.1 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29** 40 [DL/G, No R]
Liquids for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	55	3500	54
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	40 gals	110	7,000	110
	Almonds	0.1 lb ai/gal	40 gals	220	14,000	220
Liquids for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**8.8** **13 [DL/G]**	42 210 [PF5] 420 [PF10]	**7.3** **12 [DL/G, PF5]** **13 [DL/G, PF10]**
	Lemon, Pome Fruit (Crop Group 11), Stone Fruit (Crop Group 12), Filberts, Macadamia Nuts, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Almonds	0.1 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29** 40 [DL/G, No R]

1 Risk estimates of concern are in bold.
2 Based on Tables 3.3.1.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (104.32 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). SL = Single Layer of Clothing, G = Gloves, DL = Double Layer.
5 Inhalation MOE = Inhalation POD (2.1 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). No R = No Respirator, PF5 = Respirator with Protection Factor of 5, PF10 = Respirator with a Protection Factor of 10.
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
Mixer/Loader						
DF/WDG for Chemigation Application	Sweet Corn, Field Corn	1.0 lb ai/A	350 A	400	46	41
Liquids for Chemigation Application	Grapefruit, Oranges	4.0 lb ai/A	350 A	140	470	110
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	4.0 lb ai/A	350 A	140	470	110
	Almonds, Peaches, Nectarines	2.0 lb ai/A	350 A	270	950	210
	Sod	4.0 lb ai/A	350 A	140	470	110
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	350 A	140	470	110
	Field Corn	2.0 lb ai/A	350 A	270	950	210
	Nursery Ornamentals	3.0 lb ai/A	60 A	1,100	3,700	850
	Sweet Corn	2.0 lb ai/A	350 A	270	950	210
	Strawberries	1.0 lb ai/A	350 A	550	1,900	430
DF/WDG for Groundboom Application	Golf Course	2.0 lb ai/A	40 A	1,700	200	180
	Nursery Ornamentals	3.0 lb ai/A	60 A	770	90	81
	Sod	4.0 lb ai/A	80 A	440	50	45
	Grapefruit, Oranges	8.0 lb ai/A	40 A	440	50	45
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries,	4.0 lb ai/A	40 A	870	100	90

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
	Macadamia Nuts					
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	1,700	200	180
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	440	50	45
	Sweet Corn	2.0 lb ai/A	80 A	870	100	90
	Strawberries	1.0 lb ai/A	80 A	1,700	200	180
	Field Corn	2.0 lb ai/A	200 A	350	40	36
Liquids for Groundboom Application	Golf Course	2.0 lb ai/A	40 A	2,400	8,300	1,900
	Nursery Ornamentals	3.0 lb ai/A	60 A	1,100	3,700	850
	Sod	4.0 lb ai/A	80 A	600	2,100	470
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts	4.0 lb ai/A	40 A	1,200	4,100	930
	Field Corn	2.5 lb ai/A	200 A	380	1,300	290
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	2,400	8,300	1,900
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	600	2,100	470
	Grapefruit, Oranges	8.0 lb ai/A	40 A	600	2,100	470
	Strawberries	1.0 lb ai/A	80 A	2,400	8,300	1,900
	Sweet Corn	2.5 lb ai/A	80 A	960	3,300	740
Applicator						
Applying Sprays via Groundboom	Golf Course	2.0 lb ai/A	40 A	5,600	5,300	2,700
	Nursery Ornamentals	3.0 lb ai/A	60 A	2,500	2,400	1,200

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	**MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]**	**MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]**
	Sod	4.0 lb ai/A	80 A	1,400	1,300	670
	Grapefruit, Oranges	8.0 lb ai/A	40 A	1,400	1,300	670
	Lowbush Blueberries, Cranberries	4.0 lb ai/A	80 A	1,400	1,300	670
	Sweet Corn	2.5 lb ai/A	80 A	2,200	2,100	1,100
	Strawberries	1.0 lb ai/A	80 A	5,600	5,300	2,700
	Field Corn	2.5 lb ai/A	200 A	890	850	430
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts; Blueberries, Blackberries, Boysenberries, Raspberries, Loganberries, Macadamia Nuts	4.0 lb ai/A	40 A	2,800	2,700	1,400
	Almonds, Peaches, Nectarines	2.0 lb ai/A	40 A	5,600	5,300	2,700
Mixer/Loader/Applicator						
DF/WDG Formulations for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	55	3,500	54
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	40 gals	110	7,000	110
	Almonds, Peaches, Nectarines	0.1 lb ai/gal	40 gals	220	14,000	220
	Christmas Tree Farm	0.2 lb ai/gal	40 gals	110	7,000	110
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	150	9,300	150
	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	45	400	40
	Landscape Turf	0.13 lb ai/gal	40 gals	170	11,000	170

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
	[Spot]					
	Forestry	0.2 lb ai/gal	40 gals	110	7,000	110
DF/WDG for Manually Pressurized Handwand Applications	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	3,200	930	720
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	2,800	800	620
DF/WDG for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**8.8** **13 [DL/G]**	42 210 [PF5] 420 [PF10]	**7.3 [SL/G, No R]** **12 [DL/G, PF5]** **13 [DL/G, PF10]**
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15 [SL/G, No R]** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Almonds, Peaches, Nectarines, Macadamia Nuts, Blueberries, Blackberries, Loganberries, Raspberries	0.1 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29 [SL/G, No R]** 40 [DL/G, No R]
	Golf Course	2.0 lb ai/A	5 A	510	340	200
	Nursery Ornamentals	0.15 lb ai/gal	1000 gals	**23** 35 [DL/G]	110 560 [PF5] 1,100 [PF10]	**19 [SL/G, No R]** **27 [DL/G, No R]** 33 [DL/G, PF5]
	Landscape Turf	2.0 lb ai/A	5 A	510	340	200
	Lowbush Blueberries	0.1 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29 [SL/G, No R]** 40 [DL/G, No R]
	Cranberries	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15 [SL/G, No R]** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Strawberries	0.05	1000 gals	70	330	58

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
	Sweet Corn	0.13	1000 gals	**27** 41 [DL/G]	130	**22 [SL/G, No R]** 31 [DL/G, No R]
Liquids for Backpack Sprayer Applications	Grapefruit, Oranges	0.4 lb ai/gal	40 gals	55	3500	54
	Christmas Tree Farm	0.2 lb ai/gal	40 gals	110	7,000	110
	Nursery Ornamentals	0.15 lb ai/gal	40 gals	150	9,300	150
	Landscape Turf [Broadcast]	0.13 lb ai/gal	40 gals	44	390	40
	Landscape Turf [Spot]	0.13 lb ai/gal	40 gals	160	11,000	160
	Aquatic areas (ponds, lakes, fountains)	0.19 lb ai/A	5 A	920	59,000	910
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	40 gals	110	7,000	110
	Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts; Almonds, Nectarines, Peaches	0.1 lb ai/gal	40 gals	220	14,000	220
Liquids for Manually Pressurized Handwand Applications	Nursery Ornamentals	0.15 lb ai/gal	40 gals	2,800	800	620
	Landscape Turf	0.13 lb ai/gal	40 gals	3,100	910	700
Liquids for Mechanically Pressurized Handgun Applications	Grapefruit, Oranges	0.4 lb ai/gal	1000 gals	**8.8** **13 [DL/G]**	42 210 [PF5] 420 [PF10]	**7.3 [SL/G, No R]** **12 [DL/G, PF5]** **13 [DL/G, PF10]**
	Golf Course	2 lb ai/A	5 A	820	7,600	740
	Nursery Ornamentals	0.15 lb ai/gal	1000 gals	**23** 35 [DL/G]	110 560 [PF5] 1,100 [PF10]	**19 [SL/G, No R]** **27 [DL/G, No R]** 33 [DL/G, PF5]

Table G.8. Occupational Handler Non-Cancer Exposure and Risk Estimates for the Existing Uses of Simazine 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) [SL/G unless otherwise specified]	MOE[5] (LOC = 30) [Baseline/No Respirator Unless Otherwise Specified]	MOE[6] (LOC = 30) [SL/G, No R, Unless Otherwise Specified]
	Landscape Turf	2.0 lb ai/A	5 A	820	7,600	740
	Aquatic Areas (fountains, ponds)	0.19 lb ai/A	5 A	3,700	18,000	3,100
	Cranberries	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15 [SL/G, No R]** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Sweet Corn	0.13 lb ai/gal	1000 gals	**27** **41 [DL/G]**	130	**22 [SL/G, No R]** 31 [DL/G, No R]
	Lowbush Blueberries	0.10 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29 [SL/G, No R]** 40 [DL/G, No R]
	Strawberries	0.05 lb ai/gal	1000 gals	70	330	58
	Lemons, Apples, Pears, Tart Cherries, Avocadoes, Filberts, Grapes, Olives, Peaches, Plums, Sweet Cherries, Pecans, Walnuts	0.2 lb ai/gal	1000 gals	**18** **26 [DL/G]**	83 420 [PF5] 830 [PF10]	**15 [SL/G, No R]** **24 [DL/G, PF5]** **25 [DL/G, PF10]**
	Blueberries, Blackberries, Boysenberries, Loganberries, Raspberries, Macadamia Nuts; Almonds, Nectarines, Peaches	0.1 lb ai/gal	1000 gals	35 53 [DL/G]	170	**29 [SL/G, No R]** 40 [DL/G, No R]

1 Risk estimates of concern are in bold.
2 Based on Table 3.3.2.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (104.32 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). SL = Single Layer of Clothing, G = Gloves, DL = Double Layer.
5 Inhalation MOE = Inhalation POD (2.1 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). No R = No Respirator, PF5 = Respirator with Protection Factor of 5, PF10 = Respirator with a Protection Factor of 10.
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Table G.9. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for the Proposed and Existing Uses of Simazine Using PODs that Assume a Shower Occurs 8 Hours After Initial Exposure[1].

Crop/Site	Activities	Application Rate (lb ai/A)	Transfer Coefficient (cm^2/hr)	DFR/TTR[2]	Dermal Dose (mg/kg/day)[3]	MOE (LOC = 30)[4]
Almond	Transplanting	2.0	230	3.32	0.088	1,200
Apple, Avocado, Blackberry, Highbush Blueberry, Lowbush Blueberry, Cherry, Cranberry, Grape (Wine), Grape (Juice), Grape (Table), Grape (Raisin), Hazelnuts (Filberts), Lemon, Macadamia Nuts, Olive, Peach, Pear, Pecan, Plum, Raspberry, Walnut	Transplanting	4.0	230	6.64	0.177	590
Blackberry, Highbush Blueberry, Grape (Wine), Grape (Juice), Raspberry	Scouting	4.0	640	6.64	4.92	210
Highbush Blueberry, Lowbush Blueberry	Handset Irrigation	4.0	1,900	6.64	1.46	71
Cherry, Pear	Scouting	4.0	580	6.64	0.446	230
Field Corn, Sweet Corn (Grain), Sweet Corn (Processing)	Scouting	2.5	210	4.15	0.101	1,000
	Handset Irrigation	2.5	1,900	4.15	0.914	110
	Hand Weeding	2.5	70	4.15	0.034	3,100
Grape (Wine), Grape (Juice)	Propagating	4.0	640	6.64	0.492	210
Grapefruit, Orange	Transplanting	8.0	230	13.27	0.354	290
Nectarine	Transplanting	2.0	230	3.32	0.088	1,200
Nursery Ornamentals	Grafting, Propagating, Transplanting	3.0	230	4.98	0.133	790
Strawberry	Scouting	1.0	210	1.66	0.040	2,600
	Hand Weeding	1.0	70	1.66	0.013	7,700
	Transplanting	1.0	230	1.66	0.044	2,400
Golf Course Turf	Maintenance	2.0	3,700	0.385	1.65	630
Sod	Maintenance, Slab Harvesting, Transplanting/Planting	4.0	6,700	0.770	0.598	170

1 The registered uses on turf (golf courses and sod farms) are not specifically soil-directed and, therefore, could result in potential post-application exposures and have been assessed assuming full high "crop" height and full foliage density. Since atrazine is mostly applied as an early season herbicide and is a ground/soil directed application, the dermal post-application exposure assessment assumed low crop height and minimum foliage density for the rest of the registered agricultural crops.

2 DFR Data Source: Field Corn – MRID 44883601: Day 0 residue = 4.147 ug/cm^2, study application rate = 2.5 lb ai/A. Turf – MRID 44958701: Day 0 residue: 0.385 ug/cm^2, study application rate = 2.0 lb ai/A.

3 Daily Dermal Dose = [DFR/TTR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

4 MOE = POD (104.32 mg/kg/day) / Daily Dermal Dose.