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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: July 10, 2018

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

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Decision Nos.: 488213
Petition No.: NA
Risk Assessment Type: Single Chemical
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MRID No.: NA

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

The most recent human health risk assessment for the chlorotriazine herbicides (atrazine, simazine, and propazine) was completed in 2006 (J. Morales *et al.*, D317976, 3/28/2006). A scoping document for Registration Review was completed in 2013 (W. Donovan *et al.*, D407489, 06/04/2013). The following risk assessment updates have been included in the current risk assessment:

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

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

Use Profile

Atrazine is currently registered for use against broadleaf and some grassy weeds. It is registered for use on various food crops (corn, sorghum, sugarcane, macadamia nuts, guava); non-food crops (turf for sod production, conifers, fallow crop lands); and on non-agricultural areas [roadsides; conservation reserve program (CRP) areas; turfgrass on golf course fairways; and turf in residential areas such as homes, daycares, schools, playgrounds, parks, recreational areas, and sports fields].

Atrazine is formulated as liquid, water dispersible granule (WDG), wettable powder in water soluble bags (WSP), and granules (G). It may also be applied to various field crops in dry bulk fertilizers (DBF). The use pattern, personal protective equipment (PPE) requirements, and restricted entry interval (REI) requirements were compiled by using master use information provided by the technical registrants of atrazine, a screening-level review of the 190 available registered labels, and the 2006 atrazine Interim Reregistration Eligibility Decision (IRED)[1]. Of the liquid, WDG, and WSP labels evaluated, all require baseline attire (long sleeved shirts, long pants, shoes, and socks) and chemical resistant gloves. Some, but not all, granular formulations require occupational handlers to wear baseline attire and/or additional PPE. Specific PPE requirements are detailed in Section 11.1 under *Mitigation/Personal Protective Equipment.*

HED also reviewed a representative subset of the 190 registered atrazine labels for REI requirements; the REIs on the registered labels for the liquid, WDG, and WSP formulations ranged from 12-24 hours. All labels requiring a 24-hour REI are co-formulated with other pesticide active ingredients. Some granular labels are intended for residential use and do not list an REI. Of those granular labels that list an REI, the required REI is 12 hours. All liquid, WDG, and WSP formulations are restricted use pesticides (RUPs) due to ground and surface water concerns.

Hazard Characterization

Atrazine, simazine, and propazine have a common mechanism of neuroendocrine toxicity. These common mechanism group (CMG) triazines and their chlorinated metabolites are considered to be equivalent in toxicity to atrazine for this neuroendocrine effect. This health-protective assumption is based on the evaluation of endocrine-related data on the chlorotriazine herbicides demonstrating either equal or less potency than atrazine (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2011-0399). Exposure to the

[1] https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-080803_1-Apr-06.pdf

CMG triazines results in reproductive and developmental effects in laboratory animals that are considered relevant to humans. These effects form the basis for the most sensitive risk assessment endpoint for triazines. The toxicity mode of action (MOA) involves perturbation of the hypothalamic-pituitary-gonadal axis (HPG) axis resulting in suppression of the LH (luteinizing hormone) surge leading to a number of neuroendocrine effects (*e.g.,* estrous cyclicity disruption and delays in puberty onset). These neuroendocrine effects are considered the primary toxicological effects of regulatory concern. Other neurological effects of atrazine include alterations in dopaminergic and somatostatinergic systems as well as on gonadotropin releasing hormone (GnRH) releasing neurons.

Besides neuroendocrine-related effects, other systemic effects of atrazine include body weight decrements and renal histopathology in rats as well as cardiac effects in dogs following subchronic and/or chronic exposure. In addition, delay in ossification in fetuses was the effect observed after gestational exposure for all the triazines. These effects, however, occur at higher doses than the LH surge attenuation which is the most sensitive effect.

Between 2009 and 2011, the Agency held five meetings of the FIFRA Scientific Advisory Panel (SAP) on topics related to non-cancer and cancer effects of atrazine and its chlorotriazine metabolites (https://www.epa.gov/sap/fifra-scientific-advisory-panel-meetings). The SAP has supported the Agency's conclusions regarding atrazine's neuroendocrine MOA and the potential noncancer and cancer health effects associated with atrazine exposures.

A weight of the evidence (WOE) analysis has been completed using the draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment." The WOE analysis integrated quantitative and qualitative findings from experimental toxicology studies, epidemiology studies, and PBPK modeling. A PBPK model has been utilized to estimate human equivalent doses and toxicological points of departure (PODs) for repeated dose exposures. These PODs are applicable to exposures of four days (or longer) since that is the time to elicit a decrease of the LH surge in rats. PODs for relevant lifestages (infants, children, youths, and adults) were derived for the standard routes of exposure (oral, dermal, and inhalation) (excluding acute dietary for atrazine and its chlorinated metabolites and chronic dietary for hydroxyatrazine and its hydroxy metabolites as discussed below). The dermal component also included an hourly flux rate to determine the rate of absorption through the skin. The model was used to derive scenario-specific PODs for residential and occupational exposures. To derive scenario specific PODs, a shower is incorporated into the modeling as a way to "turn off" or end daily exposure times. For residential, non-occupational, and occupational scenario-specific PODs, showers were assumed to occur 24 hours after initial exposure to account for any residues left on the skin following exposure.

Because the PBPK modeling quantitatively considers differences in pharmacokinetic, but not pharmacodynamic parameters between laboratory animals and humans, the default interspecies uncertainty factor is reduced to 3X. Furthermore, the toxicology and exposure databases for atrazine are complete, and there are no remaining uncertainties with regard to the potential for increased susceptibility to infants and children; therefore, the Food Quality Protection Act (FQPA) safety factor has been reduced to 1X. The total uncertainty factor for 4-day risk

assessment is 30X (3X interspecies factor, 10X intraspecies factor, and 1X FQPA when applicable).

For atrazine acute dietary assessments, a POD of 10 mg/kg/day was selected based on delayed ossification in fetuses observed in the developmental toxicity studies in rats and rabbits. The acute endpoint is only relevant to females of reproductive age. The total uncertainty factor for acute risk assessment is 100X (10X interspecies factor, 10X intraspecies factor, and 1X FQPA).

In contrast to the chlorotriazines and their chlorinated metabolites, hydroxyatrazine is the major metabolite in plants, but a minor metabolite in animals. The available toxicity data indicate that the kidney, and not the neuroendocrine system, is the primary target organ for hydroxyatrazine associated toxicity. A toxic effect attributable to a single dose was not identified in the hydroxyatrazine database. A benchmark dose lower bound corresponding to a benchmark response of 10% change from control levels (bench mark dose level, $BMDL_{10}$) of 6.76 mg/kg/day, based on histopathological lesions of the kidney in rats noted in a combined chronic toxicity/carcinogenicity study, was selected for the chronic dietary POD for hydroxyatrazine. Dermal and inhalation exposures are not expected for hydroxyatrazine. There are no residual uncertainties in the hazard or exposure databases for the hydroxy compounds, so the FQPA safety factor is reduced to 1X. The total uncertainty factor for chronic risk assessment is 100X (10X interspecies factor, 10X intraspecies factor, and 1X FQPA).

Exposure Profile

The residues of toxicological concern for atrazine neuroendocrine risk assessment are parent compound atrazine and its three chlorinated metabolites DEA, DIA, and DACT. Atrazine and its three chlorinated metabolites are assumed to have equivalent toxicity. The residues of concern for atrazine risk assessment for kidney effects are atrazine's metabolite hydroxyatrazine, along with the three associated hydroxylated metabolites desethylhydroxyatrazine (DEHA), desisopropylhydroxyatrazine (DIHA), and ammeline. These hydroxylated residues of concern are assumed to have equivalent toxicity. Dietary exposure to atrazine 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 for atrazine and its chlorinated metabolites, the toxicological endpoint is delayed ossification in fetuses and is only applicable to females 13-49 years old. For the 4-day assessment for atrazine and its chlorinated metabolites, the endpoint is attenuation of LH surge and is applicable to all lifestages. The duration appropriate for assessing dietary risks for hydroxyatrazine and its hydroxylated metabolites is chronic. The chronic endpoint (kidney effects) is applicable to all lifestages.

Non-dietary exposure to parent compound atrazine may occur from occupational and residential exposure sources; non-dietary exposure to the chlorinated and hydroxylated metabolites are not expected to occur. Based on the currently registered uses of atrazine, the durations of exposure are expected to be both short- (1 to 30 days) and intermediate-term (1 to 6 months) for agricultural handlers and post-application workers. Residential exposures and exposures from

non-occupational spray drift are expected to be short-term only. However, for the chlorotriazine herbicides, only 4-day exposure durations are assessed since they will be protective for longer durations of exposure.

Food Exposure and Risk

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

Acute and 4-day dietary (food-only) exposure to atrazine and its chlorinated metabolites do not exceed HED's level of concern (100% of the population adjusted dose (PAD)). The acute dietary risk estimate for females 13-49 years old (the acute toxicological endpoint is only applicable to females of reproductive age) is <1% of the acute population adjusted dose (aPAD). The 4-day dietary risk estimate for children 1-2 years old, the most highly exposed subpopulation, is 3% of the 4-day PAD.

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

Residential Handler Exposure and Risk Assessment

Atrazine is registered for use in residential settings; these uses have been assessed to reflect the updates in HED's 2012 Residential SOPs[2].

Of all the registered labels evaluated, all liquid, WDG, and WSP labels require the use of baseline attire and/or additional PPE, and are assumed to be marketed for commercial use. However, some granular formulations did not require specific attire or PPE. Therefore, the residential handler assessment included only granular products. There are no residential handler combined (dermal + inhalation) risk estimates of concern for the registered uses of atrazine on turf; residential handler MOEs $\geq$ 93 (LOC = 30).

Residential Post-Application Exposure and Risk Assessment

Atrazine-specific turf transferrable residue (TTR) data are available for both granular and dry flowable (applied as a spray) formulations of atrazine. A 4-day average turf transferable residue was used to estimate risk from contact with treated turf because the POD is based on decreased LH surge; and available toxicity data indicate that the decrease occurs after a 4-day exposure. Using the available chemical-specific data, there are post-application dermal and combined (dermal + incidental oral) risk estimates of concern from the registered use of atrazine on residential turf for children 1 to < 2 years old. The combined (dermal + incidental oral) MOEs for children 1 to < 2 years old ranged from 28 to 49 (LOC = 30) on the day of application, depending on the formulation and assuming the maximum registered application rate. The

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

dermal MOEs for adults, children 11 to < 16, children 6 to < 11 ranged from 42 to 3,600 on the day of application (LOC = 30).

Aggregate Exposure and Risk Assessment
The durations of exposure identified for atrazine aggregate assessment are acute and 4-day. The duration of exposure identified for hydroxyatrazine 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 uses. 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 atrazine, the acute DWLOC for females 13-49 years old is greater than the acute EDWCs for TCTs in surface water or ground water. There is no acute aggregate risk of concern.

Atrazine 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, children 1-2 years old playing on turf sprayed with atrazine were not included since there is a risk estimate of concern for combined dermal and incidental oral exposures when assuming the maximum labeled rate for spray applications (2.0 lb ai/A). However, a screening aggregate assessment was performed for this scenario assuming that the application rate for turf spray is reduced to 1.2 lb ai/A. This results in a DWLOC which would not be of concern for 4-day aggregate exposures.

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 atrazine residential post-application turf assessment resulted in risk estimates of concern for children 1-<2 years old, a quantitative spray drift assessment was conducted for atrazine. Non-occupational spray drift exposures were estimated assuming a 4-day average turf transferable residue following spray applications to turf available from the chemical-specific atrazine TTR study. There were no dermal risk estimates of concern at the field edge for adults or combined (dermal + incidental oral) risk estimates of concern for children 1 to < 2 years old following applications to all registered crops at the maximum registered application rates and assuming screening-level droplet sizes and boom heights (MOEs $\geq$ 30). The dermal MOEs for adults range from 95 to 1,000 at the field edge (LOC = 30). Combined (dermal + incidental oral) MOEs ranged from 55 to 600 (LOC = 30).

Occupational Exposure and Risk Assessment
Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of atrazine. The occupational handler exposure and risk assessment was conducted assuming the lowest-level of PPE consistently required across all labels evaluated (baseline attire + chemical resistant gloves). The occupational handler exposure and risk estimates indicate that many scenarios result in combined dermal and inhalation risk estimates of concern (MOE < LOC of 30). There are several scenarios that do not result in acceptable risk estimates with the maximum available PPE or engineering controls.

Occupational post-application dermal exposures were assessed for the registered uses of atrazine using chemical-specific TTR and dislodgeable foliar residue (DFR) data, and assuming predicted TTR and DFR residues on the day of application because post-application workers (especially scouters) could move from field to field encountering day 0 residue estimates across multiple days. Therefore, use of an average residue may not be appropriate. Using atrazine-specific DFR and TTR data, there are no occupational post-application MOEs of concern for the registered uses on the day of application. The occupational post-application MOEs range from 41 to 1,100 (LOC = 30) on the day of application.

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

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

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix F provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40CFR Part 26) have been satisfied.

2.0 Risk Assessment Summary & Conclusions

There are no dietary (food), residential handler, non-occupational spray drift, or occupational post-application risk estimates of concern for the registered uses of atrazine.

There are some residential post-application risk estimates of concern for the registered spray uses on residential turf. There are no post-application risk estimates of concern for the granular turf uses of atrazine.

There are no aggregate (food, drinking water, and residential exposures) risk estimates of concern for the scenarios that were included in the aggregate assessments. However, the atrazine 4-day aggregate assessment excluded residential exposure scenarios that were already of risk concern (i.e., children 1-2 years old playing on turf sprayed with atrazine). A screening aggregate assessment was performed for this scenario assuming that the maximum application rate for turf spray is reduced; this reduction would result in an acceptable aggregate risk estimate.

The occupational handler exposure and risk estimates indicate that many scenarios result in combined dermal and inhalation risk estimates of concern (MOE < LOC of 30) assuming baseline attire and chemical resistant gloves. However, most scenarios result in acceptable risk estimates with the addition of a double layer of clothing and/or a PF5 respirator.

2.1 Data Deficiencies

There are no multiresidue method testing results (OCSPP 860.1360) for the regulated chloro metabolites of atrazine: G-30033, G-28279, and G-28273) (DEA, and DIA and DACT; see Figure 3.1.1.).

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Suitable analytical enforcement methods are available for atrazine and its three regulated chloro metabolites G-28273, G-30033, and G-28279 (DACT, DEA, and DIA; see Figure 3.1.1). Method AG-484 (a gas chromatography nitrogen phosphorous detector (GC/NPD) based method) provides separate determination of atrazine, G-30033, and G-28279 in one fraction and G-28273 in another. This method has been validated on many plant matrices and has undergone successful radiovalidation. The validated limit of quantitation (LOQ) is 0.05 ppm for all four regulated compounds. Additionally, Method GRM052.01A, a liquid chromatography with tandem mass spectroscopy (LC-MS/MS) method with a validated LOQ of 0.01 ppm for residues of simazine, G-28279, and G-28273 in plant matrices, is also available for tolerance enforcement.

For livestock matrices, Methods AG-463 and AG-476 are the enforcement methods for milk and tissues, respectively. These methods determine residues of atrazine and its three regulated chloro metabolites The LOQ is 0.01 ppm for all four regulated compounds.

The Pesticide Analytical Manual (PAM) Vol. II, Method III successfully analyzes residues of atrazine *per se* in milk, and has been validated to 0.003 ppm. However, this method is not capable of determining the chloro metabolites.

Similarly, multiresidue methods (MRM) based on the Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method as used by the USDA Pesticide Data Program (PDP), provide results for the parent triazine compound (atrazine, propazine, and simazine) but not the corresponding chloro metabolites. There are no MRM recovery data for G-30033, G-28279, or G-28273, and these data should be submitted.

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

Analytical Standard	CAS#	Expiration Date
Atrazine	1912-24-9	8/28/24
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 §180.220 for the combined residues of atrazine and its three chlorinated metabolites in/on a variety of crops and livestock commodities. HED recommends that the residue definition for the tolerance expression for atrazine be modified in accordance with current policy on tolerance definitions (S. Knizner, 5/27/2009), to read:

> *"Tolerances are established for residues of the herbicide atrazine, 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 atrazine,6-chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine, its metabolites 2-amino-4-chloro-6-isopropylamino-s-triazine, 2-amino-4-chloro-6-ethylamino-s-triazine, and 2,4-diamino-6-chloro-s-triazine, calculated as the stoichiometric equivalent of atrazine, in or on the commodity."*

A summary of the established and recommended tolerances for atrazine is listed in Table 2.2.2. Under 180.220(a), harmonization with Canada's Pest Management Regulatory Agency (PMRA) may be achieved by setting tolerances for meat, milk, poultry, and eggs all at 0.04 ppm. Also, based on modified label instructions concerning the PHI, it is appropriate to lower the established tolerance for sweet corn forage from 15 ppm to 1.5 ppm, as detailed previously (C. Eiden, D272009, 04/16/2002). Under 180.220(d), the established tolerance for inadvertent residues for the group 4 leafy vegetables, except *Brassica*, can be converted to the new crop grouping. Following the conversion plan for implementation, this crop group can be deleted from the federal register and replaced with the establishment of leafy greens subgroup 4-16A at 0.25 ppm, and leaf petiole vegetable subgroup 22B at 0.25 ppm. To cover individual crops included in the established group 4, but not in either subgroup 4-16A or subgroup 22B, individual tolerances should be set on the following crops, all at 0.25 ppm: arugula, garden cress, upland cress, celtuce, and Florence fennel. Rotational crop studies support the establishment of a tolerance for "Vegetable, foliage of legume, group 7" at 0.50 ppm under 180.220(d).

Table 2.2.2. Tolerance Summary for Atrazine.			
Commodity	**Established Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
180.220(a)			
Cattle, fat	0.02	0.04	Harmonizes with PMRA
Cattle, meat	0.02	0.04	Harmonizes with PMRA
Cattle, meat byproducts	0.02	0.04	Harmonizes with PMRA
Corn, field, forage	1.5	1.5	
Corn, field, grain	0.20	0.20	
Corn, field, stover	0.5	0.50	
Corn, pop, grain	0.20	0.20	
Corn, pop, stover	0.5	0.50	
Corn, sweet, forage	15	1.5[1]	
Corn, sweet, kernel plus cob with husks removed	0.20	0.20	
Corn, sweet, stover	2.0	2.0	
Egg	--	0.04	Harmonizes with PMRA
Goat, fat	0.02	0.04	Harmonizes with PMRA
Goat, met	0.02	0.04	Harmonizes with PMRA
Goat, meat byproducts	0.02	0.04	Harmonizes with PMRA
Grass, forage[2]	4.0	4.0	
Grass, hay[2]	4.0	4.0	
Guava	0.05	0.05	
Hog, fat	--	0.04	Harmonizes with PMRA
Hog, meat	--	0.04	Harmonizes with PMRA
Hog, meat byproducts	--	0.04	Harmonizes with PMRA
Horse, fat	0.02	0.04	Harmonizes with PMRA
Horse, meat	0.02	0.04	Harmonizes with PMRA
Horse, meat byproducts	0.02	0.04	Harmonizes with PMRA
Milk	0.02	0.04	Harmonizes with PMRA
Nut, macadamia	0.20	0.20	
Poultry, fat	--	0.04	Harmonizes with PMRA
Poultry, meat	--	0.04	Harmonizes with PMRA
Poultry, meat byproducts	--	0.04	Harmonizes with PMRA
Sheep, fat	0.02	0.04	Harmonizes with PMRA
Sheep, meat	0.02	0.04	Harmonizes with PMRA
Sheep, meat byproducts	0.02	0.04	Harmonizes with PMRA
Sorghum, forage, forage	0.25	0.25	
Sorghum, grain, forage	0.25	0.25	
Sorghum, grain, grain	0.20	0.20	
Sorghum, grain, stover	0.50	0.50	
Sugarcane, cane	0.20	0.20	
Wheat, forage	1.5	1.5	
Wheat, grain	0.10	0.10	
Wheat, hay	5.0	5.0	
Wheat, straw	0.50	0.50	
180.220(d)[3]			
Leafy greens subgroup 4-16A	0.25	0.25	*Updated crop group conversion*
Leaf petiole vegetable subgroup 22B	--	0.25	*Updated crop group conversion*
Celtuce	--	0.25	*Commodity displaced by the crop group conversion*
Arugula	--	0.25	*Commodity displaced by the crop group conversion*
Garden cress	--	0.25	*Commodity displaced by the crop group conversion*
Upland cress	--	0.25	*Commodity displaced by the crop group conversion*

Table 2.2.2. Tolerance Summary for Atrazine.			
Commodity	**Established Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
Fennel, Florence, fresh leaves and stalk	--	0.25	*Commodity displaced by the crop group conversion*
Vegetable, foliage of legume, group 7	--	0.50	

[1] See C. Eiden, D272009, 04/16/2002.
[2] Limited to grass grown along roadsides in CO, KS, MT, ND, NE, SD, and WY and in Conservation Reserve Program (CRP) land in OR, NE, TX, and OK. Atrazine labels prohibit the use of these crops for grazing or hay production.
[3] Indirect or inadvertent residues of atrazine due to drift of atrazine treated soils from fields adjacent to leafy vegetable fields as occasionally observed in Florida (J. Morales, D27042, 09/19/2006).

2.2.3 International Harmonization

No Codex maximum residue levels (MRLs) have been established for atrazine. Canada Pest Management Regulatory Agency (PMRA) has established atrazine MRLs for corn grain (field, pop, and sweet), and meat, milk, poultry, and eggs (MMPE) (Appendix D). The U.S. and PMRA have harmonized residue definitions for atrazine and harmonized MRLs for corn grain. Upon establishment of the recommended tolerances, the U.S. tolerances and PMRA MRLs for MMPE will be harmonized.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

- The rotational crop restriction may include a 10-month plantback interval for potato; vegetable, legume, group 6; and vegetable, foliage of legume, group 7.

2.3.2 Recommendations from Occupational Assessment

- This risk assessment relies on a 2015 study by the Agricultural Handler Exposure Task Force (AHETF) that measured dermal and inhalation exposure for workers who mixed and loaded water-soluble packet pesticide products. Commensurate with the behaviors and practices represented by these data, labels for products formulated in water-soluble packaging should incorporate the Agency's revised instructions for proper mixing and loading of water-soluble packets. This revised language is aimed at ensuring that water-soluble packets are allowed to dissolve in water via mechanical agitation as intended and prevent them from being ruptured by streams of water or other means.

- HED has identified several risk estimates of concern for occupational handlers. Some of these risk estimates are not of concern with the addition of PPE beyond what is currently on labels and should be considered as potential options for mitigating any risks identified in this assessment.

2.3.3 Recommendations from Residential Assessment

- HED notes that there are residential post-application scenarios for registered uses that have non-cancer risk estimates of concern where potential mitigation may impact label

language.

3.0 Introduction

3.1 Chemical Identity

Table 3.1.1. Atrazine Nomenclature.	
Chemical structure	
Common name	Atrazine
Company experimental name	G-30027
IUPAC name	6-Chloro-N-ethyl-N-isopropyl-[1,3,5]triazine-2,4-diamine
CAS name	6-chloro-N-ethyl-N′-(1-methylethyl)-1,3,5-triazine-2,4-diamine
CAS registry number	1912-24-9

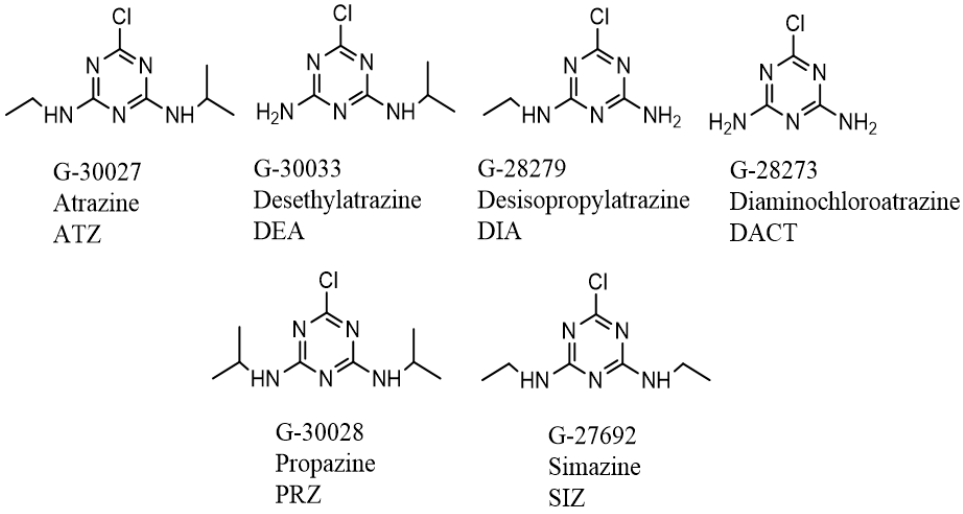


Figure 3.1.1. Chemical Structures for the Total Chlorinated Triazines (TCTs).

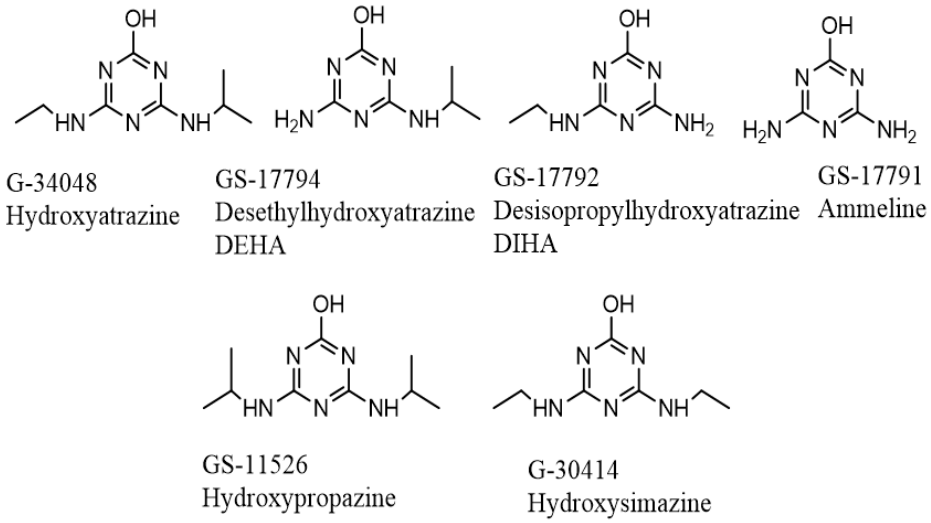


Figure 3.1.2. Chemical Structures for the Total Hydroxy Triazines (THTs).

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 atrazine are provided in Appendix C.

3.3 Pesticide Use Pattern

Atrazine is registered for use on various food crops, non-food crops, non-agricultural areas, turfgrass on golf course fairways, turf in residential areas, and for weed control on fallow crop lands. It is formulated as liquid, WDG, WSP, and granular products. The use pattern, PPE requirements, and REI requirements were compiled by using master use information provided by the technical registrants of atrazine, a screening-level review of the 190 available registered labels, and the 2006 atrazine IRED[3]. All liquid, WDG, and WSP formulations are RUPs due to ground and surface water concerns.

Table 3.3. Summary of the Registered Uses of Atrazine.

Application Equip.	Formulation	Application Rate	Max. No. Applications per Season or Growing Cycle	PHI (days)	Use Directions and Limitations
Corn (Field[1], Pop[1], Sweet[2])					
Aerial, Ground	Liquid	2.0 lb ai/A (0.2 lb ai/gal)	2	60 (field, pop) 45 (sweet)	Chemigation application is prohibited.

[3] https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-080803_1-Apr-06.pdf

Table 3.3. Summary of the Registered Uses of Atrazine.					
Application Equip.	**Formulation**	**Application Rate**	**Max. No. Applications per Season or Growing Cycle**	**PHI (days)**	**Use Directions and Limitations**
Ground only	WDG				Aerial and chemigation application prohibited.
Aerial, Ground	WSP				Chemigation application prohibited.
Commercial Impregnation Equipment, Tractor Drawn Spreaders	Dry Bulk Fertilizer	20 lb ai/ton			Impregnation is restricted to commercial facilities. On-farm fertilizer impregnation is prohibited. No more than 500 tons of bulk fertilizer can be impregnated per day. Apply in a minimum of 200 lbs of fertilizer per acre.
Sorghum[1]					
Aerial, Ground	Liquid	2.0 lb ai/A	2	60 (pre-emergent applications) 45 (post-emergent applications)	Chemigation application is prohibited.
Aerial, Ground	WDG				
Aerial, Ground	WSP				
Commercial Impregnation Equipment, Tractor Drawn Spreaders	Dry Bulk Fertilizer	20 lb ai/ton			Impregnation is restricted to commercial facilities. On-farm fertilizer impregnation is prohibited. No more than 500 tons of bulk fertilizer can be impregnated per day. Apply in a minimum of 200 lbs of fertilizer per acre.
Winter Weed Control in Corn or Sorghum Fields[1]					
Aerial, Ground	Liquid	2.0 lb ai/A	1	N/A	Chemigation application is prohibited.
Ground only	WDG	1.0 lb ai/A	1		Aerial and chemigation application prohibited.
Fallow Crop Lands (prior to planting corn or soybeans, or post wheat harvest)[1]					
Aerial, Ground	Liquid	2.25 lb ai/A	1	N/A	Chemigation application is prohibited.
Ground	WDG	2.25 lb ai/A			Aerial and chemigation application prohibited.
Aerial, Ground		0.5 lb ai/A			Chemigation application is prohibited.
Aerial, Ground	WSP	2.25 lb ai/A			
Roadsides[3]					
Ground, Aerial	Liquid	2.0 lb ai/A (0.2 lb ai/gal)	1	N/A	Chemigation application is prohibited.
Ground	WDG	2.0 lb ai/A (0.2 lb ai/gal)			Aerial and chemigation application prohibited.
Ground, Aerial	WSP	1.0 lb ai/A (0.1 lb ai/gal)			Chemigation application is prohibited.
Conservation Reserve Programs (CRP)[1]					
Ground, Aerial	Liquid	2.0 lb ai/A	1	N/A	Chemigation application is prohibited.
	WDG		1		
	WSP		1		
Sugarcane[1]					
Ground, Aerial	Liquid	4.0 lb ai/A	4	NS	Chemigation application is prohibited.

Table 3.3. Summary of the Registered Uses of Atrazine.					
Application Equip.	**Formulation**	**Application Rate**	**Max. No. Applications per Season or Growing Cycle**	**PHI (days)**	**Use Directions and Limitations**
Ground	WDG				Aerial and chemigation application prohibited.
Ground, Aerial	WSP				Chemigation application is prohibited.
Turf for Sod Production (Sod)					
Ground, Aerial	Liquid	4.0 lb ai/A	2	30	Chemigation application is prohibited.
Ground	WDG				Aerial and chemigation application prohibited.
Ground, Aerial	WSP				Chemigation application is prohibited.
Turfgrass for Fairways and Residential Sites (Including Homes, Daycare Facilities, Schools, Playgrounds, Parks, Recreational Areas, and Sports Fields)[4]					
Ground & Handheld	Liquid	2.0 lb ai/A (0.133 lb ai/gal)	2	N/A	Apply in 15 gals water per A.
	WDG	2.0 lb ai/A (0.133 lb ai/gal)			
	WSP	1.0 lb ai/A (0.067 lb ai/ gal)			
	Granules	2.2 lb ai/A			Most labels require application via drop or broadcast spreaders and restrict application by hand. Hand application allowed on labels with max single application rates of 2.0 lb ai/A. Handheld devices (i.e., belly grinders) may be used for spot treatments.
Macadamia Nuts[5]					
Ground	Liquid	4.0 lb ai/A (0.4 lb ai/gal)	4	Do not apply when nuts are on the ground.	Aerial and chemigation application prohibited. Apply in 10 gals water per A.
	WDG				
	WSP				
Guava[5]					
Ground, Aerial	Liquid	4.0 lb ai/A (0.2 lb ai/gal)	4	NS	Chemigation application is prohibited. Apply in 20 gals water per A.
Ground	WDG				Aerial and chemigation application prohibited. Apply in 20 gals water per A.
Ground, Aerial	WSP				Chemigation application is prohibited. Apply in 20 gals water per A.
Conifers[6]					
Ground	Liquid	4.0 lb ai/A (0.4 lb ai/gal)	1	Do not apply to seedbeds	Chemigation application is prohibited.
Ground	WDG				Aerial and chemigation application prohibited.
Ground	WSP				Chemigation application is prohibited.
Application via Dry Bulk Fertilizers to Bioenergy Crops (e.g., Corn)					

Table 3.3. Summary of the Registered Uses of Atrazine.					
Application Equip.	**Formulation**	**Application Rate**	**Max. No. Applications per Season or Growing Cycle**	**PHI (days)**	**Use Directions and Limitations**
Commercial Impregnation Equipment, Tractor Drawn Spreaders	Dry Bulk Fertilizer	15 lb ai/ton	N/A	N/A	Impregnation is restricted to commercial facilities. On-farm fertilizer impregnation is prohibited. No more than 500 tons of bulk fertilizer can be impregnated per day. Apply in a minimum of 200 lbs of fertilizer per acre.

1. Occupational Handler Assessment Surrogate Scenario: Field Crop, High Acreage.
2. Occupational Handler Assessment Surrogate Scenario: Field Crop, Typical Acreage.
3. Occupational Handler Assessment Surrogate Scenario: Rights-of-Way.
4. Occupational Handler Assessment Surrogate Scenarios: Golf Course Turf (Fairways, Tees, and Greens) and Landscape Turf (Lawns, Athletic Fields, Parks, etc.).
5. Occupational Handler Assessment Surrogate Scenario: Orchard/Vineyard.
6. Occupational Handler Assessment Surrogate Scenario: Christmas Tree Farm.

3.4 Anticipated Exposure Pathways

Humans may be exposed to atrazine and its chlorinated and hydroxylated metabolites in food and drinking water, since atrazine 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 atrazine in residential settings due to the existing uses. Non-occupational bystanders may be exposed to spray drift/volatilization from occupational applications. Occupational exposures are expected from the application of atrazine and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all the existing uses of atrazine.

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. Atrazine is considered to be equivalent in neurodevelopmental toxicity to the chlorotriazines, simazine and propazine, as well as their shared chlorinated metabolites (see Section 4.1). The risks associated with exposure to atrazine and its chlorinated and hydroxylated metabolites are presented in this atrazine risk assessment.

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

4.1 History of Toxicological & 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, desethyl-s-atrazine (DEA), desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (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, 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 workers.

In recent years, numerous governmental and academic research groups have published experimental toxicology and epidemiologic studies evaluating the toxicity profile and/or MOA of atrazine. These new studies have considered a variety of adverse outcomes such as reproductive toxicity in males and females, adverse birth outcomes, hormone disruption, neurotoxicity, immunotoxicity, respiratory health, effects on the mammary gland, and carcinogenicity. To consider the extent to which these new studies may influence the Agency's human health risk characterization for atrazine, OPP, in collaboration with the Office of Research and Development (ORD), has evaluated the new research on atrazine and its chloro-s-triazine metabolites (DEA, DIA, and DACT). To ensure that the best science possible is used to inform the atrazine human health risk assessment, and to ensure transparency in regulatory decision making, EPA sought advice from the FIFRA SAP on a variety of challenging scientific issues. Between 2009 and 2011, the Agency held five meetings of the FIFRA SAP on topics related to non-cancer and cancer effects of atrazine and its chlorinated metabolites of concern (https://www.epa.gov/sap/fifra-scientific-advisory-panel-historical-meetings). A summary of the charge and outcomes of each SAP meeting is provided below:

- **2009:** The first SAP meeting held in November of 2009 announced the Agency's approach to this re-evaluation and set forth an ambitious schedule for a series of SAP meetings to discuss various topics related to the potential impact of atrazine exposure on human health.
- **2010:**
    - **February 2010:** The Agency solicited the SAP's advice on a draft framework for implementing the use of epidemiology and incident data into human health risk assessment. The Agency's analysis included an evaluation of several ecological and retrospective cohort epidemiology studies for atrazine. OPP, in collaboration with EPA ORD and Office of Water (OW), solicited comment on the strengths and weaknesses of these types of epidemiology studies, and sought advice on the appropriate use of such studies in the atrazine human health risk assessment (Public Docket EPA-HQ-OPP-2009-0851).
    - **April and September 2010:** The SAP reviewed the Agency's evaluations of the extensive atrazine database (100s of studies) encompassing mechanistic, *in vitro, in vivo,* toxicology, and pharmacokinetic studies as well as epidemiology studies concerning the non-cancer health effects of atrazine (Public Docket ID EPA-HQ-OPP-2010-0125 and EPA-HQ-OPP-2010-0481, respectively). Among the non-cancer effects considered during these meetings, the Agency evaluated studies on the potential impact of atrazine exposure on sexual maturation, development of prostatitis, pregnancy maintenance as well as the immune, nervous, and reproductive systems. Although effects were noted in all these systems, the dose levels at which they occur were higher than the doses eliciting attenuation of the luteinizing hormone (LH) surge. In all, the Agency concluded, and the SAP concurred, that attenuation of the LH surge continues to be the most sensitive effect (*i.e.,* occurs at the lowest dose) identified to date in the atrazine database and that the new experimental toxicology studies did not alter or contradict the

major key events in the neuroendocrine MOA leading to mammary gland tumors in the rat or the conclusion that the MOA leading to mammary gland tumors in the rat is not relevant to humans.

- **2011:** The fifth SAP meeting held in July 2011 continued the Agency's evaluation of non-cancer effects as well as the cancer epidemiology data published since 2003 (Public Docket ID EPA-HQ-OPP-2011-0399). The Agency concluded that the epidemiology evidence is not strong enough to warrant a change to its current cancer classification for atrazine. The SAP panel members reiterated their recommendation to the Agency to continue to follow the published cancer epidemiology literature regarding ovarian, thyroid, and possibly lymphohematopoietic cancers, specifically. The SAP stated that although studies of these anatomical cancer endpoints are inconclusive at this time, Panel members believed the data were suggestive of a possible association and warrant close evaluation in future assessments. The hazard assessment that is the basis of this risk assessment is a culmination of this extensive public peer review process.

4.2 Toxicology Studies Available for Analysis

The toxicology database on atrazine is extensive and consists of 100s of studies on a wide range of issues, and there is a high degree of confidence in the scientific quality of the toxicity studies conducted with atrazine (EPA-HQ-OPP-2010-0125; EPA-HQ-OPP-2010-0481; EPA-HQ-OPP-2011-0399). Toxicity studies required under the Subdivision F Guidelines have been submitted and found acceptable by the Agency. Special studies examining the toxicology, mode of action, and pharmacokinetics of atrazine have been performed by the registrant in addition to the required guideline studies. Additionally, EPA's National Health and Environmental Effects Research Laboratory (NHEERL) has performed studies investigating atrazine's neuroendocrine mode of action and related reproductive and developmental effects, in addition to numerous experimental laboratory studies conducted in academic labs and published in the peer reviewed literature. Furthermore, the database includes epidemiology studies on a variety of cancer and non-cancer outcomes. The atrazine database, including both experimental toxicity and epidemiology studies, has been the subject of several reviews by the EPA SAP. EPA's reviews of the previous literature are provided in the appendices of the 2010 and 2011 issue papers presented to the SAPs. Information from the issue papers supports this risk assessment. As part of the revised human health risk assessment, EPA has reviewed and updated experimental toxicology literature since the 2011 SAP. The experimental toxicology literature search was conducted in PubMed for the time period between May 2011 and January 2017 (J. Liccione, D444631, 02/01/2018). EPA has also updated the epidemiology literature search regarding atrazine 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. This document highlights the 11 epidemiology studies identified in the literature that reported a statistically significant estimate of effect for atrazine that emanated from a prospective cohort and/or were

otherwise of a moderate or high quality study design[4] or were often cited in the epidemiology literature, and that were unavailable at the time of the 2009-2011 SAPs (Appendix B).

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 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, and thus 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 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 estimation of human point of departure. A more detailed description of the PBPK model, as well as the review process for the model, is provided in Section 4.6.2. of this document.

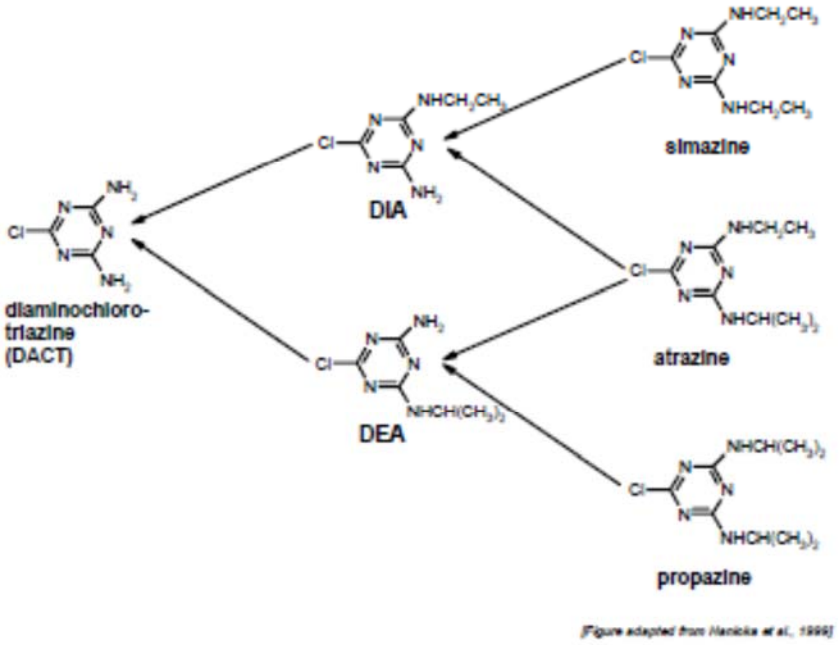
4.3 Absorption, Distribution, Metabolism, & Elimination (ADME)

Characterization of the pharmacokinetics and internal dosimetry of atrazine and its metabolites represents a critical step for elucidating the link between exposure and attenuation of the pre-ovulatory LH surge for the application of a MOA approach to risk assessment. Atrazine is quickly metabolized via the oral route to its dealkylated chlorinated metabolites (DEA, DIA, and DACT) as illustrated in Figure 4.3. DACT is the major metabolite (MRID 44713802; McMullin, 2003). 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).

[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

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 curve (AUCs)] for the chlorotriazines scaled linearly with administered dose indicating that absorption and metabolic processes were not saturated over the 20-fold dose range investigated. Ninety percent of the chlorotriazines identified were found in urine and 10% in feces.

[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 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 hrs. The rate of appearance of DACT in blood peaked at 5 hrs 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 11.54 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

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

For most pesticides, there is little information on the MOA/adverse outcome pathway (AOP), and even fewer pesticides with 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

[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.

MOA understanding, human relevance of animal studies informed qualitatively by epidemiology studies, refined analysis of critical durations of exposure, and a PBPK model to extrapolate internal dosimetry from animals to humans. The following sections will describe the critical data/studies that form the basis for the atrazine hazard assessment. 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 to tumorigenesis.

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

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 pre-ovulatory LH surge) from atrazine's toxicity pathway as the basis for setting the points of departure (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 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 proceed to discuss how this MOA informs our understanding of the reproductive and developmental effects observed after atrazine exposure.

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

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

Testing the hypothesis that atrazine-induced changes in the regulation of LH ultimately alter gonadal function in rodents, several studies reported adverse effects on reproductive development and adult function including delayed puberty in both sexes (Stoker *et al.*, 2000; Laws *et al.*, 2000), disruption of regular ovarian cycles in the adult female (Cooper *et al*., 1996, 2000), and reduced testicular hormone secretion in the male (Stoker *et al*., 2000; Trentacoste *et al*., 2001; Rosenberg *et al*., 2007) after atrazine exposure. Atrazine has also been demonstrated to cause pregnancy loss – manifested as litter resorptions – in F344 rats when administered during the LH-dependent period of pregnancy, but not when administered afterwards (Narotsky et al., 2001). Pregnancy maintenance is dependent upon progesterone from the corpora lutea (CL). After the first week of gestation, the CL becomes dependent on LH during GD 7 through 10. The findings of Narotsky et al. (2001) support the hypothesis of an LH-mediated mechanism of pregnancy loss. It should be noted that litter resorptions occurred at doses that were 5-fold higher than the dose used as the POD for the acute dietary risk assessment and approximately 25-fold higher than the POD used for all other assessments. Of these potential adverse outcomes, the two that appear to be the most sensitive (*i.e.* occur at the lowest dose levels) and/or occur after the shorter duration of exposure are the disruption of the ovarian cycles and the delays in puberty onset (Figure 4.5.1.2). Although other effects ranging from immune suppression to mitochondrial and insulin dysfunction have been reported in the peer reviewed literature, these effects occur at doses well above the no observed adverse effect levels (NOAELs)/lowest observed adverse effect levels (LOAELs) for LH surge attenuation.

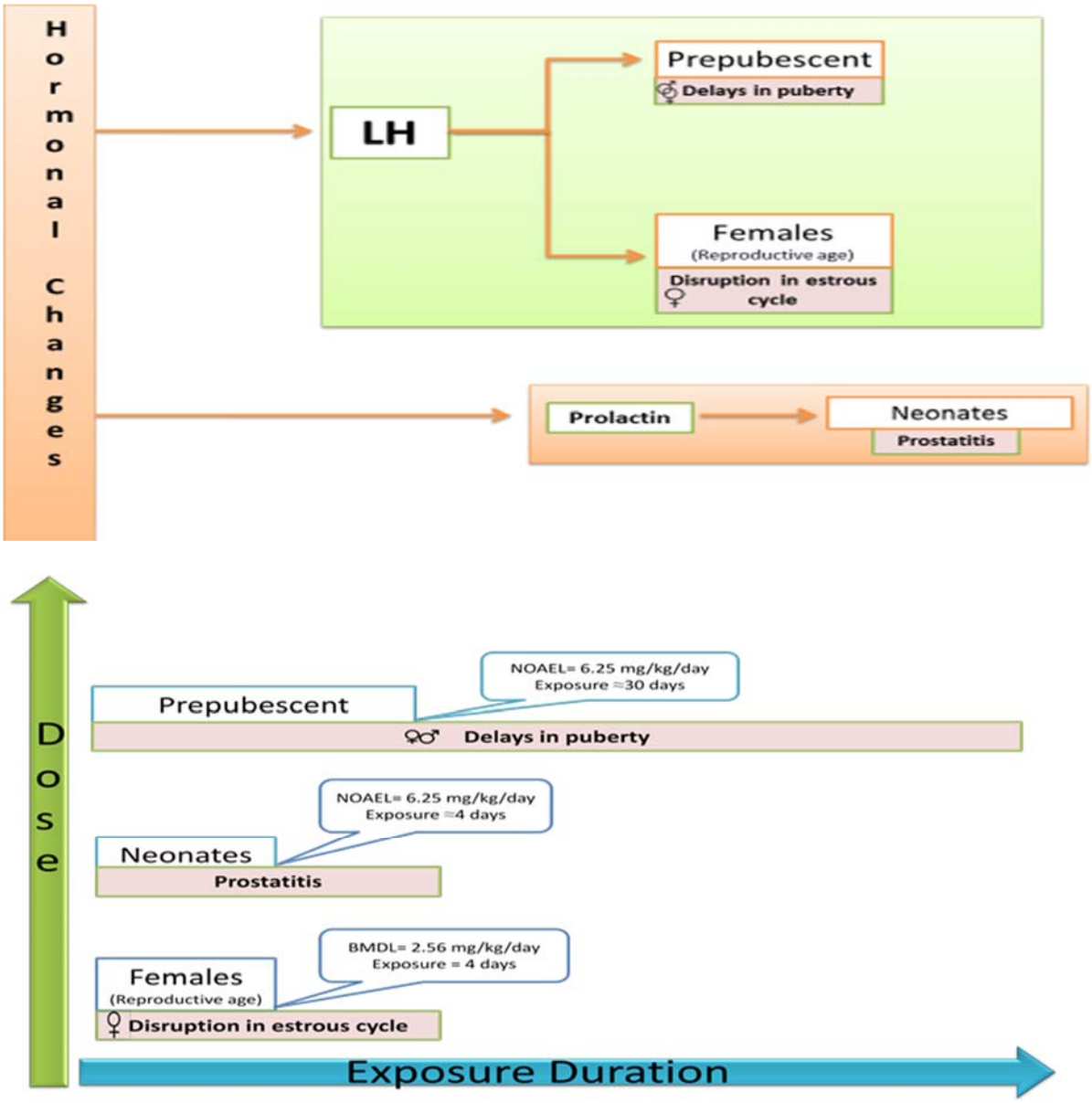


Figure 4.5.1.2. LH Suppression and Adverse Outcomes Observed in Rats

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

LH Surge Attenuation and Estrous Cyclicity

The most sensitive apical endpoint (effect) associated with LH surge attenuation is disruption of the estrous cycle. Potential effects of atrazine on LH surge attenuation and estrous cyclicity have been evaluated over a wide dose range (1.56-300 mg/kg/day) by several researchers (Cooper *et al.,* 1996, 2000, 2007, 2010; Minnema *et al.,* 2001, 2002; McMullin *et al.*, 2004; Morseth *et al.,*

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

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

The HPG Axis across Lifestages

LH and the HPG Axis during Prenatal and Postnatal Periods

In addition to the critical role that HPG axis has in reproduction, there is evidence that it is also functional during fetal and neonatal life (de Zegher et al.1992). The HPG axis is active in the fetus during mid-gestation, but is diminished towards term due to negative feedback from placental hormones (Kuiri-Hanninen et al. 2014). At birth, however, the axis is reactivated leading to increased gonadotrophin levels (LH and FSH) in both males and females. This reactivation period has been termed mini-puberty (Kuiri-Hanninen et al. 2014; Abreu and Kaiser 2016; Copeland and Chernausek, 2016). Gonadotropin concentrations gradually decrease towards age 6 months, with the exception of FSH concentration in females, which remains elevated until age 3 - 4 years. In males, testosterone concentration increases to a peak at age 1 -

3 months, then declines thereafter. In females, estradiol levels are elevated during mini-puberty. HPG axis activity during the pre- and postnatal period has been implicated in male genitalia development. In females, HPG activation during early life leads to increased concentrations of gonadotropins resulting in ovarian follicle maturation and an increase in estradiol. It has been postulated that this minipuberty serves to "prime" the system for its pituitary LH and follicle stimulating hormone (FSH) response to GnRH later in life (Abreu & Kaiser, 2016).

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

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

LH Attenuation and Delays in Puberty Onset

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

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

rodent's reproductive axis is dependent upon a pubertal increase in GnRH pulse generator activity and a progressive increase in the ability of the hypothalamus to generate surge-like releases of GnRH.

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

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

Over the last decades, a number of studies demonstrated that atrazine also delays male puberty following both peripubertal and perinatal exposure (Stoker *et al.*, 2000; Friedmann, 2002; Trentacoste *et al.,* 2001; Rayner *et al.*, 2006 and Rosenberg *et al.,* 2008; Pogrimic *et al.*, 2009). These studies support the hypothesis that impaired reproductive development is the result of an apparent delay in the maturation of the GnRH pulse generating mechanism and lower LH concentrations leading to insufficient stimulation of the gonads during the period that puberty would normally occur. The low testosterone concentrations result in delayed maturation of the androgen dependent sex accessory tissues. A reduction in testosterone levels following atrazine exposure has been reported in a number of studies in mammals, as well as other species, revealing a consistency in the effects of atrazine on androgens. It is well known that the development of the size of the penis and cornification of the epithelium of the prepuce and preputial separation in immature rats are regulated by androgens (Marshall, 1966). A decrease in testosterone secretion during the juvenile period can delay PPS (Lyons *et al.*, 1942) and reduce the size of the androgen-dependent tissues, such as the ventral prostate and seminal vesicles.

In the male rat, atrazine exposure resulted in delays in the onset of puberty, as determined by assessment of PPS. In a study with peripubertal males were exposed to atrazine at doses ranging from 6.25 to 200 mg/kg/day (Stoker *et al.,* 2000). After a 20-day exposure, PPS was delayed at doses ≥12.5 mg/kg/day, while exposure at 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 4.5.1.1. 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 4.5.1.1. 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 4.5.1.1. 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 = 2.56/4.92 mg/kg/day

4.5.2 Hydroxyatrazine

Unlike the chlorotriazines and their chlorinated metabolites, hydroxyatrazine is the major metabolite in plants, but a minor metabolite in animals. Subchronic, chronic/carcinogenicity, and developmental toxicity studies are available for this metabolite. 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.

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. In addition, onset times for mammary gland tumors in female rats were not decreased in this study.

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 atrazine. With respect to epidemiology, EPA has presented its evaluation of then-available evidence 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 evaluation for the risk assessment of atrazine were the 13 epidemiology publications identified in the literature that met one or more of the following criteria: reported a statistically significant estimate of effect for atrazine, that emanated from a prospective cohort and/or were otherwise of a moderate or high quality study design[10] or were often cited in the epidemiology literature, and that were unavailable/unpublished at the time of the recent SAPs (Appendix B). Seven of these studies (Chevrier *et al.* (2011), Cragin *et al*. (2011), Rinsky *et al.* (2012), and Agopian *et al*. (2013a), Agopian *et al*. (2013b), Agopian *et al*. (2013c), and Strayner *et al.* (2017)) investigated birth and reproductive system health effects; four reported on non-reproductive non-carcinogenic effects (James and Hall (2015) on Parkinson's Disease, LaVerda *et al.* (2015) on weight gain, Hoppin *et al.* (2016) on wheeze, and Lebov *et al.* (2016) on end-stage renal disease); one investigated childhood leukemia (Garcia-Perez *et al.* (2015); and one investigated prostate cancer (Koutros *et al.* (2013)). Reported associations from these studies are further discussed below, with additional characterization on the consistency with studies previously reviewed by OPP. Additional detail on these 13 studies are also provided in Appendix B.

> Chevrier *et al.* (2011) reported evidence of a positive association between prenatal exposure to atrazine (quantified by atrazine or metabolites in maternal urine) and risk of fetal growth restriction and small head circumference (SHC) for sex and gestational age, inconsistent evidence regarding the association between atrazine exposure and birth weight, and no evidence of a significant positive association between atrazine exposure and risk of major congenital anomalies. The evidence for birth weight and other size effects echoed some earlier ecologic studies that found higher levels of atrazine in drinking water was associated with increased risk of small for gestational age (SGA) birth (Munger *et al.* (1997), Ochoa-Acuna *et al.* (2009)), but other ecologic publications have failed to identify a significant positive association between prenatal atrazine exposure and birth weight and size effects (Sathyanarayana *et al.* (2010), Stayner *et al.* (2017)).
>
> The Chevrier *et al.* (2011) publication also included analyses of male genital anomalies and found evidence of an association, but small sample size and other study issues limited the ability to draw conclusions from the study. These issues included: the

[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

collection of only a single urine sample to reflect exposure during the period of pregnancy, sample handling which may have affected the integrity of the sample, the potential effects of fish consumption on the findings, and the potential statistical bias from the use of the backward selection process used by the authors to select the variables in the regression model (Appendix B). The several study limitations mentioned above reduced the reliability and overall confidence in interpreting the findings of this study.

Agopian *et al.* (2013c) also reported evidence of positive associations between maternal exposure (estimated by amount of atrazine application in maternal county of residence) and risk of male genital anomalies, but inconsistent results across exposure groups and the lack of statistically significant results for the high exposure group for any genital malformation suggest that the results may be spurious (Appendix B). A second study by the same research group (Agopian *et al.* (2013a)) found evidence of a positive association between maternal exposure and risk of choanal atresia/stenosis (respiratory system anomalies) in the high maternal exposure group compared to the low exposure group (Appendix B). A third study by the same research group (Agopian et al. (2013b)) investigated abdominal wall defects (gastroschisis) and reported no evidence of a positive association between county-level atrazine application and risk of gastroschisis overall, except among older (≥ 25 years) mothers, where there was evidence of a positive association in the high exposure group compared to the low exposure group (Appendix B). All of the Agopian *et al.* research group studies were ecological in design and considered only county-level atrazine application as a surrogate for exposure and did not consider or adjust for other pesticides as potential exposures affecting the outcome. These noted limitations reduced the reliability of the studies and the overall interpretation of the findings.

The additional evidence presented by the newer studies reviewed here (Chevrier *et al.* (2011), Agopian *et al.* (2013a), Agopian *et al.* (2013b), Agopian *et al.* (2013c)) does not alter the Agency's conclusions from the 2010 SAP, which considered the epidemiology evidence for an association between atrazine exposure and risk of birth defects to be weak.

- Rinsky *et al.* (2012) in a semi-ecological study found a slight positive association between high atrazine exposure (estimated by county-level drinking water atrazine concentration) and risk of preterm birth, conflicting with an earlier publication (Ochoa-Acuna *et al.* (2009)) that found no evidence of this association. Other publications (Savitz *et al.* (1997), Stayner *et al.* (2017), Villanueva *et al.* (2005)) found either no evidence of an association between atrazine exposure and risk of preterm birth, or inconsistent evidence across exposure groups. Although Rinsky *et al.* (2012) reported a slight positive association, the ecologic study design and the inconsistent monitoring of atrazine across water systems within the study, led the agency to place less emphasis on the observed study results. (Appendix B).

- Cragin *et al.* (2011) concluded that atrazine exposure through municipal drinking water was associated with reduced reproductive hormone levels and longer follicular phase in women, but study results and conclusions are considered to be severely limited by a

number of concerns with the study. These concerns include: a low overall study participation rate, the use of multiple participant subsets in their analyses and the lack of adjustment for multiple comparisons, a low number of cases, and the fact that most atrazine measurements were less than the limit of detection (LOD). The fact that "exposed" and "unexposed" individuals were defined by the authors as individuals residing in two different locations (in fact two different states from two different regions) suggests that there is opportunity for numerous other unaccounted-for differences between "exposed" and "unexposed" individuals which may have accounted for the findings with respect to reproductive hormone levels and longer follicular phase. (Appendix B).

- Other non-carcinogenic health effects identified in recent literature as having significant positive associations with atrazine exposure included Parkinson's disease (PD) (James and Hall (2015)), weight gain (LaVerda *et al.* (2015)), end-stage renal disease (ESRD) (Lebov *et al.* (2016)), and wheeze (Hoppin *et al.* (2016)). The evidence for wheeze was echoed in earlier publications from the same research group (Hoppin *et al.* (2002), Hoppin *et al.* (2006a)). However, the Hoppin *et al.* research was limited by its cross-sectional study designs which lacked relative temporal information on exposure and outcome. Likewise, the evidence from James and Hall (2015) for PD was also limited by cross-sectional characteristics and its ecological design as well as by conflicting evidence from previous publications (*e.g.*, Kamel *et al.* (2007) as part of the AHS which found no evidence of a significant positive association between atrazine exposure and risk of PD). With respect to ESRD, previous publications also conflicted with the evidence from Lebov *et al.* (2016) (*eg.*, Lebov *et al.* (2015) which found no evidence of a significant positive association between atrazine exposure and risk of ESRD). Finally, the evidence from LaVerda *et al.* (2015) was limited by statistical measures that indicated BMI was not highly determined by atrazine exposure and that other, unmeasured factors may have greatly influenced the outcome (Appendix B).

- Since the 2011 SAP, there was one study published that investigated atrazine exposure and risk of childhood leukemia (Garcia-Perez *et al.* (2015). This case-control study found a positive association between living within 2.5 km of a facility that released atrazine and risk of childhood leukemia, but relied on a limited number of cases, used an ecological design with residential distance to atrazine source as a proxy for exposure, and potential bias concerns introduced by varying success with geocoding residential addresses. Four previous studies (Brown *et al.* (1990), Rusiecki *et al.* (2004), Freeman *et al.* (2011), Mills (1998)) found no evidence of an association between atrazine exposure and risk of leukemia. There were no publications identified since the 2011 SAP that investigated atrazine exposure and risk of non-Hodgkin's lymphoma (NHL).

- For prostate cancer (both overall and aggressive), Koutros *et al.* (2013) concluded that no evidence of a significant positive association relative to atrazine exposure through a prospective cohort study designs. The prospective cohort design and the large size of the AHS cohort were study strengths, and inaccuracies in scoring aggressive prostate cancer using the Gleason score along with some associations due to chance were potential study weaknesses (Appendix B).

For the current weight of evidence evaluation for the risk assessment of atrazine, 13 epidemiology publications were identified in the literature since the 2011 SAP that met one or more of the following criteria: reported a statistically significant estimate of effect for atrazine, that emanated from a prospective cohort and/or were otherwise of a moderate or high quality study design[11] or were often cited in the epidemiology literature, and that were unavailable/unpublished at the time of the recent SAPs were reviewed. The following health endpoints considered included: birth and reproductive system health effects, prostate cancer, childhood leukemia, allergic and non-allergic wheeze, Parkinson's Disease, bodyweight gain, and end-stage renal disease. Reported associations from these studies are mentioned above (and further discussed in Appendix B); however, their interpretation was hampered by significant limitations ranging from ecologic design to inaccuracies in collecting exposure data. Overall, these studies do not provide reliable information that would cause the agency to change its conclusions regarding the epidemiological evidence.

4.6 ATRAZINE: Toxicity Endpoint and Point of Departure Selections

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

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

Exposure to any pesticide does not occur at the same level every day; instead, exposure varies significantly across time with seasonal applications and related events such as run-off. As such, chlorotriazine exposure can occur from 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

[11] 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

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[12]). 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[13]). 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[14]). 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)[15]. 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

[12] 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

[13] 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

[14] 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

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

atrazine, the POD for the intermediate and chronic exposure risk assessments was based on the attenuation of the LH surge reported by Morseth *et al.* (1996b) at doses ≥ 3.65 mg/kg/day (NOAEL/LOAEL = 1.8/3.65 mg/kg/day). In the 2002 assessment, the drinking water assessment was conducted using a 90-day duration of concern. 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 health 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 atrazine (summarized in Table 4.6.2.2), a POD of 10 mg/kg/day for females 13-49 years of age was selected from an atrazine developmental toxicity study (MRID no. 40566302). In this study, atrazine was administered to 104 Charles River CD rats 27/dose by gastric intubation at dose levels of 0, 10, 70, or 700 mg/kg/day from days 6 through 15 of gestation. The NOAEL of 10 mg/kg/day was based on delayed ossification seen at 70 mg/kg/day (LOAEL). The dose and endpoint were selected based on a weight of evidence approach using four studies (MRID #'s 00143006, 41065201, 40566301, 40566302); three of the four studies evaluated the developmental toxicity potential in rats [Charles River (CR) and SD] and the other was conducted with New Zealand White rabbits. There is a striking similarity in the suite of effects noted after *in utero* exposure to atrazine in both rats and rabbits. In both species, delay in ossification was the critical effect identified for the conceptus, albeit at maternally toxic doses. The range of LOAELs for this effect was 70-100 mg/kg/day regardless of species or strain. The NOAELs ranged between 5 and 25 mg/kg/day. The lowest NOAEL identified in any of these studies (5 mg/kg/day in the rabbit developmental study, MRID 40566301) was not selected since it was an artifact of the wide dose gap (15-fold) between the NOAEL (5 mg/kg/day) and the LOAEL (75 mg/kg/day).

The delayed ossification observed in the developmental toxicity studies in rats and rabbits 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 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 factors for acute dietary are 100X. The FQPA Safety Factor of 10x was reduced to 1x based on the SAP conclusion, and discussed in Section 4.8. The SAP concluded that "there is sufficient information available to reach the conclusion that the issue of differential sensitivity has been adequately studied. This relatively extensive database, spanning all life stages from conception to adulthood indicates no unique susceptibility to atrazine in the developing organism." (SAP Report on July 2011 meeting, EPA-HQ-OPP-2011-0399-0080.pdf; pp. 52-54).

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

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Atrazine Acute Dietary (Females 13-49 years of age)	NOAEL = 10 mg/kg/day	UF_A= 10X UF_H=10X FQPA SF= 1X	Acute RfD = 0.1 mg/kg/day	Developmental toxicity studies in rat & rabbit (weight of evidence from four studies) w/ atrazine MRID 40566302 LOAEL =70 mg/kg/day based on delayed ossification of certain cranial bones in fetuses

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)

In the 2002 human health risk assessment for atrazine (C. Eiden, D272009, 04/16/2002), the chronic RfD and intermediate-term oral, dermal and inhalation exposures were based on the attenuation of the LH surge reported by Morseth *et al.* (1996b) (MRID 44152102) at atrazine doses ≥ 3.65 mg/kg/day (NOAEL/LOAEL = 1.8/3.65 mg/kg/day). The current atrazine risk assessment has been revised based on the Cooper et al. (2010) dataset which provided the most robust LH data in terms of dose selection (number of dose levels – particularly at the low dose range, spacing between dose levels, and variability of the data). The study design addressed the low-dose region of the dose-response curve and exhibited less data variability (i.e., smaller standard deviations).

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)[16]; 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 benchmark dose (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[17] 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.

[16] 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.

[17] 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*.

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

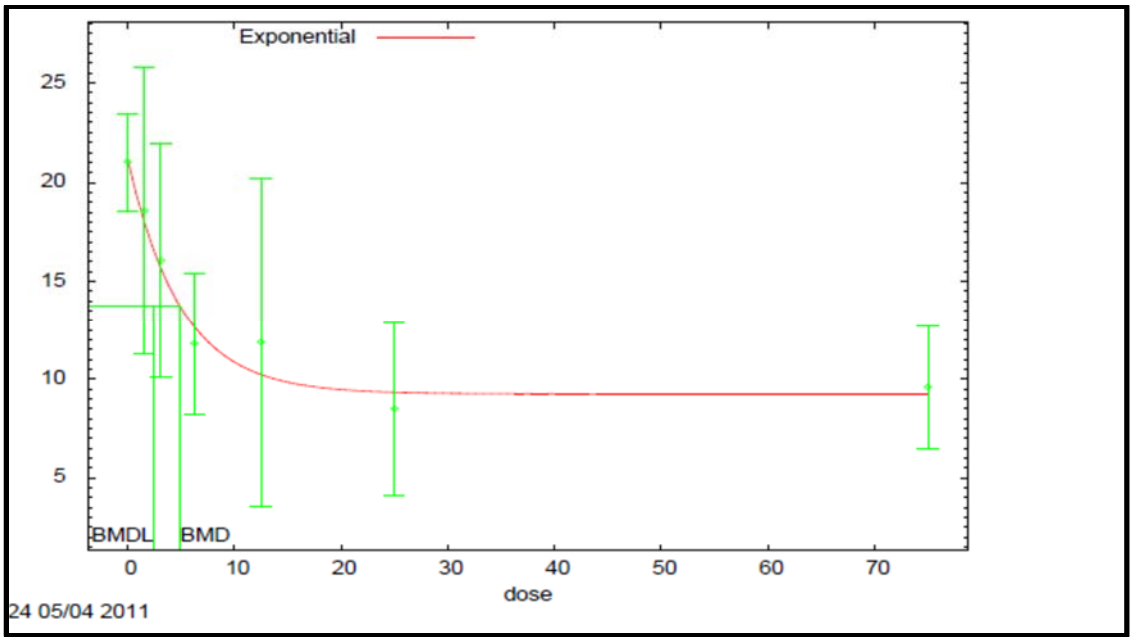


Figure 4.6.2.3. Plot of benchmark dose analysis from Cooper *et al* (2010) using the exponential model.

The current chlorotriazine risk assessment continues to rely on atrazine's established neuroendocrine MOA. Based on the robust data from reliable, well-designed and conducted studies, attenuation of 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 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 chemical-specific parameters (simazine, propazine) where applicable. The only differences between the three models are molecular weight for each chemical, and adjustments of the liver and gut metabolism rates for chloro metabolites of simazine and propazine. For simazine, the liver and gut metabolism rates for simazine to DEA were set to zero since DEA is not a metabolite of simazine. Similarly, the liver and gut metabolism rates from propazine to DIA were set to zero to reflect the lack of metabolism to this particular metabolite.

Another recent refinement to the atrazine PBPK model is the addition of dermal and inhalation routes. For the dermal route, the dermal absorption rate constant (6%/day) was obtained from an *in vivo* human dermal study on atrazine see Section 4.4 – dermal absorption). Since the only model parameter that is specific to the dermal route is dermal absorption rate, the value for this parameter 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 interspecies 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 neurodevelopmental 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 & Structure of the PBPK Model

The PBPK model for atrazine used here was based on an earlier model developed by McMullin *et al*. (2007a) in rats. The McMullin model has since undergone several revisions and refinements by the researchers at the Hamner Institutes and Syngenta (Campbell 2011; Campbell 2014; Hinderliter 2015; Campbell 2015) to include new metabolism rate constants scaled from *in vitro* experiments using rat and human hepatocytes. In addition, the McMullin model described oral uptake using an empirical function which cannot be extrapolated from rats to humans, and thus, a two-compartment sub-model was developed for simulating oral uptake and absorption of atrazine, as well as pre-systemic metabolism of atrazine to DEA and DIA. Atrazine, DEA, and DIA were 100% absorbed in this model. The revised model (which is referred to as "the 2015 PBPK model") expanded the original two-compartment (liver and rest of body) structure (McMullin *et al*., 2007a) to contain 10 tissue compartments, including mammary, fat, brain, hypothalamus, pituitary, testes/ovaries, adrenals, liver, and rapidly and poorly perfused tissues. All tissues were described as flow limited compartments. Metabolism of atrazine to DIA and DEA, as well as the subsequent metabolism of DIA and DEA to DACT, were described as saturable processes. The competitive inhibition of metabolism was retained from the McMullin model (2007a) in which DIA and DEA inhibited atrazine metabolism, atrazine and DEA inhibited DIA metabolism, and atrazine and DIA inhibited DEA metabolism. A schematic of the atrazine PBPK model is presented in Figure 4.6.2.4.1 (extracted from Campbell *et al*., 2015).

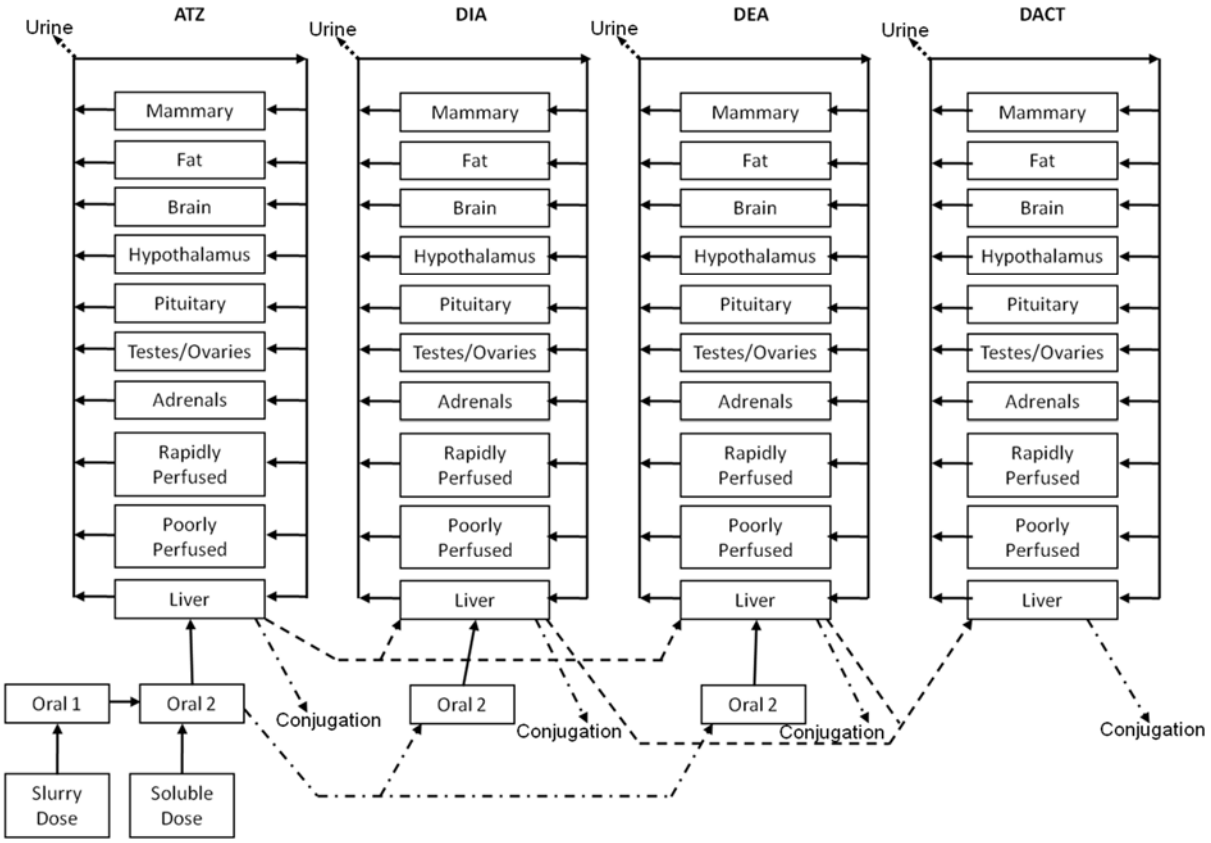


Figure 4.6.2.4.1. Schematic of the PBPK model for atrazine and triazine metabolites (dashed line represents metabolism in liver of atrazine to DIA and DEA and conversion of DIA and DEA to DACT)

In the 2015 PBPK model, most physiological parameters for rats and humans were obtained from Brown *et al*. (1997) and O'Flaherty *et al*. (1992). Human adrenal volume and blood flow, mammary volume, and testes/ovaries volume were obtained from the International Commission on Radiological Protection (ICRP) Pub 89 (2002). Tissue volumes and blood flows for monkeys were obtained from Davies and Morris (1993). For parameters that are unavailable for rats and monkeys, their values were taken from the human values adjusted for body weight. Values of physiological parameters are summarized in Table 4.6.2.4.1 (extracted from Campbell *et al*., 2016). Chemical-specific tissue to blood partition coefficients for liver and brain were measured (Tremblay *et al*., 2012), but no measured values were available for other tissues. It was found that the measured values for brain and liver were very similar (0.69 for liver and 0.73 for brain), and thus, a simplified approach to use the value of 0.7 for all tissue to blood partition coefficients was adopted by the Agency. No partition coefficients have been measured for any of the three metabolites, and thus, the value of 0.7 used for atrazine was also used for DIA, DEA, and DACT given the structural similarity between atrazine and these metabolites. Such an approach is a common practice in PBPK modeling, and the values for these blood to tissue partition coefficients estimated using a 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, 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
Metabolism of ATZ to DIA in Oral 2 (/hr*BW$^{0.75}$)	KMETRTRA_ISO_OR2C	0.917	0.317	1.05
Absorption rate DIA in Oral 2 (/hr*BW$^{0.25}$)	KAOR2ISOC	0.8	0.8	0.8
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
Maximum velocity liver ATZ to DIA (µmol/hr/kg$^{0.75}$)	VMAXCATRA_ISO	202.5	202.5	188.2
Affinity constant for ATZ (µmol/L)	KMATRA	30.0	30.0	30.0
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
Maximum velocity liver DIA (µmol/hr/kg$^{0.75}$)	VMAXCISO	13.5	13.5	25.1
Affinity constant for DIA (µmol/L)	KMISO	13.0	13.0	13.0
Elimination of 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**

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**
Volume of hepatocyte suspension (mL)	VSUSP	0.25	0.25	10
Initial number of hepatocytes (10^6)	INITNOHEPAT	0.5	0.5	20
Atrazine				
Vmax (µmol/10^6 cells/min)	VMAXCATRA	0.0023	0.0015	0.0023
Affinity constant atrazine (µM)	KMATRA	30.0	30.0	30.0
Fraction atrazine metabolized to DIA	FRAC	0.35	0.2	0.35
DIA				
Vmax (µmol/10^6 cells/min)	VMAXCISO	0.00008	0.00004	0.00008
Affinity constant DIA (µM)	KMISO	13.0	13.0	13.0
DEA				
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)[18], 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.

[18] 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.

The human PBPK model parameterized for an average adult (based on physiological parameters in Table 4.6.2.4.1) was later modified to include description of growth from birth to adulthood. This life-stage model was modified based on previous work on chlorpyrifos (Smith *et al*. 2014). Body weights are described using an age-dependent Gompertz equation (Luecke *et al.* 2007, Smith *et al.* 2014). All tissue volumes were adjusted by body weight using a high order polynomial function[19] (Luecke *et al.* 2007, Young *et al.* 2009, Smith *et al.* 2014[20]). 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.

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)[21], 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-

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

[20] 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.

[21] 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.

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 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. 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 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

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.

In addition to route-specific PODs, the PBPK model for atrazine was also used to derive scenario-specific PODs for dietary food, dietary drinking water, residential, non-occupational spray drift, and occupational exposures (Table 4.6.2.4.2.2) based on the same internal dose metric, an average TCT concentration in plasma at 2.6 µmol/L in the last 4 days of exposure.

Table 4.6.2.4.2.1. Body Weight Assumptions Incorporated into PBPK Model for Atrazine						
Exposure Scenario	**Exposure Pathway**		**Population & Body Weight (kg)**			
		Infants (<1 year old)	**Young Children (<1 - 2 years old)**	**Children (Residential:6-11 years old; Dietary:6-12 years old)**	**Youths (Residential:11-16 years old; Dietary:13-19 years old)**	**Females (13 – 49 years old)**
Dietary	Food and Drinking Water	4.8[1]	12.6[2]	37.1[2]	67.3[2]	72.9[2]
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. For dietary food, exposures are summed for each 24 hour period. 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. For youths and female adults, they were assumed to consume water 4 times a day, and a total consumption volume of 1.71 L/day.

The dermal component of the PBPK model included an hourly flux rate to determine the rate of absorption through the skin. Available information in the Exposure Factors Handbook[22] indicates that the median frequency for baths and showers was estimated to be 7 times per week (i.e., once per day) for children[23]. 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

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

occurs within one hour or within a few hours after exposure[24]. 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. All scenario-specific PODs were calculated as the average daily blood area under the curve (AUC) for TCTs 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 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 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's skin 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 exposed, and that a daily shower occurred 24 hours after initial exposure. For adults and children 1-2 years old engaged in other turf activities (including residential and non-occupational exposures), dermal PODs were estimated assuming that 50% of the skin's surface was exposed, and that a daily shower occurred 24 hours after initial exposure. The incidental oral PODs for children 1 to < 2 years old for other turf activities were estimated assuming that there were six events, 15 minutes apart, per 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.

[24] 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

Table 4.6.2.4.2.2. Atrazine PBPK Modeled External Doses (PODs) Corresponding to a $BMDL_{1SD}$ for LH Surge Attenuation						
RA Type	Exposure Pathway (all triazines unless noted)	Infants (< 1 yr old)	Young Children (1 - 2 years old)	Children (Residential: 6-11 years old; Dietary:6-12 years old)	Youths (Residential:11 -16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
		Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)
Dietary	Drinking Water (conc, ppb)	2.12E+04	5.14E+04	1.19E+05	7.72E+04	9.22E+04
	Food (ug/kg/day)	3060 (3.060 mg/kg/d)	3240 (3.240 mg/kg/d)	2570 (2.570 mg/kg/d)	2330 (2.330 mg/kg/day)	2290 (2.29 mg/kg/day)
Residential Handlers	Dermal (mg/kg/day)					29.78
	Inhalation (concn. in air mg/m^3)					194 (4.67 mg/kg/day)[1]
Residential (Golfers)	Dermal (mg/kg/day)			33.83	30.33	29.67
Residential (Mowing)	Dermal (mg/kg/day)				30.42	29.79
Residential (Other Turf Scenarios)	Dermal (mg/kg/day)		42.94			29.69
	Oral (ug/kg/day)		3320 (3.320 mg/kg/day)			
Non-Occupational Spray Drift	Dermal (mg/kg/day)		42.94			29.67
	Oral (mg/kg/day)		3.32			
Occupational	Dermal (mg/kg/day)					29.7
	Inhalation (concn. in air mg/m^3)					15.5 30.9 8.9 (1.8 mg/kg/day)[2]

1. Residential handler:
   a. 4.67 mg/kg/day = 194 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. 1.8 mg/kg/day = 15.5 mg/m^3 (POD derived from the PBPK model) × 1 m^3/hr (or 16.7 L/min) × 8 hr/day ÷ 69 kg.
   b. 1.8 mg/kg/day = 30.9 mg/m^3 (POD derived from the PBPK model) × 0.5 m^3/hr (8.9 L/min) × 8 h/day ÷ 69 kg.
   c. 1.8 mg/kg/day = 8.9 mg/m^3 (POD derived from the PBPK model) × 1.74 m^3/hr (or 29 L/min) × 8 hr/day ÷ 69 kg.

4.6.2.4.3 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 atrazine 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 Exposures 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

Atrazine was first reviewed by the SAP in 1988 (FIFRA SAP, 1998) for evaluation of rat mammary gland tumor response. 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 MOA. In 2000, the Agency sought the SAP’s advice (FIFRA SAP, 2000) on atrazine’s proposed MOA leading to mammary gland tumors, reproductive and developmental effects in rats, as well as the human relevance of these findings. In brief, upon exposure to atrazine, the release of GnRH from the hypothalamus is reduced resulting in a lessening of the afternoon pituitary LH surge. As a result, the estrus cycle lengthens. This, in turn, leads to increased estrogen levels which leads to an increased incidence of mammary tumors in SD female rats. However, with respect to human relevance, reproductive aging (menopause) in humans initiates differently than in rats. Unlike rats, reproductive senescence in humans (menopause) is caused by the depletion of follicles and a concomitant decrease in estrogen instead of changes in the LH surge (which remains normal during menopause). The key events in the MOA leading to mammary gland tumors in rats are not relevant for breast tumorigenesis in humans. The Panel concurred with the Agency’s proposed MOA as it relates to mammary gland tumorigenesis and its lack of relevance in humans. However, the panel advised the Agency to continue to monitor the cancer epidemiology literature as more information became available, particularly for prostate cancer and Non-Hodgkin’s lymphoma. In 2003, the Agency presented its evaluation on prostate cancer to the SAP. At that meeting, the FIFRA SAP concurred with EPA’s conclusion on these epidemiology studies that Prostate-Specific Antigen (PSA) screening could explain the observed increase in prostate cancer incidence in workers.

Given the totality of the data, the CARC concluded that atrazine should be classified as a "Not Likely To Be Carcinogenic To Humans” (K. Baetcke, TXR#0045531, 12/13/2000). The newer studies reviewed for the 2010-2011 SAPs did not change the Agency’s current determination.

At the 2011 SAP, panel members agreed with the Agency's conclusion that based on the nature of the epidemiology studies available (*e.g.,* ecologic design, hypothesis- generating studies, etc.) and their inherent limitations, there was no convincing evidence on most cancer types that would warrant deviating from the Agency's previous classification of atrazine as "Not Likely To Be Carcinogenic To Humans." While the Panel made this conclusion for most cancer types reviewed, the Panel did express some concerns about possible associations with thyroid, ovarian, and two lymphohematopoietic (i.e., NHL and Hairy Cell Leukemia, or HCL) cancers; specifically, the Panel believed based on the AHS study reviewed that there was "inadequate information to assess carcinogenic potential" and urged the Agency to continue to follow the published cancer epidemiology literature with regard to these cancers types specifically. With regard to thyroid cancer, the Panel indicated that the one AHS study suggested a strong relationship, but also acknowledged that a single study is not sufficient to determine a causal relationship, so replication in a larger study and more experimental evidence is needed. The Panel also indicated that the association with ovarian cancer was suggestive, but more rigorous investigation was needed. Similarly, the Panel noted that while early studies on NHL and HCL suggested a possible association with atrazine use, the results have not been replicated in more recent studies with larger samples sizes and stronger study designs. The Agency notes, too, that in most cases, the numbers of exposed cases were small and inadequate to develop firm conclusions. The Agency agrees with the SAP that it is important for OPP to continue to monitor the literature.

Since the 2011 SAP meetings, four independent reviews, including one from California OEHHA, have been published which have evaluated the association between atrazine exposure and cancer in humans (Jowa and Howd, 2011; Sathiakumar *et al*, 2011; Simpkins *et al*, 2011, only evaluated breast cancer; Boffetta *et al*, 2013). Each one concludes that there is no association between atrazine exposure and human cancer.

In 2017, the Agency conducted a formalized literature review to collect, evaluate, and integrate evidence from recent epidemiological literature on the association between triazine exposure and human health outcomes including cancer (Appendix B). This review identified four studies on prostate cancer that were not available at the time of the 2011 SAP. Two of these studies (Koutros *et al.* (2013), Karami *et al.* (2013)) emanated from a prospective cohort and/or were otherwise of a high quality study design. Although both studies found no evidence of a significant positive association between atrazine exposure and risk of prostate cancer, Karami *et al.* (2013) failed to meet the inclusion criteria outlined in Appendix B[25] for this epidemiology literature review, as the study explores the association between atrazine exposure and vitamin D pathway genes among prostate cancer cases. As a result, this study was not one of the epidemiological studies included within this atrazine risk assessment. These studies both came from the AHS, and while the exact overlap of participants between these studies cannot be ascertained, the fact that they were derived from the same AHS cohort population should be recognized.

[25] 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.

Other recent studies from the AHS produced inconsistent or weak evidence regarding the association between atrazine exposure and prostate cancer risk. Koutros *et al.* (2011) found no evidence of a significant positive association between prostate cancer risk and atrazine exposure overall, but did find a positive interaction between atrazine exposure and a single nucleotide polymorphism (SNP) in an oxidative stress gene (GSS), with one genotype variant showing evidence of a positive association with prostate cancer risk among men who were in both the low and the high exposure groups. Andreotti *et al.* (2012) investigated the potential interaction of atrazine and other pesticides with genetic variances in the lipid metabolism pathway and the risk of prostate cancer through a nested case control study of the AHS participant cohort, and found a significant interaction between genotype group and atrazine in the risk of prostate cancer. The limited evidence of an association between atrazine and risk of prostate cancer from both Koutros *et al.* (2011) and Andreotti *et al.* (2012) is moderated by results from other studies of the AHS cohort that investigated prostate cancer as the main effect and found no significant positive association between atrazine exposure and prostate cancer (Alavanja *et al.* (2003), Rusiecki *et al.* (2004), Freeman *et al.* (2011), Koutros *et al.* (2013)) (Appendix B). Similar to Karami *et al*. (2013) mentioned above, Koutros *et al.* (2011) and Andreotti *et al.* (2012) failed to meet the inclusion criteria outlined in Appendix B[26] for this epidemiology literature review, as these studies explore gene pathway interactions and variants. As a result, these two studies were not part of the epidemiological studies included within this atrazine risk assessment.
Since the 2011 SAP, there was one study published that investigated atrazine exposure and risk of leukemia (Garcia-Perez *et al.* (2015). This case-control study found a positive association between living within 2.5 km of a facility that released atrazine and risk of childhood leukemia. Four previous studies (Brown *et al.* (1990), Rusiecki *et al.* (2004), Freeman *et al.* (2011), Mills (1998)) found no evidence of an association between atrazine exposure and risk of leukemia. There were no studies published since the 2011 SAP that investigated atrazine exposure and risk of non-Hodgkinma (NHL).

Taking into consideration the recent epidemiology publications since the 2011 SAP, including the strongest evidence derived from AHS, as well as the WOE, the Agency concludes that, while uncertainties remain, the totality of the available evidence does not support an association between atrazine exposure and human cancer.

4.7 HYDROXYATRAZINE: Toxicity Endpoint and Point of Departure Selections

For the hydroxyatrazine metabolite, only the chronic endpoint is applicable as it is the only relevant duration of exposure associated with a toxic effect. No residential or occupational assessments were conducted for hydroxyatrazine. Hydroxyatrazine is a plant metabolite, and to a lesser extent a livestock metabolite; therefore, hydroxyatrazine residues are not expected on the surfaces of plants limiting the potential for non-dietary exposures in residential and occupational settings. However, chronic dietary exposures to hydroxyatrazine are considered (See Section 5).

[26] 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.

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using all available dichotomous models for incidence data for various histopathological renal lesions in male and female rats from a combined chronic toxicity/oncogenicity study (MRID 43532001) on hydroxyatrazine in the rat. Criteria used to assess the best fit included statistical (goodness-of-fit) values, model criteria (Akaike Information Criteria; AIC), BMD/BMDL (Benchmark Dose/lower 95% confidence limit on the Benchmark Dose) ratios, visual inspection of fits, and comparison of male and female dose-response relationships. The benchmark response (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 values ($BMDL_{10}$ 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.

For the chronic dietary endpoint, a $BMDL_{10}$ of 6.76 mg/kg/day was obtained from BMD analyses of renal histopathological effects in Sprague-Dawley (BR strain) rats from a combined chronic/carcinogenicity study of hydroxyatrazine (MRID 43532001).

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} = 7.72 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.

4.8 Safety Factor for Infants and Children (FQPA Safety Factor)[27]

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

[27] 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).

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 CRA, the Agency retained the FQPA 10X safety factor for uncertainties related to both available toxicology data and exposure information on drinking water. Specifically, the 2006 CRA states "there remains some degree of residual uncertainty as to the effects of triazines on the young……. In particular, exposures at all critical periods." These critical developmental periods were noted as gestation through puberty in both sexes, in particular, early in development (USEPA, 2002b[28]). 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 cumulative risk assessment was conducted, the available information on toxicology of various pre- and post-natal lifestages and on drinking water exposure has substantively changed. The drinking water assessment is described in Section 5.3. The exposure databases and modeling are sufficient to assure that residues in drinking water will not be underestimated. The exposure assessment for drinking water provides a conservative approach for estimating chlorotriazine concentrations in ground and surface source water for drinking water.

The atrazine 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[29] 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

[28] USEPA, 2002b, *ATRAZINE/DACT* - Reassessment Report of the FQPA Safety Factor Committee. April 8, 2002. TXR NO. 0050638
[29] 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

evidence of increased susceptibility in the prenatal developmental toxicity study in rats with hydroxyatrazine. Although there was increased qualitative susceptibility in the atrazine rabbit study [increased resorptions (deaths) at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal], the observed effects occur at higher doses than the BMDL of 2.42 mg/kg/day used to assess risk. The BMDL of 2.42 mg/kg/day is protective of developmental effects in the rabbit.

Laboratory Animal Toxicity Data 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) AGD and 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:
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:
Several research articles identified in the epidemiological literature were considered as part of the FQPA Safety Factor determination.

Briefly, several studies investigated female reproductive and birth effects and a single study investigated parameters of semen quality. Female reproductive effects investigated included premature intrauterine growth retardation, miscarriages, and spontaneous abortions.[30] Although associations were reported in some studies, these studies had several important limitations, including inadequate exposure assessments, ecologic study designs, and insufficient control of potential confounders. Due to these limitations, these studies provide inadequate evidence to evaluate if a causal relationship between atrazine exposure and female reproductive effects exists at this time. A number of studies investigated birth effects among infants, including preterm delivery, low birthweight, and various birth defects/abnormalities (e.g., gastroschisis, and genital abnormalities).[31] While several of these studies reported positive associations between atrazine exposure and effects on birth size, concerns were identified within the review of these studies (further explained in Appendix B) involving their study design, exposure assessment approach, statistical methods, and the small number of exposed cases. Therefore, there is insufficient evidence for the Agency to determine if a causal relationship between atrazine exposure and birth effects exists at this time. With respect to male reproductive health effects, the one study (Swan *et al*. 2003) reviewed by the 2010 SAP reported increased prevalence of poor semen quality among men with urinary concentrations of atrazine mercapturate, a metabolite of atrazine, above the limit of detection.[32] The 2010 SAP concluded that this study had a number of deficiencies due to its small sample size, low participation rates, and the cross-sectional study design. Since the 2010 SAP, no additional epidemiologic studies have investigated the relationship between atrazine exposure and semen quality. Due to the study limitations identified by the 2010 SAP and absence of reliable corroborative evidence from additional studies, there is insufficient information available to the Agency to assess the potential association between atrazine exposure and semen quality.

In sum, while some studies suggest a possible association between atrazine exposure and several measures potentially indicative of reproductive or birth effects, the overall evidence is weak given the significant limitations inherent to the exposure measures, statistical treatment, or study design(s). Based on review of these studies, no evidence was found that lead the Agency to conclude that there is a causal association between exposure to atrazine and neuroendocrine toxicity, including increased sensitivity to infants and children. The reviewed studies do not introduce significant uncertainty in the risk assessment or the Agency's conclusion that the POD

[30] Reviewed studies included: Farr *et al*. 2004, 2006, Cragin *et al.* 2011, Ochoa-Acuna *et al.* 2009, Villanueva *et al.* 2005, Chevrier *et al.* 2011, Stayner *et al.* 2017, Migeot *et al.* 2013, Limousi *et al.* 2014, Ochoa-Acuna *et al.* 2009, Villanueva *et al.* 2005, Munger *et al.* 1997, Sathyanarayana *et al.* 2010, Dabrowski *et al.* 2003, Savitz *et al.* 1997, Arbuckle *et al.* 2001, and Waller *et al.* 2010.
[31] Ochoa-Acuna *et al.* 2009, Villanueva *et al.* 2005, Chevrier *et al.* 2011, Stayner *et al.* 2017, Migeot *et al.* 2013, Limousi *et al.* 2014, and Agopian *et al.* 2013b, 2013c.
[32] Swan *et al.* 2003

based on LH surge attenuation is protective of any potential non-cancer effect reported in the epidemiology data.

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. LH attenuation continues to be the most sensitive endpoint identified in the database, and would be protective of potential health outcomes associated with the chlorotriazines.

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

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

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

Life Stage	LH Hormone (NOAEL/LOAEL)	Apical Endpoint NOAEL/LOAEL
Pre-Natal (Fetus)		• 10/70 mg/kg/day; delays in ossification • 10/50 mg/kg/day; delayed PPS
Perinatal		• 6.25/12.5 mg/kg/day; increased prostatitis
Peripubertal		• 6.25/12.5 mg/kg/day; increased prostatitis, delayed PPS • 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 (26 week exposure)	• 1.8/3.65 mg/kg/day; disrupted cyclicity • 50/100 mg/kg/day; disrupted cyclicity

† After BMD analysis the BMDL/BMD @ 1 standard deviation = 2.56/4.92 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 atrazine residue chemistry database is robust. The exposure assessment for drinking water provides a conservative approach for estimating chlorotriazine 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). These assessments of exposure are not likely to underestimate the resulting estimates of risk from exposure to atrazine.

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 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[33] 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.

Atrazine 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-2013-0266).

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.[34]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

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

Plant and animal metabolism of atrazine is well understood. In general, atrazine is metabolized in plants through replacement of the chlorine-atom with either a hydroxy group or by a glutathione conjugate. This leads to three families of metabolites: the chlorinated metabolites, the 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 conjugate. All of the major modes of metabolism described above have been identified in plants and can be summarized as replacement of the chloro-atom with a hydroxy-group (hydrolytic dehalogenation), glutathione conjugation, and removal of either one or both of the N-alkyl groups (dealkylation). All routes leave the central triazine ring intact, and, since these modes exist in competition, all three families of metabolites (chloro-, hydroxy-, and glutathione conjugates) can exist in combination with each of the N-dealkylated forms. Metabolism by hydrolytic-dehalogenation dominates for residues absorbed through the roots while metabolism by glutathione conjugation dominates for residues absorbed through the foliage. Atrazine'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 atrazine are not produced in tissues of animals dosed with atrazine, per se. As in plants, all metabolic routes in the animal leave the central triazine ring intact.

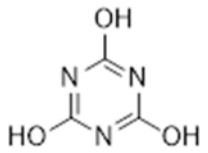
5.1.2 Summary of Environmental Degradation

Similar environmental degradation pathways are operative for all chlorotriazine herbicides, 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, atrazine use may result in ground or surface water contamination. Consequently, extensive water monitoring data have been collected for atrazine.

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

5.1.3 Comparison of Metabolic Pathways

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



Cyanuric Acid

Figure 5.1.3 Chemical Structure for Cyanuric Acid

5.1.4 Residues of Concern Summary and Rationale

The nature of the residue in plants and livestock is adequately understood for atrazine. Plant metabolism involves replacement of the chlorine with either a hydroxyl group or glutathione. Further metabolism occurs through dealkylation of the N-alkyl moieties attached to the triazine ring. Livestock metabolism is similar to plant metabolism, although dehalogenation to form hydroxy metabolites occurs to a lesser degree. Metabolic routes in plants and livestock leave the central triazine ring intact. As a result, atrazine parent plus its chlorinated and hydroxylated metabolites comprise the residues of concern for risk assessment. Risks are quantified separately for chloroatrazine and hydroxyatrazine residues, based on different toxicological endpoints. For tolerance enforcement, the residues of concern are atrazine 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 Atrazine Risk Assessment and Tolerance Expression.

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

[1] desethyl-s-atrazine (DEA), desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT). See Figure 3.1.1.
[2] hydroxyatrazine, desethylhydroxyatrazine (DEHA), desisopropylhydroxyatrazine (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 atrazine is considered complete for the purposes of Registration Review. Plant and livestock metabolism studies have successfully established the metabolic profile of atrazine, 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 tolerances for plant commodities. Further, adequate analytical methods are available for tolerance enforcement in plant and livestock commodities. Storage stability studies are adequate to support sample storage intervals from field trial studies. Processing studies indicate no residue concentration in processed corn, sorghum, sugarcane, or wheat

commodities. The current rotational crop restrictions are adequate. Rotational crop studies support addition of a 10-month plant back interval (PBI) for potato; vegetable, legume, group 6; and vegetable, foliage of legume, group 7. To support a 10-month PBI for crop group 7, a tolerance level of 0.50 ppm for inadvertent residues is recommended. Livestock feeding studies combined with dietary burden considerations indicate that limit of quantification (LOQ) level tolerances are appropriate for ruminant commodities while there is no reasonable expectation of finite residues in poultry or swine.

5.3 Water Residue Profile

Determination of EDWCs for the chlorotriazines (atrazine, propazine, and simazine) have been provided by the Environmental Fate and Effects Division (EFED) (J. Hetrick and M. Biscoe, D428938, 10/28/2015). The EDWCs were derived using a total toxic residue (TTR) approach and include all chlorotriazine residues of concern in drinking water from all the triazine uses [parent chlorotriazines (atrazine, simazine, and propazine), desisopropylatrazine (DIA), desethylatrazine (DEA), and diaminochlorotriazine (DACT)], referred to as TCT (total chlorotriazines). The TTR approach was also used for the hydroxytriazine residues of concern (hydroxysimazine, hydroxypropazine, hydroxyatrazine, desethylhydroxyatrazine (DIHA), desisopropylhydroxyatrazine (DIHA), and ammeline), referred to as THT (total hydroxytriazines). Separate ground water (monitoring data) and surface water (SWCC and FIRST modeling) concentrations were provided for TCT and THT for the daily peak (acute exposures), 4-day average (4-day exposures), and annual average (chronic exposures) for use in the individual triazine assessments (propazine, atrazine, and simazine) and for use in the cumulative triazine assessment. Since the EDWCs were based on total triazine residues, which include atrazine, propazine, and simazine, and all the related metabolites, and are not just based on atrazine and its chlorinated and hydroxylated metabolites, these EDWCs may be considered high-end estimates for the atrazine 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		
					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) atrazine and its chlorinated metabolites and 2) hydroxyatrazine and hydroxylated metabolites because of the different

toxicity endpoints 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 atrazine 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 assessments were partially refined, and incorporated residue levels from field trial studies, default processing factors, and assumed 100% of all crops with atrazine registrations are treated. The background dietary exposure assessment was also partially refined, and incorporated residue levels from field trial studies, default processing factors, and average percent crop treated data.

For the hydroxyatrazine 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 atrazine.

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

The toxicological PODs, uncertainty factors, and PADs for use in the dietary (food) risk assessments for atrazine are summarized in the tables below.

Table 5.4.2.1. Summary of Toxicological Doses and Endpoints for Atrazine for Use in Dietary (Food) 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 = 10 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1X	aRfD = 0.10 mg/kg/day aPAD = 0.10 mg/kg/day	Development study in rats & rabbit (weight of evidence from four studies) w/ atrazine Delayed ossification of certain cranial bones in fetuses (LOAEL = 70 mg/kg/day). Decreased body weight gain in adult (LOAEL = 70 mg/kg/day).
Acute Dietary (All Populations)	No toxic effect attributable to a single dose was identified for the general population.			
4-Day Infants <1 yr	3.06 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)
4-Day Children 1-2	3.24 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.11 mg/kg/day	

Table 5.4.2.1. Summary of Toxicological Doses and Endpoints for Atrazine for Use in Dietary (Food) Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure (POD)**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD for Risk Assessment**	**Study and Toxicological Effects**
4-Day Children 6-12	2.57 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.086 mg/kg/day	$BMDL_{1SD}$ = 2.42 mg/kg/day based on attenuation of LH surge. PODs for population subgroups indicated were derived via PBPK modeling.
4-Day Youth 13-19	2.33 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.078 mg/kg/day	
4-Day Females13-49	2.29 mg/kg/day	UF_A 3x UF_H 10x FQPA SF = 1X	4-day PAD = 0.076 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.

Table 5.4.2.2. Summary of Toxicological Doses and Endpoints for Hydroxyatrazines for Use in Acute and Chronic Dietary Human Health Risk Assessments.				
Hydroxyatrazine Exposure Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All Populations)	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 PAD = 0.0676 mg/kg/day	Combined chronic toxicity/carcinogenicity in the rat BMD_{10} = 7.72 mg/kg/day based on histopathological lesions of the kidney. LOAEL = 7.75; NOAEL = 1.00

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. LOAEL = lowest 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).

5.4.3 Percent Crop Treated Used in Dietary Assessment

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

The atrazine and its chlorinated metabolites chronic (background) assessment and the chronic hydroxyatrazine and hydroxylated metabolites assessment incorporated average percent crop treated estimates as provided by Biological and Economic Analysis Division (BEAD) (see Attachment 1 of D442826: Atrazine Screening Level Usage Analysis (SLUA), 8/11/2017). The following average percent crop treated estimates were used in the chronic dietary risk assessments for the following crops that are currently registered for atrazine: field corn: 60%; sweet corn: 70%; sorghum: 65%; sugarcane: 65%; and wheat: <1%.

5.4.4 Acute Dietary Risk Assessment

Atrazine 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 toxicological endpoint is delayed ossification in fetuses and is only applicable to females of reproductive age).

Hydroxyatrazine and its hydroxylated metabolites
A toxic effect attributable to a single dose was not found in the toxicity database; therefore, an acute endpoint has not been identified and 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.

Atrazine 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 risk is 3.0% of the 4-day population adjusted dose (4-day PAD) for children 1-2 years old, the most highly exposed population subgroup.

Hydroxyatrazine 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 hydroxyatrazine. The chronic dietary assessment is protective for any multi-day or long-term exposures.

5.4.6 Background and Chronic Dietary Risk Assessment

Atrazine 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 residues, default processing factors, and average percent crop treated data the chronic

DEEM module. The highest estimated food exposure is 0.000820 mg/kg/day for the children 1-2 years old population subgroup. (See Table 5.4.7.1 for exposure estimates for all population subgroups).

Hydroxyatrazine 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 0.000011 mg/kg/day for the children 1-2 years old population subgroup. This exposure level corresponds to < 1% cPAD for chronic exposures to hydroxyatrazine.

5.4.7 Cancer Dietary Risk Assessment

As atrazine 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 5.4.7.1. Summary of Dietary (Food only) Exposure and Risk for Atrazine and its Chlorinated Metabolites.

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	Dietary Exposure (mg/kg/day)	% 4dPAD	Dietary Exposure (mg/kg/day)
All Infants (< 1 year old)	N/A	N/A	0.10	0.002176	2.2	0.000337
Children 1-2 years old			**0.11**	**0.003336**	**3.0**	**0.000820**
Children 6-12 years old			0.086	0.001638	1.9	0.000377
Youth 13-19 years old			0.078	0.000918	1.2	0.000204
Females 13-49 years old	0.000741	< 1	0.076	0.000695	< 1	0.000144

[1]Highest exposure identified in bold.

Table 5.4.7.2. Summary of Chronic Dietary (Food Only) Exposure and Risk for Hydroxyatrazine and its Hydroxy Metabolites.

Population Subgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD
All Infants (< 1 year old)	0.000008	< 1
Children 1-2 years old	**0.000011**	**< 1**
Children 6-12 years old	0.000008	< 1
Youth 13-19 years old	0.000005	< 1
Females 13-49 years old	0.000004	< 1

[1]Highest exposure identified in bold.

6.0 Residential Exposure/Risk Characterization

There are no proposed residential uses at this time; however, there are existing residential uses that have been reassessed in this document to reflect updates to the atrazine PODs/UFs, HED's

2012 Residential SOPs[35], and to incorporate policy changes for body weight assumptions. The revision of residential exposures will impact the human health aggregate risk assessment for atrazine.

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.

In order to determine whether there are labels registered for use in residential areas that may be marketed for homeowner use, a query of EPA's Office of Pesticide Programs Information Network (OPPIN) system was conducted to identify those labels registered for use on various turf grasses that may be found in residential sites (e.g., bermudagrass, centipedegrass, St. Augustinegrass, and zoysiagrass). Based on this query, approximately 55 labels were identified[36]. These labels were evaluated with respect to PPE requirements. All liquid, WDG, and WSP labels required baseline attire (long sleeved shirts, long pants, shoes, and socks) and chemical resistant gloves, and were assumed to be marketed for commercial use. Some registered labels of granular formulations require occupational handlers to wear baseline attire; however, many registered granular labels do not require specific attire or PPE. Therefore, only granular products were assumed to be for use by residential handlers and these labels have been considered in the residential handler assessment for atrazine.

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

- Loading/applying granular formulations for application to turf via push-type rotary spreaders and belly grinders; and application via spoons, cups, and shaker cans.
- Application via hand was also evaluated because registered labels allow hand dispersal for spot applications.

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.

Application Rate: A summary of the registered application rates is provided in Table 3.3. Based on the labels evaluated, the maximum single application rate to turf is 2.2 lb ai/A (0.000051 lb

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

[36] The following use site codes were queried: 3330170216 [Bermudagrass (lawns) (soil treatment)], 330170217 [Bermudagrass (ornamental turf)(soil treatment)], 330230208 [Centipedegrass (lawns)(soil treatment)], 330230209 [Centipedegrass (ornamental turf)(soil treatment)], 330500206 [St. Augustinegrass (lawns)(soil treatment)], 330500207 [St. Augustinegrass (ornamental turf)(soil treatment)], 330560207 [Zoysiagrass (lawns)(soil treatment)], and 330560208 [Zoysiagrass (ornamental turf)(soil treatment)].

ai/ft^2). Most registered granular labels restrict application by hand; however, some labels allow hand dispersal for spot applications up to 2.0 lb ai/A (0.000046 lb ai/ft^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[37].

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 relevant; the 4-day assessment 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[38].

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

$$Total\ MOE = 1 \div [(1 \div Dermal\ MOE) + (1 \div Inhalation\ MOE)]$$

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
As shown below in Table 6.1.1, all of the residential handler combined (dermal + inhalation) risk estimates were not of concern (MOEs > LOC of 30), and ranged from 93 to 2,100,000.

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

Table 6.1.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Atrazine.										
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										
Granular Formulations via Push Type Rotary Spreader	30	0.81	0.0026	2.2 lb ai/A	0.5 A	0.013	2,300	0.000041	110,000	2,300
Granular Formulations via Belly Grinder		360	0.039	0.000051 lb ai/ft^2	1200 ft^2	0.32	93	0.000035	140,000	93
Granular Formulations via Spoon		6.2	0.087	0.000051 lb ai/ft^2	100 ft^2	0.00046	65,000	0.0000064	730,000	60,000
Granular Formulations via Cup		0.11	0.013	0.000051 lb ai/ft^2	100 ft^2	0.0000081	3,700,000	0.00000096	4,900,000	2,100,000
Granular Formulations via Hand Dispersal		160	0.38	0.000046 lb ai/ft^2	100 ft^2	0.011	2,800	0.000025	180,000	2,800
Granular Formulations via Shaker Can		0.11	0.013	0.000051 lb ai/ft^2	100 ft^2	0.0000081	3,700,000	0.00000096	4,900,000	2,100,000

1 See Table 3.3. Based on the labels evaluated, the maximum single application rate to turf is 2.2 lb ai/A (0.000051 lb ai/ft^2). Most labels restrict application by hand; however some labels allow hand dispersal for spot applications up to 2.0 lb ai/A (0.000046 lb ai/ft^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 (29.78 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 (4.67 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 atrazine. The quantitative exposure/risk assessment for residential post-application exposures is based on dermal and incidental oral exposure to turf following liquid, DF/WDG, WSP and granular applications.

Ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning rather than short-term residue exposure. Therefore, an acute dietary dose is used to estimate exposure and risk resulting from episodic ingestion of granules. However, a POD for acute/episodic granular ingestion was not selected for atrazine. The acute dietary endpoint for females 13-49 was selected from an atrazine developmental toxicity study based on delayed ossification of certain cranial bones in fetuses. This endpoint is not applicable to children 1 to < 2 years old (the index lifestage considered for episodic ingestion), and no other single dose effects were seen in the atrazine database; therefore, a POD for episodic granular ingestion of atrazine was not selected and an episodic granular ingestion assessment was not conducted.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[39]. 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[40].

Application Rate: The maximum single application rate for each formulation is listed in Table 3.3.

Exposure Duration: Residential exposures to treated turf are expected to be short-term in duration. However, as mentioned earlier, for the chlorotriazine herbicides, only 4-day exposure durations are applicable. Therefore, for the purposes of the residential risk assessments, only the 4-day duration is relevant.

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

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

Turf Transferrable Residues[41]*:* Chemical-specific turf transferrable residue (TTR) data have been submitted for atrazine using both dry flowable and granule formulations. Both TTR studies were reviewed and found to be acceptable for risk assessment (K. Rickard, D443002, 09/26/2017 and K. Rickard, D443647, 09/26/2017). The predicted day 0 residues were adjusted in the post-application assessment for any differences between the study application rate and the registered application rates for atrazine. Then, a 4-day average residue (0.180 µg/cm^2 and 0.096 µg/cm^2) 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. Details can be found in the occupational and residential exposure assessment (K. Rickard, D428609, 06/12/2018).

Table 6.2.1. Review of Dissipation of Turf Transferrable Residues (Dry Flowable) of Atrazine on Turf (MRID No. 44958001).

Statistic	Atrazine 90 DF (North Carolina) 0-21 DAT [Excluding 12 hour Samples]	Atrazine 90 DF (Georgia) 0-21 DAT
Application Rate (lb ai/A)	1.96 (0.72 oz. ai/1000 ft^2)	
Measured Average Day 0 Residue (µg/cm^2)	0.2188	0.1824
Predicted Day 0 Residue (µg/cm^2)	**0.226**	0.155
Slope	-0.181	-0.044
Half-Life (days)	3.8	15.7
R^2	0.9009	0.2305
4-Day Average Residue (µg/cm^2) – 0DAT – 3DAT	**0.180**	0.148

Table 6.2.2. Summary Statistics for Turf Transferrable Residues of Atrazine on Turf (MRID 44958801, D443647).

Statistic	Florida		Georgia	
	Irrigated	Non-Irrigated	Irrigated	Non-Irrigated
Application Rate (lb ai/A)	2.0 lb ai/A			
Measured Average Day 0 Residue (µg/cm^2)	0.0744	0.1622	0.117	0.0585
Predicted Day 0 Residue (µg/cm^2)	0.013	**0.117**	0.009	0.026
Slope	-0.120	-0.141	-0.076	-0.100
Half-Life (days)	5.8	4.9	9.1	6.9
R^2	0.7665	0.9338	0.7383	0.9091
4-Day Average Residue (µg/cm^2) - 0DAT – 3DAT	0.011	**0.096**	0.008	0.023

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[42].

Combining Exposure and Risk Estimates

[41] A chemical-specific study measuring the transfer efficiency of granular atrazine residues from turf to dry and wetted palms is available and was reviewed for ethical requirements (MRID 45622310). These data could be used to refine the fraction of application rate available for transfer from treated turf (1.1% found in the study) to hands if chemical-specific TTR data are not available. However, chemical-specific TTR data are available for granular atrazine formulations and have been incorporated into the residential post-application assessment. The TTR of 0.13 µg/cm^2 (when adjusted for the registered application rate of 2.2 lb ai/A) represents a more refined input to the exposure assessment than if the hand press data had been used to derive the fraction of application rate available for transfer.

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

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 these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each 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

Atrazine-specific TTR data are available for granular and dry flowable formulations of atrazine. These data were incorporated into the residential post-application assessment for evaluating exposures to turf treated with liquid and granular formulations of atrazine.

Using the available chemical-specific data, there are post-application dermal and combined (dermal + incidental oral) risk estimates of concern from the registered use of atrazine on residential turf for children 1 to < 2 years old. There are no dermal risk estimates of concern for all subpopulations(MOEs > LOC of 30); and no incidental oral risk estimates of concern for children 1 to < 2 years old (MOEs > LOC of 30). The combined (dermal + incidental oral) MOEs for children 1 to < 2 years old ranged from 28 to 49 (LOC = 30) on the day of application, depending on the formulation and assuming the maximum registered application rate. The dermal MOEs for adults, children 11 to < 16, children 6 to < 11 ranged from 42 to 3,600 on the day of application.

Because risk estimates of concern were identified 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 1.8 lb ai/A on residential turf results in no risk estimates of concern for children 1 to < 2 years old.

Table 6.2.3.1. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Atrazine.

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
		Activity	Route of Exposure					
Adult	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0552	540		
		Golfing after Granular Application		2.2 lb ai/A	0.0324	910		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.0143	2,100		
		Mowing after Granular Application		2.2 lb ai/A	0.0084	3,500		
	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	0.703	42		
		High Contact Activities after Granular Application		2.2 lb ai/A	0.459	65		
Children 11 to < 16 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0555	550		
		Golfing after Granular Application		2.2 lb ai/A	0.0326	930		

Table 6.2.3.1. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Atrazine.

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
		Activity	Route of Exposure					
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.142	2,100		
		Mowing after Granular Application		2.2 lb ai/A	0.0083	3,600		
Children 6 to < 11 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0651	520		
		Golfing after Granular Application		2.2 lb ai/A	0.0383	880		
Children 1 to < 2 Years Old	Turf Treated with Sprays [Using 4-day average TTR (0.180 µg/cm^2)]	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	1.20	36	X	**28**
			Hand-to-Mouth		0.0246	130	X	
			Object-to-Mouth		0.000747	4,400		
			Soil Ingestion		0.0000677	49,000		
	Turf Treated with Sprays [Using 4-day average TTR (0.180 µg/cm^2)]	High Contact Activities after Spray Application	Dermal	1.8 lb ai/A[5]	1.08	40	X	31
			Hand-to-Mouth		0.0221	150	X	
			Object-to-Mouth		0.000673	4,900		
			Soil Ingestion		0.0000339	98,000		
	Turf Treated with Granules	High Contact Activities after Granular Application	Dermal	2.2 lb ai/A	0.778	55	X	49
			Hand-to-Mouth		0.00717	460	X	
			Object-to-Mouth		0.000439	7,600		
			Soil Ingestion		0.0000745	45,000		

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). PODs are summarized 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 6.2, some exposure scenarios on treated turf resulted in risk estimates of concern for children. Therefore, the scenarios resulting from liquid atrazine 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. Reducing the application rate results in no risk estimates of concern for children 1 to < 2 years old.

Of the remaining residential exposure scenarios, only the most conservative, or worst-case, residential adult and child scenarios have been selected to be included in the aggregate risk assessment; however, because the spray formulation results in risk estimates of concern for children, the granular exposure scenario resulting in the highest risk estimates for adults is also presented. Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for atrazine:

- Adults: post-application dermal exposures from high contact lawn activities following spray applications to turf.

- Children 11 to < 16 years old: post-application dermal exposures from golfing following a spray application to turf.
- Children 6 to < 11 years old: post-application dermal exposures from golfing following a spray application to turf.
- Children 1<2 years old: dermal + hand-to-mouth exposures from post-application high contact lawn activities following granular applications to turf.

Table 6.3.1. Recommendations for the Residential Exposures for the Atrazine Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adults	Post-Application High Contact Activities after Granular Applications	0.459	N/A	N/A	0.459	65	N/A	N/A	65
	Post-Application High Contact Activities after Spray Applications	0.703			0.703	42			42
Children 11 to < 16 Years Old	Golfing after Spray Application	0.0555			0.0555	550			550
Children 6 to < 11 Years Old	Golfing after Spray Application	0.0651			0.0651	520			520
Children 1 to < 2 Years Old	High Contact Activities after Granular Application	0.778		0.00717	0.78	55		460	49

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/Inhalation 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 atrazine aggregate assessment are acute and 4-day. The duration of exposure identified for hydroxyatrazine 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 compared to the estimated concentrations in drinking water (EDWCs; see Table 5.3). 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 propazine, simazine, 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 U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) 2003-2008 consumption database, making use of the appropriate analysis settings and percentiles.

For the atrazine 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, but the PODs are different for food, drinking water, and residential exposures. This entailed calculating the allowable 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 aggregate 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

Atrazine

The acute aggregate assessment considers food and water exposures. The acute DWLOC for females 13-49 years old is 1800 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- Atrazine.

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]
Female 13-49	10	100	0.1	0.0544	--	0.000741	1800

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

[2]Table 5.4.6.1.
[3]DWLOC = [(aPAD – Food Exposure)]/[water consumption (L/kg) * 0.001 mg/ug]

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

7.2 Four-Day Aggregate Risk

Atrazine
The 4-day aggregate risk assessments determined the DWLOCs based on background dietary exposures from food (Table 5.4.6.1) and exposures from residential turf uses of atrazine (See Table 6.3.1 and 6.3.2 for selected turf scenarios). DWLOCs were calculated for infants, children, youths, and adults. DWLOCs are then compared to the EDWCs (Table 5.3).

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 children 1-2 years old (granular turf use) at 650 ppb. The highest 4-day EDWC is 585 ppb based on ground water modeling.

This aggregate assessment excluded the residential post-application exposures for children 1-2 years old from playing on turf sprayed with atrazine since combined dermal and oral exposures were of concern when assuming the maximum labeled rate for spray applications (2.0 lb ai/A). However, a screening aggregate assessment was performed for this scenario assuming that the application rate for turf spray is reduced to 1.2 lb ai/A. This results in a 4-day DWLOC of 610 ppb for children 1-2 years old, which would not be of risk concern.

Table 7.2.1 Atrazine 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	4-Day POD For Drinking Water (ppb)[4]	4-Day DWLOC[5] (ppb)
Infants <1 Year Old	NA	30	9100	NA	NA	NA	2.12E+04	700
Children 1 to < 2 Years Old	High Contact Activities after ***Granular*** Application	30	4000	55	460		5.14E+04	650
Children 6 to < 11 Years Old	Golfing after ***Spray*** Application	30	6800	520	NA		1.19E+05	3,700
Children 11 to < 16 Years Old	Golfing after ***Spray*** Application	30	11000	550			7.72E+04	2,400
Adult	High Contact Activities after	30	16000	65			9.22E+04	1,600

Table 7.2.1 Atrazine 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**	**4-Day POD For Drinking Water (ppb)[4]**	**4-Day DWLOC[5] (ppb)**
	Granular Applications							
	High Contact Activities after ***Spray*** Applications			42				870

[1] **Food:** $MOE_{food} = POD_{food}$ (from Table 4.6.2.4.2.2)/ *Background* Food Exposure (from Table 5.4.7.1).
[2] **Dermal:** MOE_{dermal} (from Table 6.3.1).
[3] **Oral:** MOE_{oral} (from Table 6.3.1).
[4] **POD** from Table 4.6.2.4.2.2.
[5] **DWLOC:** DWLOC ppb= POD_{water} ppb /$MOE_{water;}$; Where $MOE_{water} = 1/ [(1/MOE_{agg}) – ((1/MOE_{food}) + (1/MOE_{dermal}) + (1/MOE_{oral}))]$; Where MOE_{agg} =LOC (30).

7.3 Chronic Aggregate Risk

Atrazine
The 4-day aggregate risk assessments (Section 7.2) are protective for chronic aggregate exposure 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.

Hydroxyatrazine
The chronic aggregate risk assessment for the hydroxyatrazine considers food and water exposures. No residential exposures to the hydroxyatrazine metabolites are expected from the atrazine uses. The lowest chronic DWLOC for hydroxyatrazine is for all infants (<1 year old) at 1200 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- Hydroxyatrazine.							
Age(years) /Population	**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]**
<1	6.76	100	0.0676	0.0540	--	0.000008	1200
1-2	6.76	100	0.0676	0.0302	--	0.000011	2200
6-11	6.76	100	0.0676	0.0184	--	0.000008	3600
11-16	6.76	100	0.0676	0.0153	--	0.000005	4400
Adult	6.76	100	0.0676	0.0209	--	0.000004	3200

[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 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for atrazine.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

A quantitative spray drift assessment was conducted for atrazine 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[43]. Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of atrazine. 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*

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

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[44,45]. 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. Atrazine is used on a variety of agricultural and non-agricultural areas and can be applied via ground and aerial equipment (airblast application is not expected). The recommended drift scenario screening level options are listed below:

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

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event)[46].

A 4-day average residue was used to estimate risk from contact with treated turf because the POD is based on decreased LH surge; and available toxicity data indicate that the decrease occurs after a 4-day exposure. The applicable LOC for adult and children non-occupational spray drift exposures is an MOE of 30. Dermal and incidental oral risk estimates were combined for children 1 to < 2 years old because the toxicity endpoint for each route of exposure is the

[44] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift
[45] 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.
[46] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

same. Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. There were no dermal risk estimates of concern at the field edge for adults following applications to all registered crops at the maximum registered application rates and assuming screening-level droplet sizes and boom heights as noted above (MOEs > 30). The dermal MOEs for adults range from 95 to 1,000 at the field edge assuming screening-level droplet sizes and boom heights (LOC = 30). There were no combined (dermal + incidental oral) risk estimates of concern at the field edge for children 1 to < 2 years old, assuming maximum registered application rates and screening-level droplet sizes and boom heights (MOEs > 30). At the field edge, combined (dermal + incidental oral) MOEs ranged from 55 to 600 with screening-level droplet sizes and boom heights (LOC = 30).

The impact of changing nozzle types resulting in coarser sprays, which drift less, reduces risks from aerial applications. Similarly, using coarser sprays and lowering boom height for groundboom sprayers or applications to denser crop canopies with airblast sprayers lowers risk concerns.

Table 9.1. Summary of Spray Drift Risk Estimates Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Atrazine[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
Sugarcane, Sod, Macadamia Nuts (ground only), Guava, Conifers (ground only)	4.0	0	95	130	N/A	55	76	N/A
Fallow Crop Lands	2.25	0	170	230		98	130	
Corn, Sorghum, Roadsides, Conservation Reserve Program Areas	2	0	190	260		110	150	
Winter Weed Control, Roadsides	1	0	380	520		220	300	
Fallow Crop Lands	0.5	0	760	1,000		440	600	

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 D428609. "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 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)[47] and conducting cumulative risk assessments (CRA)[48]. A separate updated CRA with atrazine, simazine, propazine, and their common metabolites is available (K. Rickard *et al.*, D447476, 07/10/2018). Propazine is included in the CAG based on the potential for food and drinking water exposures from the currently registered domestic use on sorghum.

11.0 Occupational Exposure/Risk Characterization

11.1 Occupational Handler Exposure and Risk Estimates

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

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios listed in Table 11.1.

Occupational Handler Exposure Data and Assumptions

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

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

[47] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[48] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

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[49]", 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[50].

For the dry bulk fertilizer scenarios, HED assumed a closed mixing/loading scenario for commercial impregnation of dry bulk fertilizer. For all applications of dry bulk fertilizer, HED assumed the use of an open-cab spreader.

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

HED does not have data regarding the mixing/loading or the application of atrazine-impregnated dry bulk fertilizer. The mixing/loading processing rate for commercial impregnation of dry bulk fertilizer has been estimated to be 500 tons of fertilizer processed per 8-hour day based on information found on the registered atrazine labels. Application of dry bulk fertilizer was assessed assuming application to up to 320 acres/day for commercial equipment based on information supplied by a registrant concerning the chemical alachlor (as referenced in its reregistration eligibility document (RED) document[51]).

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

For atrazine, based on the registered uses, both short- and intermediate-term exposures are expected for occupational handlers. As mentioned earlier, however, currently available toxicity data indicate that a 4-day exposure is sufficient to elicit a decrease of the LH surge in rats, and this is the length of the estrous cycle in rats and also the exposure duration needed for the triazines to reach a pseudo steady-state. Therefore, for the purposes of the occupational risk assessments, only the 4-day duration is relevant, and is protective for longer durations of exposure.

[49] Available: https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[50] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[51] http://archive.epa.gov/pesticides/reregistration/web/pdf/0063fact.pdf

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: Registered atrazine labels vary with respect to required attire and PPE. HED reviewed a subset of the 190 registered atrazine labels for PPE requirements. Of the liquid, WDG, and WSP labels evaluated, all required baseline attire (long sleeved shirts, long pants, shoes, and socks) and chemical resistant gloves; and most required additional PPE for some activities (e.g., coveralls and/or a National Institutes for Occupational Safety and Health (NIOSH) dust/mist respirator). Applicators and other handlers of dry bulk fertilizers impregnated with atrazine must wear baseline attire. Some registered labels of granular formulations require occupational handlers to wear baseline attire; however, many registered labels have no attire or PPE requirements.

Most registered labels for liquid formulations require:

- Mixer/loader/applicators and flaggers to wear baseline attire, and chemical resistant gloves; and a chemical resistant apron when cleaning up spills or otherwise exposed to the concentrate.
- Applicators using spray equipment on their backs to wear baseline attire, coveralls, chemical resistant gloves, and chemical resistant footwear.
- Mixer/loaders supporting aerial applications at application rates $\geq$ 3.0 lb ai/A must use a closed system.
- Pilots must use an enclosed cockpit and wear the PPE required for applicators without chemical resistant gloves.
- Flaggers must use enclosed cabs.

Most registered labels for WDG formulations require:

- Mixer/loaders or cleaners of equipment/spills and other handlers exposed to the concentrate to wear baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, a chemical resistant apron, and a NIOSH dust/mist respirator.
- Applicators using spray equipment on their backs must wear baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, and goggles or a face shield.
- All other applicators and handlers exposed to the dilute formulations to wear baseline attire and chemical resistant gloves.

The registered WSP label (EPA Reg. No. 5905-522) requires:

- Mixer/loaders/Cleaners of equipment or spills/Other handlers exposed to the concentrate to wear: baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, a chemical resistant apron, and a NIOSH dust/mist respirator.
- Applicators using spray equipment on backs must wear baseline attire, coveralls, chemical resistant gloves, chemical resistant footwear, and goggles or a face shield.
- All other applicators and handlers must wear baseline attire, and chemical resistant gloves.

Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Liquid, DF/WDG, and spray formulations were evaluated assuming baseline attire and chemical resistant gloves, the lowest amount of PPE consistently required on all registered labels evaluated, and

any additional PPE/mitigation required to result in risk estimates not of concern. Granular formulations were evaluated assuming baseline attire and any additional PPE/mitigation required to result in risk estimates not of concern. WSP formulations are considered an engineering control.

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 D428609 (K. Rickard, 06/12/2018).

Combining Exposures/Risk Estimates:
Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. 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
Some combined (dermal + inhalation) occupational handler scenarios resulted in risk estimates of concern assuming baseline attire and chemical resistant gloves, the lowest amount of PPE consistently required on all registered labels evaluated. Assuming baseline attire and chemical resistant gloves, the occupational handler (dermal + inhalation) MOEs ranged from 2.3 to 820.

Dermal exposures were the highest contributors to all scenarios resulting in combined (dermal + inhalation) risk estimates of concern assuming baseline attire and the PPE consistently required across all reviewed atrazine labels. The following scenarios were of concern:

- Mixing/loading DF/WDG formulations for aerial application to sorghum and CRP areas (2.0 lb ai/A).
    - *This scenario is still **of concern** with engineering controls.*
- Mixing/loading DF/WDG formulations for aerial application to fallow areas (0.5 lb ai/A).
    - *This scenario is not of concern with the addition of a PF5 respirator.*
- Mixing/loading DF/WDG formulations for groundboom application to sugarcane (4.0 lb ai/A); corn and CRP areas (2.0 lb ai/A); and fallow areas (2.25 lb ai/A).
    - *These scenarios are not of concern with the addition of a PF5 respirator.*
- Mixing/loading liquid formulations for aerial application to corn, sorghum, winter weed control, and CRP areas (2.0 lb ai/A); fallow areas (2.25 lb ai/A), and sugarcane (4.0 lb ai/A).
    - *These scenarios are not of concern with engineering controls.*
- Mixing/loading liquid formulation for impregnated dry bulk fertilizer application to corn, sorghum, and bioenergy crops (20 lb ai/ton).
    - *This scenario **is still of concern** with engineering controls.*
- Mixing/loading WSP formulations for aerial application to guava (4.0 lb ai/A); sod (4.0 lb ai/A); corn, sorghum, winter weed control, and CRP areas (2.0 lb ai/A); fallow (2.25 lb ai/A); and sugarcane (4.0 lb ai/A).
    - *These scenarios are **still of concern** with engineering controls.*
- Applying sprays via mechanically pressurized handgun equipment to roadsides (0.2 lb ai/gal).

  - *This scenario is **still of concern** with the addition of a double layer of clothing and PF10 respirator.*
- Mixing/loading/applying DF/WDG and liquid formulations via backpack spray equipment to macadamia nuts (0.4 lb ai/gal) and conifers (0.4 lb ai/gal).
  - *These scenarios are not of concern with the addition of a double layer of clothing.*
- Mixing/loading/applying DF/WDG and liquid formulations via backpack spray equipment to landscape turf (broadcast only) (0.133 lb ai/gal).
  - *These scenarios are **still of concern** with the addition of a double layer of clothing and PF10 respirator.*
- Mixing/loading/applying DF/WDG, liquid, and WSP formulations via mechanically pressurized handgun spray equipment to macadamia nuts (0.4 lb ai/gal), sweet corn (0.2 lb ai/gal), and guava (0.2 lb ai/gal).
  - *These scenarios are **still of concern** with the addition of a double layer of clothing and PF10 respirator.*
- Mixing/loading/applying WSP formulations via backpack spray equipment to macadamia nuts (0.4 lb ai/gal), landscape turf (broadcast) (0.067 lb ai/gal), and conifers (0.4 lb ai/gal).
  - *These scenarios are not of concern with the addition of a double layer of clothing.*
- Loading/applying DF/WDG and liquid, formulations for backpack spray applications to roadsides (0.2 lb ai/gal).
  - *These scenarios are **still of concern** with the addition of a double layer of clothing and PF10 respirator.*
- Loading/applying WSP formulations for backpack spray applications to roadsides (0.1 lb ai/gal).
  - *These scenarios are not of concern with the addition of a double layer of clothing and PF5 respirator.*

Therefore, the following scenarios are **of concern** when assuming the maximum available PPE and/or engineering controls:

- Mixing/loading DF/WDG formulations for aerial application to sorghum and CRP areas (2.0 lb ai/A).
- Mixing/loading liquid formulation for impregnated dry bulk fertilizer application to corn, sorghum, and bioenergy crops (20 lb ai/ton).
- Mixing/loading WSP formulations for aerial application to guava (4.0 lb ai/A); sod (4.0 lb ai/A); corn, sorghum, winter weed control, and CRP areas (2.0 lb ai/A); fallow (2.25 lb ai/A); and sugarcane (4.0 lb ai/A).
- Applying sprays via mechanically pressurized handgun equipment to roadsides (0.2 lb ai/gal).
- Mixing/loading/applying DF/WDG and liquid formulations via backpack spray equipment to landscape turf (broadcast only) (0.133 lb ai/gal).
- Mixing/loading/applying DF/WDG, liquid, and WSP formulations via mechanically pressurized handgun spray equipment to macadamia nuts (0.4 lb ai/gal), sweet corn (0.2 lb ai/gal), and guava (0.2 lb ai/gal).
- Loading/applying DF/WDG and liquid, formulations for backpack spray applications to roadsides (0.2 lb ai/gal).

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

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

Water-soluble packaging is an engineering control designed to prevent direct contact between users and the pesticide formulation in the packages, thereby reducing exposures. Users place the packets into water which dissolves the packaging, releasing the formulation into the water without exposure to significant dusts or liquid aerosols. The formulation within the packaging then mixes with the water so it can be applied as a liquid spray.

This risk assessment relies on a 2015 study by the Agricultural Handler Exposure Task Force (AHETF) that measured dermal and inhalation exposure for workers who mixed and loaded water-soluble packet pesticide products. This data is considered the most reliable data for conducting exposure and risk assessments for such products. During the initial stages of the AHETF field study, the AHETF identified work practices that the Agency agreed were inconsistent with the use of water-soluble packaging as an engineering control intended to reduce exposures. For example, AHETF observed that some workers placed the packets in removable baskets hanging from the open tank hatch and used streams of water from hoses or overhead recirculation systems as agitation methods to break open and dissolve the packaging, resulting in visible and substantial amounts of airborne powder and/or liquid aerosol where the mixer/loader was working. Current labels, including those under consideration in this risk assessment, are silent or unclear on the use of baskets in the hatch and methods of agitation.

The AHETF, in consultation with the Agency, California's Department of Pesticide Regulation (CDPR) and the Canadian Pest Management Regulatory Agency (PMRA), drafted a set of best practices for handling and adding water-soluble packets to spray tanks. The resulting AHETF "mixing/loading water-soluble packet" dataset excludes monitoring results for activities inconsistent with these practices. Commensurate with use of the new dataset, the Agency has since formatted those best practices into label language to be included on all water-soluble packet pesticide products. This revised language ensures that users know water-soluble packets are intended to dissolve in water via mechanical agitation and not to rupture them via streams of water or other means. In order to achieve the intended benefits from proper use of water-soluble

packaging, these best practices should be incorporated directly on product labels, conflicting language should be removed from the same labels, and users should receive effective and timely training on the new procedures.

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
Mixer/Loader						
Water Soluble Packets for Backpack Sprayer and Mechanically Pressurized Handgun Application	Roadsides	0.1 lb ai/gal	1,000 gals	1,600 [EC]	480 [EC]	370 [EC]
Liquids for Backpack Sprayer and Mechanically Pressurized Handgun Application	Roadsides	0.2 lb ai/gal		270 [SL/G]	2,800 [No R]	250 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations for Backpack Sprayer or Mechanically Pressurized Handgun Application	Roadsides	0.2 lb ai/gal		200 [SL/G]	69 [No R]	51 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations for Aerial Applications	Sorghum, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	**17 [SL/G]** **21 [DL/G]** 68 [EC]	5.8 [No R] **29 [PF5]** 58 [PF10] **20 [EC]**	**4.3 [SL/G, No R]** **11 [SL/G, PF5]** **13 [SL/G, PF10]** **15 [DL/G, PF10]** **15 [EC]**
	Fallow	0.5 lb ai/A	1,200 A	66 [SL/G]	**23 [No R]** 110 [PF5]	**17 [SL/G, No R]** 41 [SL/G, PF5]
Dry Flowable/Water Dispersible Granular Formulations for Groundboom Applications	Sod	4.0 lb ai/A	80 A	120 [SL/G]	43 [No R]	32 [SL/G, No R]
	Macadamia Nuts	4.0 lb ai/A	40 A	250 [SL/G]	87 [No R]	65 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	250 [SL/G]	87 [No R]	65 [SL/G, No R]
	Corn, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	99 [SL/G]	35 [No R] 170 [PF5]	**26 [SL/G, No R]** 63 [SL/G, PF5]
	Fallow	2.25 lb ai/A	200 A	200 [SL/G]	69 [No R]	51 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	200 A	88 [SL/G]	31 [No R] 150 [PF5]	**23 [SL/G, No R]** 55 [SL/G, PF5]
Liquids for Aerial Application	Guava	4.0 lb ai/A	350 A	50 [SL/G]	**17 [No R]** 87 [PF5]	**13 [SL/G, No R]** 32 [SL/G, PF5]
	Sod	4.0 lb ai/A	350 A	39 [SL/G]	400 [No R]	36 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	350 A	39 [SL/G]	400 [No R]	36 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	78 [SL/G]	810 [No R]	71 [SL/G, No R]

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Fallow	2.25 lb ai/A	1,200 A	**23 [SL/G]** **29 [DL/G]** 99 [EC]	240 [No R] 1200 [PF5] 2400 [PF10] 630 [EC]	**21 [SL/G, No R]** **23 [SL/G, PF5]** **23 [SL/G, PF10]** **29 [DL/G, PF10]** 86 [EC]
	Sugarcane	4.0 lb ai/A	1,200 A	**20 [SL/G]** **26 [DL/G]** 88 [EC]	210 [No R] 1100 [PF5] 2100 [PF10] 550 [EC]	**18 [SL/G, No R]** **20 [SL/G, PF5]** **20 [SL/G, PF10]** **26 [DL/G, PF10]** 76 [EC]
Liquids for Impregnated Dry Bulk Fertilizer Application – Commercial	Corn, Sorghum, Bioenergy Crops	20 lb ai/ton	500 tons	**11 [SL/G]** **15 [DL/G]** 50 [EC]	120 [No R] 590 [PF5] 1200 [PF10] 310 [EC]	**10 [SL/G, No R]** **11 [SL/G, PF5]** **11 [SL/G, PF10]** **15 [DL, PF10]** 43 [EC]
Liquids for Groundboom Application	Sod	4.0 lb ai/A	80 A	**24 [EC]**	150 [EC]	**21 [EC]**
	Macadamia Nuts, Guava	4.0 lb ai/A	40 A	170 [SL/G]	1,800 [No R]	160 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	340 [SL/G]	3,600 [No R]	310 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	340 [SL/G]	3,600 [No R]	310 [SL/G, No R]
	Fallow	2.25 lb ai/A	200 A	140 [SL/G]	1,400 [No R]	130 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	200 A	120 [SL/G]	1,300 [No R]	110 [SL/G, No R]
Water Soluble Packets for Aerial Application	Guava	4.0 lb ai/A	350 A	68 [SL/G]	710 [No R]	62 [SL/G, No R]
	Sod	4.0 lb ai/A	350 A	120 [EC]	34 [EC]	**26 [EC]**
	Sweet Corn	2.0 lb ai/A	350 A	120 [EC]	34 [EC]	**26 [EC]**
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	230 [EC]	68 [EC]	52 [EC]
	Fallow	2.25 lb ai/A	1,200 A	68 [EC]	**20 [EC]**	**15 [EC]**

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Sugarcane	4.0 lb ai/A	1,200 A	**61 [EC]**	**18 [EC]**	**14 [EC]**
Water Soluble Packets for Groundboom Application	Sod	4.0 lb ai/A	80 A	**34 [EC]**	**9.9 [EC]**	**7.7 [EC]**
	Guava	4.0 lb ai/A	40 A	510 [EC]	150 [EC]	120 [EC]
	Sweet Corn	2.0 lb ai/A	80 A	1,000 [EC]	300 [EC]	230 [EC]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	1,000 [EC]	300 [EC]	230 [EC]
	Fallow	2.25 lb ai/A	200 A	410 [EC]	120 [EC]	93 [EC]
	Sugarcane	4.0 lb ai/A	200 A	360 [EC]	110 [EC]	84 [EC]
Applicator						
Sprays via Aerial Equipment	Guava	4.0 lb ai/A	350 A	700 [EC]	18,000 [EC]	670 [EC]
	Sod	4.0 lb ai/A	350 A	700 [EC]	18,000 [EC]	670 [EC]
	Sweet Corn	2.0 lb ai/A	350 A	1,400 [EC]	36,000 [EC]	1,300 [EC]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	410 [EC]	11,000 [EC]	400 [EC]
	Fallow	2.25 lb ai/A	1,200 A	360 [EC]	9,400 [EC]	350 [EC]
	Sugarcane	4.0 lb ai/A	1,200 A	200 [EC]	5,300 [EC]	190 [EC]
Sprays via Groundboom Equipment	Sod	4.0 lb ai/A	80 A	400 [SL/G]	1,100 [No R]	290 [SL/G, No R]
	Macadamia Nuts, Guava	4.0 lb ai/A	40 A	790 [SL/G]	2,300 [No R]	590 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	790 [SL/G]	2,300 [No R]	590 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	320 [SL/G]	910 [No R]	240 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	200 A	160 [SL/G]	460 [No R]	120 [SL/G, No R]
	Fallow	2.25 lb ai/A	200 A	280 [SL/G]	810 [No R]	210 [SL/G, No R]
Sprays via Mechanically Pressurized Handgun	Roadsides	0.2 lb ai/gal	1,000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]**

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
						7.4 [DL/G, PF10]
Sprays via Tractor Drawn Spreader – Commercial Application of Dry Bulk Fertilizer	Corn	2.0 lb ai/A	320 A	320 [SL]	160 [No R]	110 [SL/G, No R]
Flagger						
To Support Aerial Applications	Guava	4.0 lb ai/A	350 A	120 [SL/G]	250 [No R]	81 [SL/G, No R]
	Sod	4.0 lb ai/A	350 A	120 [SL/G]	250 [No R]	81 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	350 A	240 [SL/G]	510 [No R]	160 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	350 A	240 [SL/G]	510 [No R]	160 [SL/G, No R]
	Fallow	2.25 lb ai/A	350 A	220 [SL/G]	450 [No R]	150 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	350 A	120 [SL/G]	250 [No R]	81 [SL/G, No R]
Mixer/Loader/Applicator						
Dry Flowable/Water Dispersible Granular Formulations via Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Conifers [Ground Directed]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	**13 [SL/G]** **23 [DL/G]**	340 [No R] 1,700 [PF5] 3,400 [PF10]	**13 [SL/G, No R]** **13 [SL/G, PF5]** **13 [SL/G, PF10]** **23 [DL/G, PF10]**
	Landscape Turf [Spot]	0.133 lb ai/gal	40 gals	47 [SL/G]	9,000 [No R]	47 [SL/G, No R]
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	31 [SL/G]	6,000 [No R]	31 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations via Manually Pressurized Handwand Spray Equipment	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	890 [SL/G]	780 [No R]	420 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations via Mechanically Pressurized	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**2.5 [SL/G]** **3.8 [DL/G]**	36 [No R] 180 [PF5]	**2.3 [SL/G, No R]** **2.5 [SL/G, PF5]**

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
Handgun Spray Equipment					360 [PF10]	**2.5 [SL/G, PF10]** **3.8 [DL/G, PF10]**
	Landscape Turf [Broadcast]	2.0 lb ai/A	5 A	150 [SL/G]	300 [No R]	100 [SL/G, No R]
	Sweet Corn [Ground Directed]	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**
Liquid Formulations via Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Conifers [Broadcast]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	**13 [SL/G]** **23 [DL/G]**	340 [No R] 1,700 [PF5] 3,400 [PF10]	**13 [SL/G, No R]** **13 [SL/G, PF5]** **13 [SL/G, PF10]** **23 [DL/G, PF10]**
	Landscape Turf [Spot]	0.133 lb ai/gal	40 gals	47 [SL/G]	9,000 [No R]	47 [SL/G, No R]
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	31 [SL/G]	6,000 [No R]	31 [SL/G, No R]
Liquid Formulations for Manually Pressurized Spray Equipment	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	890 [SL/G]	780 [No R]	420 [SL/G, No R]
Liquid Formulations for Mechanically Pressurized Handgun Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**2.5 [SL/G]** **3.8 [DL/G]**	36 [No R] 180 [PF5] 360 [PF10]	**2.3 [SL/G, No R]** **2.5 [SL/G, PF5]** **2.5 [SL/G, PF10]** **3.8 [DL/G, PF10]**
	Landscape Turf [Broadcast]	2.0 lb ai/A	5 A	230 [SL/G]	6,500 [No R]	220 [SL/G, No R]
	Sweet Corn [Ground Directed	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]**	71 [No R]	**4.7 [SL/G, No R]**

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
				7.5 [DL/G]	360 [PF5] 710 [PF10]	**4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**
Water Soluble Packets for Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Conifers [Ground Directed]	0.4 lb ai/gal	40 gals	**16 [SL/G]** 31 [DL/G]	3,000 [No R]	**16 [SL/G, No R]** 31 [DL/G, No R]
	Landscape Turf [Broadcast]	0.067 lb ai/gal	40 gals	**25 [SL/G]** 45 [DL/G]	670 [No R]	**24 [SL/G, No R]** 42 [DL/G, No R]
	Landscape Turf [Spot]	0.067 lb ai/gal	40 gals	93 [SL/G]	18,000 [No R]	93 [SL/G, No R]
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	31 [SL/G]	6,000 [No R]	31 [SL/G, No R]
Water Soluble Packets for Manually Pressurized Equipment	Landscape Turf [Broadcast]	0.067 lb ai/gal	40 gals	1,800 [SL/G]	1,500 [No R]	820 [SL/G, No R]
Water Soluble Packets for Mechanically Pressurized Handgun Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**2.5 [SL/G]** **3.8 [DL/G]**	36 [No R] 180 [PF5] 360 [PF10]	**2.3 [SL/G, No R]** **2.5 [SL/G, PF5]** **2.5 [SL/G, PF10]** **3.8 [DL/G, PF10]**
	Landscape Turf [Broadcast]	1.0 lb ai/A	5 A	480 [SL/G]	1,400 [No R]	360 [SL/G, No R]
	Sweet Corn [Ground Directed]	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**5.0 [SL/G]** **7.5 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**4.7 [SL/G, No R]** **4.9 [SL/G, PF5]** **5.0 [SL/G, PF10]** **7.4 [DL/G, PF10]**

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine[1].						
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**	**Inhalation**	**Total**
				MOE[4] (LOC = 30) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
Loader/Applicator						
Dry Flowable/Water Dispersible Granular Formulations via Backpack Spray Equipment	Roadsides [Broadcast]	0.2 lb ai/gal	40 gals	**8.4 [SL/G]** **15 [DL/G]**	220 [No R] 1,100 [PF5] 2,300 [PF10]	**8.1 [SL/G, No R]** **8.3 [SL/G, PF5]** **8.4 [SL/G, PF10]** **15 [DL/G, PF10]**
Liquid Formulations via Backpack Spray Equipment	Roadsides [Broadcast]	0.2 lb ai/gal	40 gals	**8.4 [SL/G]** **15 [DL/G]**	220 [No R] 1,100 [PF5] 2,300 [PF10]	**8.1 [SL/G, No R]** **8.3 [SL/G, PF5]** **8.4 [SL/G, PF10]** **15 [DL/G, PF10]**
Water Soluble Packets for Backpack Spray Application	Roadsides [Broadcast]	0.1 lb ai/gal	40 gals	**17 [SL/G]** 30 [DL/G]	450 [No R] 2,300 [PF5]	**16 [SL/G, No R]** **28 [DL/G, No R]** **17 [SL/G, PF5]** 30 [DL/G, PF5]
Granular Formulations via Belly Grinder Equipment	Landscape Turf [Broadcast]	2.2 lb ai/A	1 A	100 [SL/G]	910 [No R]	90 [SL/G, No R]
Granular Formulations via Rotary Spreader	Landscape Turf [Broadcast]	2.2 lb ai/A	5 A	780 [SL/G]	1,100 [No R]	460 [SL/G, No R]

1 Results are presented assuming baseline attire unless otherwise specified. Applying via aerial application equipment is considered in a closed system/engineering control (EC). Risk estimates of concern are in bold.
2 Based on Table 3.3.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (29.7 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, EC = Engineering Control.
5 Inhalation MOE = Inhalation POD (1.8 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg). No R = No Respirator, PF5 = Respirator with Protection Factor of 5, PF10 = Respirator with a Protection Factor of 10. EC = Engineering Control.
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

11.2 Post-Application Exposure and Risk Estimates

11.2.1 Dermal Post-Application Risk

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. Most of the atrazine used in agriculture is applied to corn and sorghum early in the season, either before weeds emerge (pre-emergence) or when the crops are quite small (generally less than 12 inches high). Treatments in macadamia nut and guava orchards, and to conifers and sugarcane, are soil directed by ground equipment; thus post-application exposures are expected to be negligible and have not been assessed. It is not anticipated that occupational post-application workers will re-enter treated fallow crop land, conservation reserve programs, or rights-of-way areas; therefore, these exposures have not been quantitatively assessed. The registered uses on turf (golf courses and sod farms) are not specifically soil-directed; therefore, could result in potential post-application exposures and have been quantitatively assessed. Therefore, only activities associated with "low" crop heights were assessed in the occupational post-application exposure assessment (scouting, hand set irrigation, etc.).

Exposure Duration: For atrazine, both short- and intermediate-term post-application exposure could occur for the registered uses. However, as noted above, only 4-day exposure durations are applicable; therefore, for the purposes of the occupational risk assessments, only the 4-day duration is relevant; the 4-day assessment is 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[52] which, along with additional information about the ARTF data, can be found at the Agency website[53]. Table 11.2.1.2 provides a summary of the anticipated post-application activities and associated transfer coefficients for the registered crops/use sites.

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

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

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

Dislodgeable Foliar Residues: Chemical-specific DFR data have been submitted for atrazine using both liquid and dry flowable formulations on field corn. The DFR study was reviewed and found to be acceptable for risk assessment (K. Rickard, D442405, 09/26/2017). The predicted

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

day 0 residues were adjusted in the occupational post-application assessment for any differences between the study application rate and the registered application rates for atrazine.

Table 11.2.1.1. Review of Dissipation of Dislodgeable Foliar Residues of Atrazine on Field Corn (MRID No. 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: As mentioned in Section 6.2, chemical-specific turf transferrable residue (TTR) data have been submitted for atrazine using both dry flowable and granular formulations. Both TTR studies were reviewed and found to be acceptable for risk assessment [K. Rickard, D443002, 09/26/2017 (MRID 44958001) and K. Rickard, D443647, 09/26/2017 (MRID 44958801)]. The study using the dry flowable formulation was incorporated into the occupational post-application risk assessment because it provided a higher predicted turf transferrable residue estimate (0.226 µg/cm^2) than the study using the granular formulation (0.117 µg/cm^2). For a description and summary of the available TTR study using the dry flowable formulation, see Section 6.2.

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 D428609 (K. Rickard, 06/12/2018).

Occupational Post-Application Non-Cancer Dermal Risk Estimates
Using atrazine-specific DFR and TTR data, the occupational post-application MOEs range from 41 to 1,100 (LOC = 30) on the day of application; therefore, are not of concern. All post-application risk estimates are presented in Table 11.2.1.2.

Table 11.2.1.2. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Atrazine.

Crop/Site	Activities	Application Rate (lb ai/A)	Transfer Coefficient (cm^2/hr)	DFR/TTR[1]	Dermal Dose (mg/kg/day)[2]	Day 0 MOE (LOC = 30)[3]
Corn, Field; Corn, Pop; Corn, Sweet Grain; Corn, Sweet, Processing	Scouting	2.0	210	3.32	0.081	41
	Hand Set Irrigation		1900		0.731	1,100
	Hand Weeding		70		0.027	300
Golf Course	Maintenance	2.0	3700	0.231	0.099	83
Sod	Maintenance; Harvesting, Slab; Transplanting/Planting	4.0	6700	0.462	0.359	370
Sorghum, Grain	Scouting	2.0	210	3.32	0.081	1,100
	Hand Weeding		70		0.027	41

i. 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 44958001: Day 0 residue: 0.226 ug/cm^2, study application rate = 1.96 lb ai/A.

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

3 MOE = POD (29.7 mg/kg/day) / Daily Dermal Dose.

Restricted Entry Interval
Atrazine is classified as acute Toxicity Category III for acute oral and acute dermal toxicity; and Toxicity Category IV for acute inhalation toxicity. It is also classified as Toxicity Category IV for eye irritation potential and for skin irritation potential. It is not a dermal sensitizer. There were no post-application risk estimates of concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to atrazine. All REIs on the evaluated atrazine labels ranged from 12 to 24 hours; therefore are considered protective of post-application exposure.

11.2.2 Inhalation Post-Application Risk

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

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.

12.0 Incident Review

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

In brief, in the current IDS analysis, from January 1, 2012 to January 12, 2017, 84 incidents were reported to IDS involving atrazine. A query of NPIC incidents from 2012 to 2017 found 14 incidents involving atrazine. A query of CA PISP incidents from 2010 to 2014 found no

incidents involving atrazine. A query of SENSOR-Pesticides from 2010-2013 identified 28 cases involving atrazine. The details regarding the reported incidents from the various sources can be found in the 11/1/2017 document (S. Recore *et. al*., D444041 11/01/2017).

Based on the low frequency and severity of atrazine 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 analysis will be conducted.

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Appendix A. Toxicology Profile and Executive Summaries

A.1.1 Toxicology Data Requirements - Atrazine

Atrazine: The requirements (40 CFR 158.340) for the food uses of atrazine are in Table A.1.1 Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

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

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

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

A.2.1 Toxicity Profiles - Atrazine

Table A.2.1.1. Acute Toxicity Profile - Atrazine technical.				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral	00024706	LD_{50} > 1,869 mg/kg (M&F combined)	III
870.1200	Acute Dermal	00024708	LD_{50} > 2,000 mg/kg (M&F combined)	III
870.1300	Acute Inhalation	42089901 and 43016502	LC_{50} > 5.8 mg/L (M&F combined)	IV
870.2400	Primary Eye Irritation	00024709	PIS[1] = 0.0/110	IV
870.2500	Primary Dermal Irritation	00024710	PIS[1] = 0.2/8.0	IV
870.2600	Dermal Sensitization	00105131	Non-sensitizing	---

1. PIS=Primary Irritation Score

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
870.3100 90-Day oral toxicity rodents	44723701 (1994) 0, 10, 50, or 500 ppm 0, 0.6, 3.3, 34.0 mg/kg/day - males 0, 0.659, 3.35, 35.3 mg/kg/day - females.	NOAEL = 3.30 mg/kg/day LOAEL = 34.5 mg/kg/day based on decreased body weight
870.3150 90-Day oral toxicity in nonrodents (dogs)	---	Study waived because an acceptable chronic oral study in the dog is available.
870.3200 21/28-Day dermal toxicity	42089902 (1989) 0, 10, 100 or 1000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on statistically significant reductions in food consumption, mean body weight, and percent weight gain in both sexes, statistically significantly increased absolute and relative spleen weights in both sexes
870.3250 90-Day dermal toxicity	---	Study not required
870.3465 90-Day inhalation toxicity	---	Study not required
870.3700a Prenatal developmental in rodents	40566302 (1984) 0, 10, 70, or 700 mg/kg/day	Maternal NOAEL = 10 mg/kg/day. Maternal LOAEL = 70 mg/kg/day, based on reduced body weight gain Developmental NOAEL = 10 mg/kg/day Developmental LOAEL = 70 mg/kg/day based on delayed or no ossification at several sites
870.3700a Prenatal developmental in rodents	41065201 (1989) 0, 5, 25, 100 mg/kg/day	Maternal NOAEL = 25 mg/kg/day. Maternal LOAEL = 100 mg/kg/day based on reduced body weight gain and food consumption. Developmental NOAEL = 25 mg/kg/day. Developmental LOAEL = 100 mg/kg/day based on increased incidence of delayed ossification of skull bones.
870.3700b	00143006, 40566301 (1984)	Maternal NOAEL = 5 mg/kg/day

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
Prenatal developmental in non-rodents	0, 1, 5, or 75 mg/kg/day	Maternal LOAEL = 75 mg/kg/day based on decreased body weight, food consumption and increased incidence of clinical signs Developmental NOAEL = 5 mg/kg/day Developmental LOAEL = 75 mg/kg/day based on reduced litter size, increased resorptions and delayed ossification.
870.3800 Reproduction and fertility effects	40431303 (1987) 0, 10, 50, and 500 ppm 0, 0.75, 3.78, 39.0 mg/kg/day - males 0, 0.86, 3.70, 42.8 mg/kg/day - females.	NOAEL = 3.78 mg/kg/day LOAEL = 39 mg/kg/day in males based on decreased body weights, body weight gains and food consumption Offspring NOAEL = 3.78 mg/kg/day Offspring LOAEL = 39 mg/kg/day based on decreased body weights in both generations of males at PND 21.
870.4100a Chronic toxicity rodents	40629302 (1986) 0, 10, 70, 500, 1000 ppm, 0, 0.5, 3.5 25, 50 mg/kg/day	This guideline satisfied by 870.4300 Combined chronic toxicity/carcinogenicity NOAEL = 3.5 mg/kg/day LOAEL = 25 mg/kg/day, based on reduced body-weight gain and food consumption See below under 870.4300 for details
870.4100b Chronic toxicity nonrodents (dogs)	40431301 (1987) 0, 15, 150, 1000 ppm 0, 0.5, 5.0 33.7 mg/kg/day	NOAEL = 5.0 mg/kg/day LOAEL = 33.7 mg/kg/day based on cardiac effects.
870.4200 Carcinogenicity (rat, Fischer-344)	42227001 (1992) 0, 10, 70, 200, 400 ppm 0, 0.5, 3.4, 9.9, 20.2 mg/kg/day - males 0, 0.6, 4.4, 12.7, 26.2 mg/kg/day - females	NOAEL = 3.4 mg/kg/day -males; 4.4 mg/kg/day - females LOAEL = 9.9 mg/kg/day - males; 12.7 mg/kg/day - females based on decreased body weight gain There was no treatment-related increase in tumor incidence when compared to controls. This study used Fischer- 344 rats. The purpose was to demonstrate a lack of tumor response in this strain following atrazine exposure.
870.4200 Carcinogenicity (mice)	40431302 (1987) 0,10,300,1500, 3000 ppm 0, 1.4, 38.4, 194, 385.7 mg/kg/day -males 0, 1.6, 47.6, 246.9, 482.7 mg/kg/day -females	NOAEL = 43 mg/kg/day LOAEL = 222.0 mg/kg/day based on decreased body weight gain in both sexes and increased cardiac thrombi in the females. No evidence of carcinogenicity was seen.
870.4300 Combined chronic toxicity/ carcinogenicity (rat, Sprague-Dawley)	40629302 (1986) 0, 10, 70, 500, 1000 ppm, 0, 0.5, 3.5 25, 50 mg/kg/day	NOAEL = 3.5 mg/kg/day LOAEL = 25 mg/kg/day, based on reduced body weight gain and food consumption. Mammary tumors increased at 3.5 mg/kg/day and above. This study used the Sprague Dawley strain of rat.
870.5100 Bacterial reverse mutation assay	00060642 (1977) 0, 50, 100, 500, 1000, 5000 µg/plate	Negative in strains TA 98, 100, 1535 and 1537 of *S. typhimurium* up to the limit concentration of 5000 µg/plate both with and without activation
870.5100 Bacterial reverse mutation assay	40246601 (1986) 0, 20, 78, 313, 1250, and 5000 µg/plate	Negative in strains TA 98, 100, 1535, 1537 and 1538 of *S. typhimurium* up to the limit concentration of 5000 µg/plate both with and without activation

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
870.5385 Micronucleus assay	40722301 (1988) 562.5, 1175, 2250 mg/kg	Negative in doses which induced death in Tif:MAGF mice.
870.5450 Rodent dominant lethal assay	42637003 (1993) 0, 500, 1000, 2000, or 2400 mg/kg	Negative in Tif: MAGf mice at doses 2400 mg/kg.
870.5550 UDS assay	00161790/40722301 (1984) 0, 1.2, 6, 30, 150 µg/mL	Negative in primary rat hepatocytes up to 150 µg/mL
870.5550 UDS assay	42547105 (1992) 0, 15, 46, 139, 417, 835, 1670 µg/mL	Negative in primary rat hepatocyte cultures up to and beyond a dose which caused precipitation (139 µg/mL)
870.7485 Metabolism and Pharmacokinetics	40431304 (1987) 0, 1, and 100 mg/kg for a single dose given through oral gavage. 1.0 mg/kg/day for 15 days by oral gavage.	*Distribution, accumulation* Distribution was dose-dependent and independent of sex. Distribution appeared to follow first-order kinetics and the half-life in the tissues was 31.3 hours. *Excretion* Approximately 95% of the atrazine excreted within 7 days of dosing. Urinary route accounted for about 75% of the excretion feces accounted for 20%. Route of excretion did not seem to vary among sexes or with dose.
870.7485 Metabolism and pharmacokinetics	MRID 40431305 (1987) The animals were dosed daily for 10 days through a stomach tube with dose levels of 0, 1, 3, 7, 10, 50 or 100 mg/kg/day.	*Distribution, accumulation* Distribution was highest in the red blood cell, followed by the liver, ovary and kidney. When the dose increased the amount distributed in the tissues increased. The distribution appeared to follow first-order kinetics and the tissue half-life was 38.6 hours. This indicates that atrazine, with possible exception of the red blood cell, does not bioaccumulate.
870.7485 Metabolism and pharmacokinetics	MRID 40431306 (1987) Rats were given test 100 mg/kg article was given through the stomach tube in a single oral dose. Other rats were given 16.18 and 19.64 mg/kg and urine was collected over a 24 hr period. The urine was analyzed for metabolites.	*Excretion* In the rats given 100 mg/kg greater than 100% of the administered radioactivity was recovered within 3 days of dosing. Urine was found to contain 47.3% of the radioactivity and the feces 49.3%. The tissues contained 5.75% and 1.4% was found in the blood. *Metabolism* Metabolites indicate that dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways for atrazine in rats. Oxidation of the alky substituents of atrazine appears to be of minor metabolic importance.
870.7485 Metabolism and pharmacokinetics	MRID 42165503 (1993) Fecal and urinary samples from rats exposed in a separate metabolism study (MRID 40431304) were obtained and analyzed to determine metabolism profiles.	*Metabolic profile* No sex differences in metabolic profiles were evident. The major fecal metabolite was DACT which accounted for 40% of the total fecal radioactivity.
870.7485	MRID 44713802 (1993)	*Distribution, accumulation*

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
Metabolism and pharmacokinetics	single oral dose of 1 or 100 mg/kg through oral gavage	Time to maximum blood concentration (t_{cmax}) was 2 hours and 24 hours for the low and high dose groups, respectively. With exception of red blood cells, whole blood, and skeletal muscle, tissue burden for any specific tissue or organ represented less than 1% of the administered dose by 14 days post dosing *Excretion* Urinary excretion was 64.72% of the total administered low dose over a 48-hour period and 66.16% of the total administered high dose over a 168-hour period. Within 48 hours urinary excretion was 100% and 94% complete for the low-dose and high-dose group, respectively. Fecal elimination accounted for 10.80% and 19.69% of the total dose for the low and high dose groups, respectively.
870.7600 Dermal penetration - *rat*	43314302 (1994) 0.01, 0.1 or 1 mg/cm^2	The percent absorbed increased with exposure time and decreased with dose. Regardless of the dose or exposure time, the majority (65 - 95%) of the radio labeled atrazine was recovered in the washes or was found associated with the skin at the site of exposure. The maximum percentage of atrazine absorbed in the rat study after a 10 hr (representative of a typical workday) exposure was 21.6%.
870.7600 Dermal penetration - *human*	44152114 (1996) 0.17 and 2.0 mg of [14C] atrazine	The majority (91.1-95.5%) of the dose was not absorbed. 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.
Special study - Assays of direct estrogenic activity	43598617 (1994) This MRID number describes more than one assay. The doses varied depending on the assay. See above under section 4.9.1 for specific details on doses used.	This study performed a trio of assays: uterotrophic response assay; progesterone receptor competitive binding assay; and, a uterine thymidine incorporation assay. All doses tested displayed a lack of clear effects on uterine weight, progesterone binding capacity, and thymidine incorporation. This indicates that atrazine (and DACT and simazine, which were also tested) do not exhibit direct estrogenic activity.
Special study - Assays of direct estrogenic activity	43598618 (1994) This MRID number describes one type of assay conducted under a variety of experimental conditions. The doses varied. See above under section 4.9.1 for specific details on doses used.	This study describes a series of estrogen receptor competitive binding assays, both *in vivo* and *in vitro*. Overall the results indicate that atrazine (and DACT and simazine, which were also tested) do exhibit some competitive binding with estradiol but only under conditions which favor binding.
Special study - Assays of direct estrogenic activity	43598619 (1995) This MRID number describes more than one assay. The doses varied depending on the assay. See above under section 4.9.1 for specific details on doses used.	This study describes four separate assays: competitive binding assay with the hepatocyte Ah receptor; MCF-7 cell proliferation; gel electrophoresis mobility shift assay using the progesterone receptor; and, luciferase reporter gene assay in MCF-7 cells. Neither atrazine (nor simazine, which was also tested) displayed estrogenic activity or interacted with the Ah receptor in the set of experiments described in this paper.
Special study -	43934403 (1995)	This study described several assays, both *in vivo* and *in vitro*. *In vivo* assays: uterine weight, progesterone receptor levels and uterine peroxidase. *In vitro* assays: MCF-7 cell proliferation; gel electrophoresis mobility shift assay

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
Assays of direct estrogenic activity	This MRID number describes more than one assay. The doses varied depending on the assay. See above under section 4.9.1 for specific details on doses used.	using the progesterone receptor; luciferase reporter gene assay in MCF-7 cells; and, a selective medium growth assay in yeast cells. The results of these experiments indicate that *in vivo* atrazine and simazine may exhibit some antiestrogenic activity but no estrogenic activity either *in vivo* or *in vitro*.
Special study - Estrous Cycle and LH Surge Measurements (Pilot study)	43934404 (1996) atrazine not given	This study was a pilot study in which the validity of a proposed protocol for testing the effect of atrazine exposure on the proestrus afternoon luteinizing hormone (LH) was evaluated. This study demonstrated that the proposed protocol adequately tested the parameters to be examined.
Special study - Estrous Cycle and LH Surge Measurements (28 day exposure)	43934406 (1996) 0, 2.5, 5, 40 and 200 mg/kg/day	NOAEL = 5 mg/kg/day. LOAEL = 40 mg/kg/day based on decreases in food consumption, body weight, body weight gain, estrous cycle alterations and LH surge attenuation
Special study - Estrous Cycle and LH Surge Measurements (6 month exposure)	44152102 (1996) 0, 25, 50, and 400 ppm 0, 1.8, 3.7, 29.4 mg/kg/day	NOAEL = 1.8 mg/kg/day LOAEL = 3.7 mg/kg/day based on estrous cycle alterations and LH surge attenuation
Special study[1]- Hormone and estrous cycle measurements in SD rats	42085001, 42743902 (1991, 1993) *See also 43598622* 0, 70, 400 ppm 0, 4.2, 26.2 mg/kg/day Ten females per dose were sacrificed at 1, 3, 9, 12, 15, 18, 24 mo.	NOAEL = none found LOAEL = 4.2 mg/kg/day based on estrous cycle alterations
Special Study [1]- Mammary Gland and Ovarian Histomorphology in SD rats	43598622 (1995) *See also 42085001, 42743902* 0, 70, 400 ppm 0, 4.2, 26.2 mg/kg/day Ten females per dose were sacrificed at 1, 3, 9, 12, 15, 18, 24 mo.	NOAEL = none found LOAEL = 4.2 mg/kg/day based early onset of anovulation as indicated by ovarian histomorphology and early onset of indicators of prolonged/increased hormone exposure in the mammary gland
Special study[2] - Two-year bioassay in F-344 rats	42146101 (1991) *See also 4274392 and 43598622* 0, 0.7, 4.8, 14, 33.4 mg/kg/day Ten females per dose were sacrificed at 1, 3, 9, 12, 15, 18, 24 mo.	NOAEL = 14 mg/kg/day LOAEL = 33.4 mg/kg/day based on decreased body weight gain. There was not an increased incidence of any tumor type, nor an early onset of mammary tumors.
Special study[2] - Hormone and estrous cycle measurements in F-344 rats	42743902 (1993) *See also 42146101 and 43598622*	NOAEL = at least 33.4 mg/kg/day LOAEL = none found This study examined hormones and estrous cycles in the animals used in 42146101.

Table A.2.1.2. Subchronic, Chronic and Other Toxicity Profile for Atrazine.		
Guideline No./ Study Type	**MRID No. (year) /Doses**	**Results**
	0, 0.7, 4.8, 14, 33.4 mg/kg/day Ten females per dose were sacrificed at 1, 3, 9, 12, 15, 18, 24 mo.	The estrous cycle evaluations from this study are deemed unreliable by HED. The ovarian histomorphology data from MRID 43598622 is used to confirm a lack of effect of atrazine treatment on estrous cycles. The animals exhibited hormone levels indicative of normally aging females of the strain. Exposure to atrazine had no effect on hormone levels.
Special study[2]- Mammary Gland and Ovarian Histomorphology in F-344 rats	43598622 (1995) *See also 42146101 and 42743902* 0, 0.7, 4.8, 14, 33.4 mg/kg/day Ten females per dose were sacrificed at 1, 3, 9, 12, 15, 18, 24 mo.	NOAEL = at least 33.4 mg/kg/day LOAEL = none found This study examined histomorphology in the animals used in 42146101. The animals exhibited ovarian and mammary gland histomorphology indicative of normally aging females of the strain. Exposure to atrazine had no effect on these histomorphologic parameters.
Special study - Two-year bioassay with the SD strain of rat	42204401 (1992) 0, 70, 400 ppm 0, 3.8, 23.0 mg/kg/day	NOAEL = 3.8 mg/kg/day LOAEL = 23 mg/kg/day based on decreased body weight gains as well as statistically significant decreases in body weights in the 0-76 week period A statistically significant increase in mammary tumors was seen at the high dose. An early onset of mammary carcinomas was seen.
Special study - Tumor incidence in ovariectomized (OVX) *vs* intact animals	44544701 (1998) 0, 25, 50, 70, 400 ppm 0, 1.5, 3.1, 4.2, 24.4 mg/kg/day - intact 0, 1.2, 2.5, 3.5, 20.9 mg/kg/day - OVX	Intact animal Mammary tumors No mammary tumors seen in any OVX animal
Special study - Long-term estrous cycle measurements	No MRID assigned (1999) 0, 25, 50, 70, 400 ppm 0, 1.5, 3.1, 4.2, 24.4 mg/kg/day	This is the unaudited draft report of the interim estrous cycle data from MRID 44544701 These data demonstrate an early onset of increased % days in estrus in atrazine-treated animals compared to controls.
Special study- Direct comparison of LH surge attenuation of atrazine, simazine, DACT	No MRID assigned (2000) 0, 2.5, 5, 40, 200 mg/kg/day	This is the unaudited draft report of a study in which SD females were exposed to atrazine, simazine or DACT for 28 days and the ability of these chemicals to attenuate the LH surge was measured. These data showed that simazine and DACT are able to attenuate the LH surge at doses similar to those at which atrazine attenuates the surge.

1. This study in SD rats contains three parts submitted under three separate MRID numbers:
    a. MRID 42085001 contains the results of the animal bioassay part of this study (the clinical observations, body weights, food consumption, gross pathology, *etc.*);
    b. MRID 42743902 contains the results of the vaginal smears/estrous cycle determinations and serum hormone measurements;
    c. MRID 43598622 contains the results of the histomorphologic analysis.
2. This study in F-344 rats contains three parts submitted under three separate MRID numbers:
    a. MRID 42146101 contains the results of the animal bioassay part of this study (the clinical observations, body weights, food consumption, gross pathology, *etc.*);

b. MRID 42743902 contains the results of the vaginal smears/estrous cycle determinations and serum hormone measurements;
c. MRID 43598622 contains the results of the histomorphologic analysis.

A.2.3 Toxicity Profiles – Hydroxyatrazine

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

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

A.3 Additional Evaluation Information on the PBPK Model

In the 2015 PBPK model, the values of metabolism-related parameters were derived from an *in vitro* approach that described the time-course concentration profiles of atrazine, DIA, DEA and DACT in incubation media for an intact hepatocyte suspension assay. The rat *in vitro* model was

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

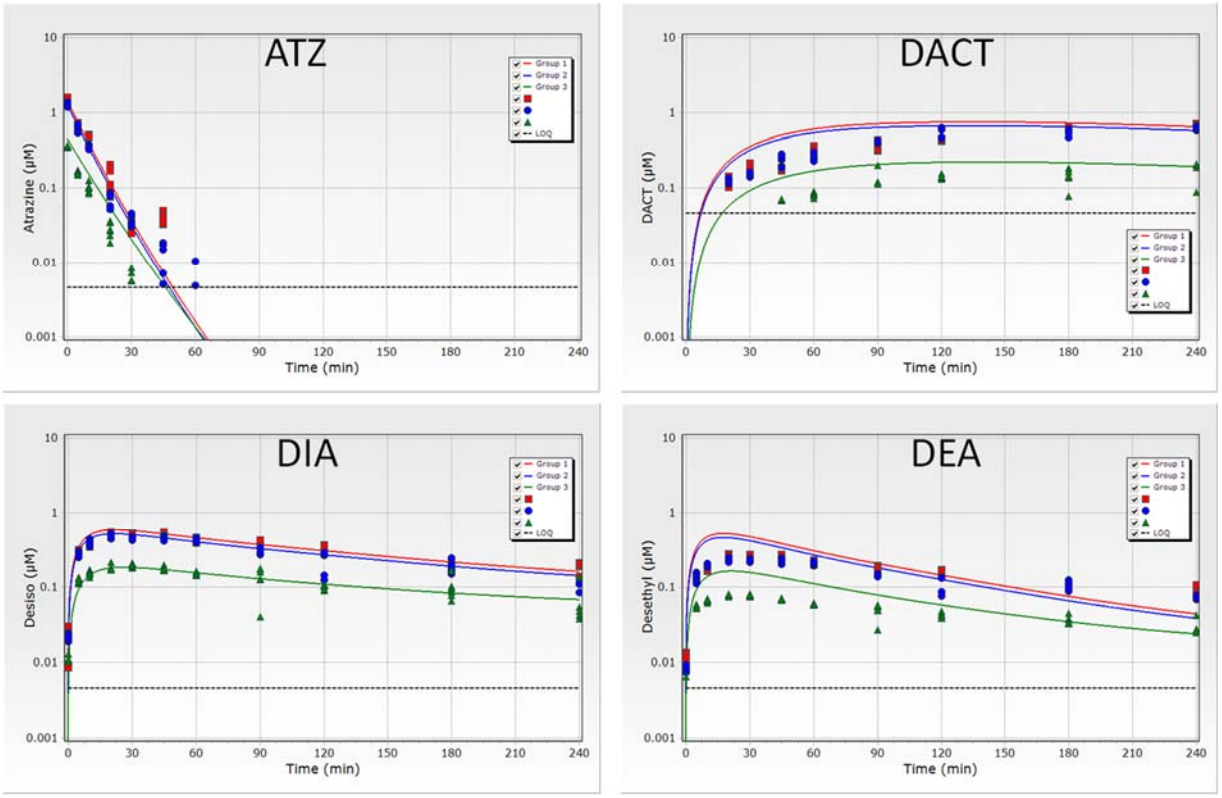

Figure A.3.1. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.26 µM – Group 2, and 0.45 µM – Group 3).

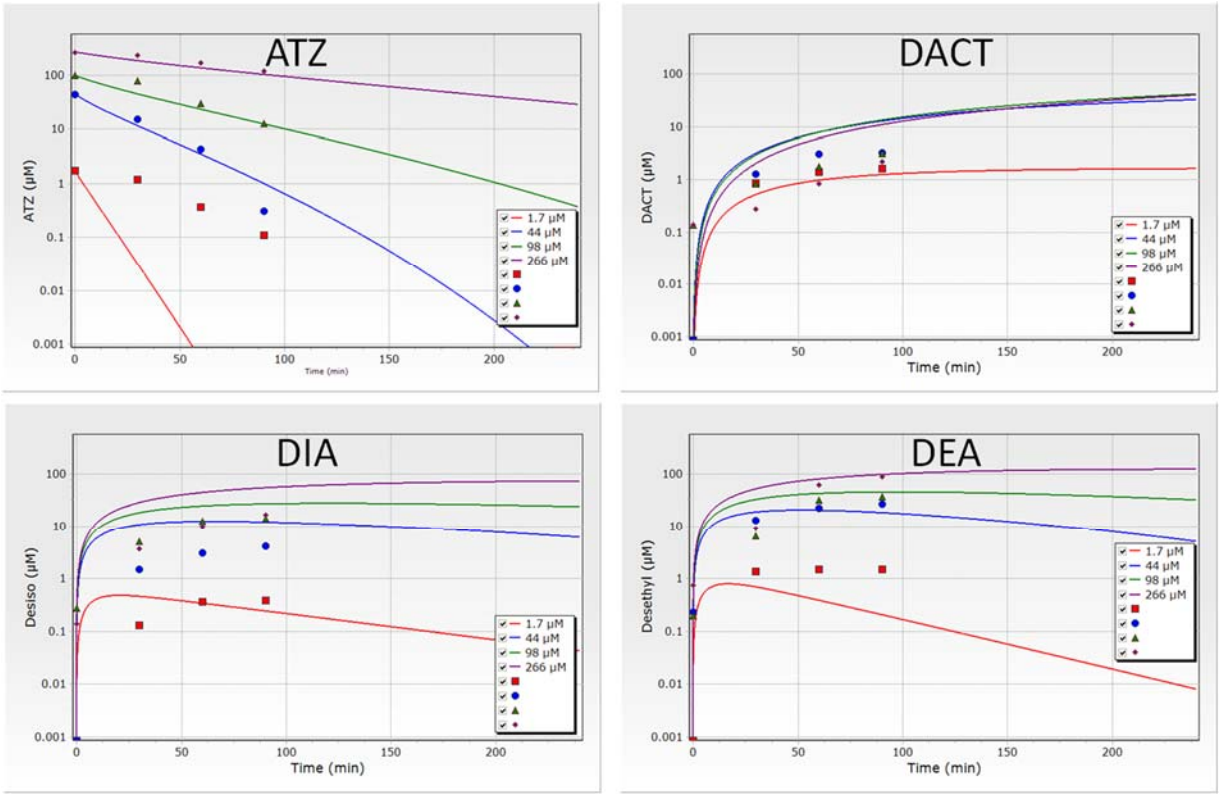

Figure A.3.2. Model prediction of intact rat hepatocyte metabolic assays for atrazine and its chlorinated metabolites (McMullin et al., 2007).

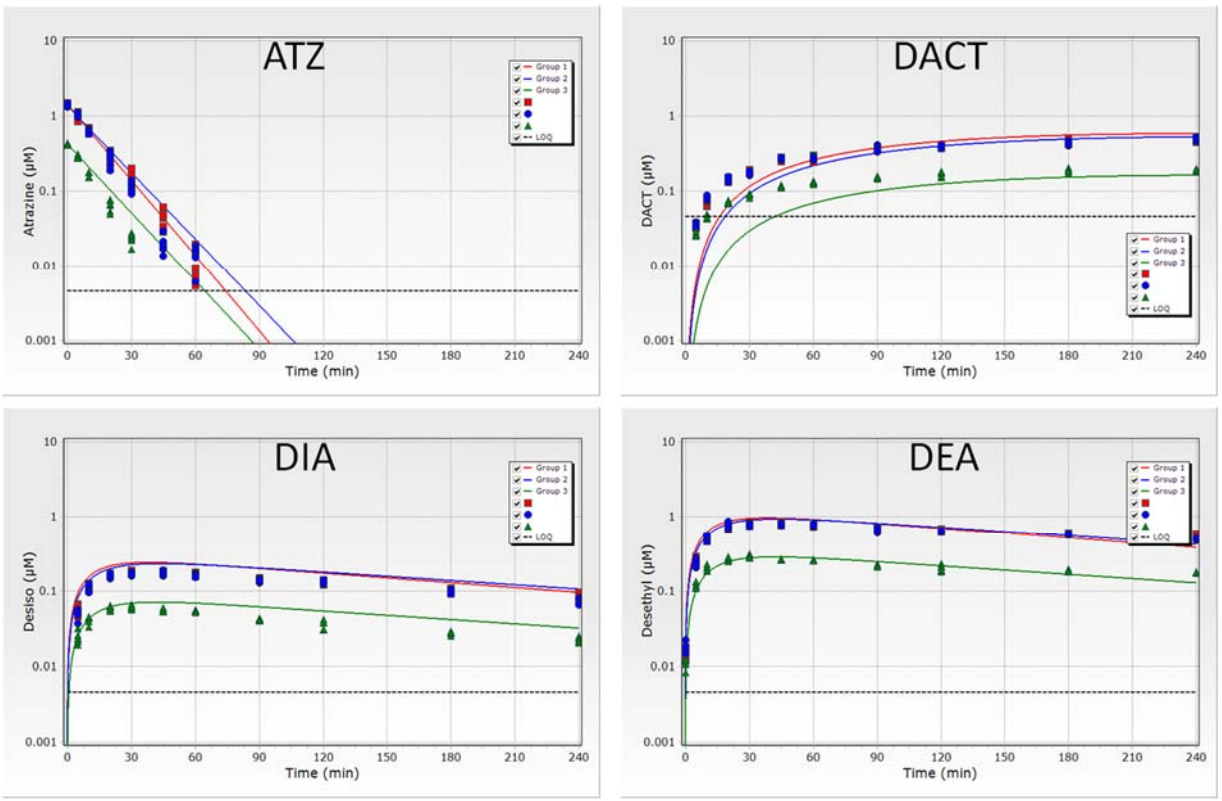

Figure A.3.3. Model prediction of intact human hepatocyte metabolic assays for atrazine and its chlorinated metabolites (0.25 ml incubations with 0.5 x 10^6 cells per well; Initial concentrations were 1.43 µM – Group 1, 1.38 µM – Group 2, and 0.42 µM – Group 3).

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

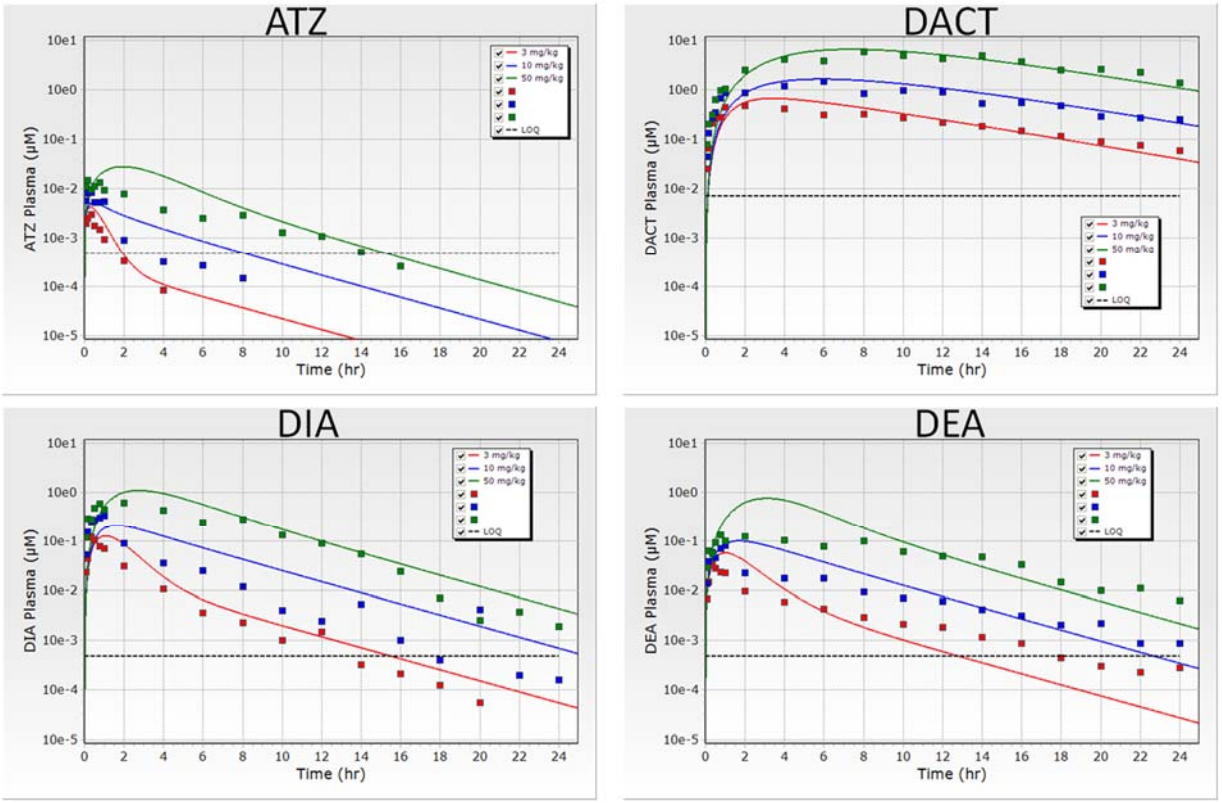

Figure A.3.4. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats after a single gavage dose of atrazine at 3, 10 and 50 mg/kg.

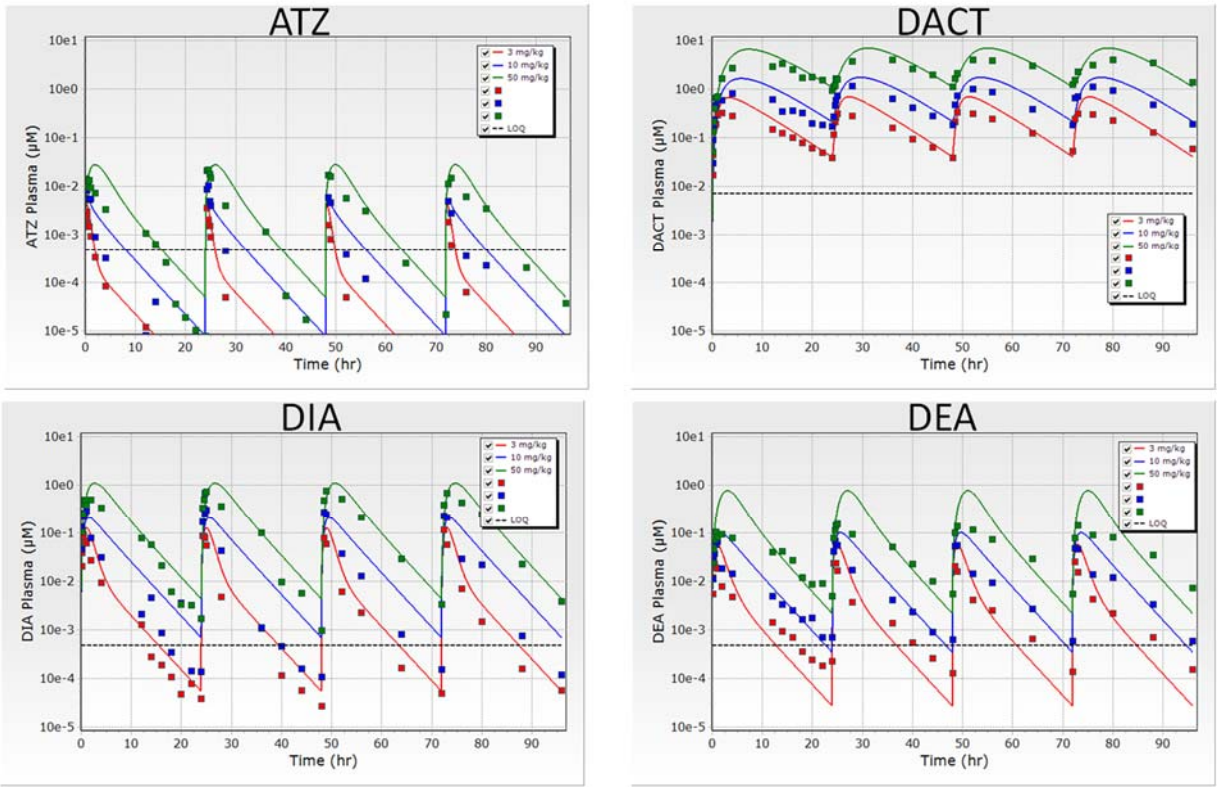

Figure A.3.5. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated daily gavage doses of atrazine at 3, 10 and 50 mg/kg.

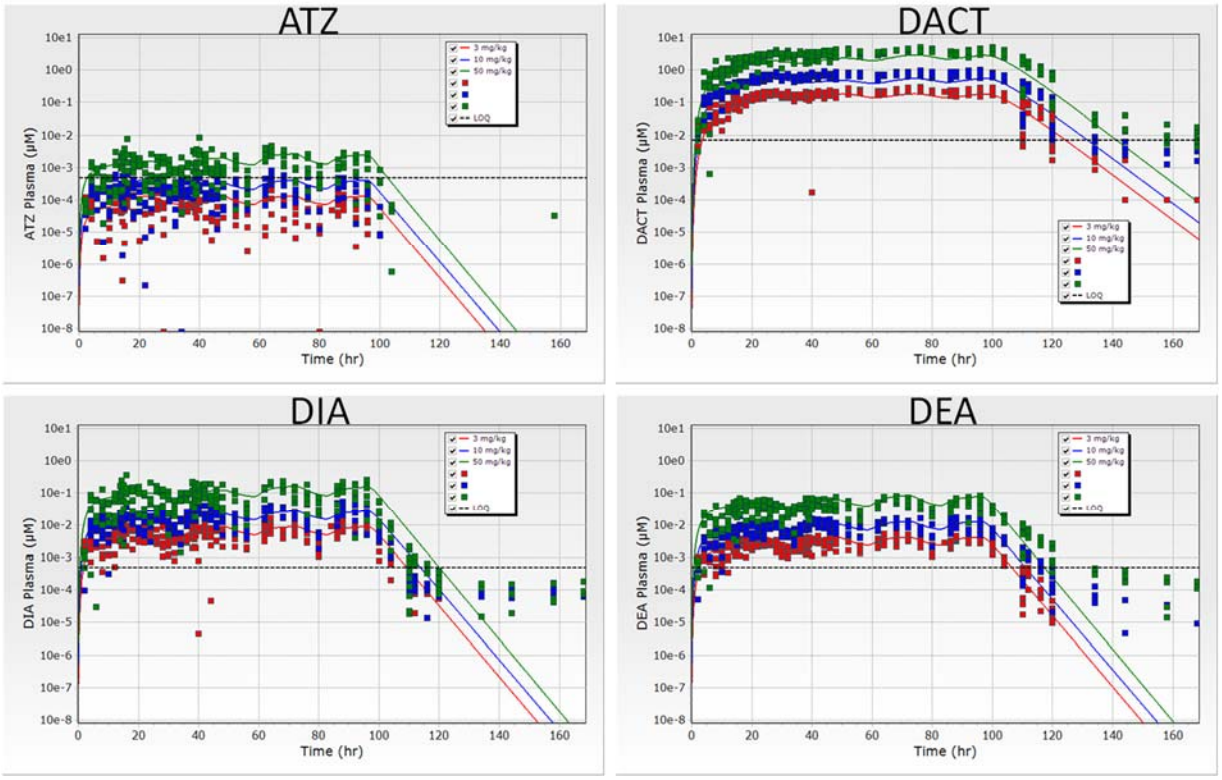

Figure A.3.6. Model prediction of atrazine and chlorinated metabolites concentrations in plasma of rats during and after repeated dietary exposure to atrazine at 3, 10 and 50 mg/kg.

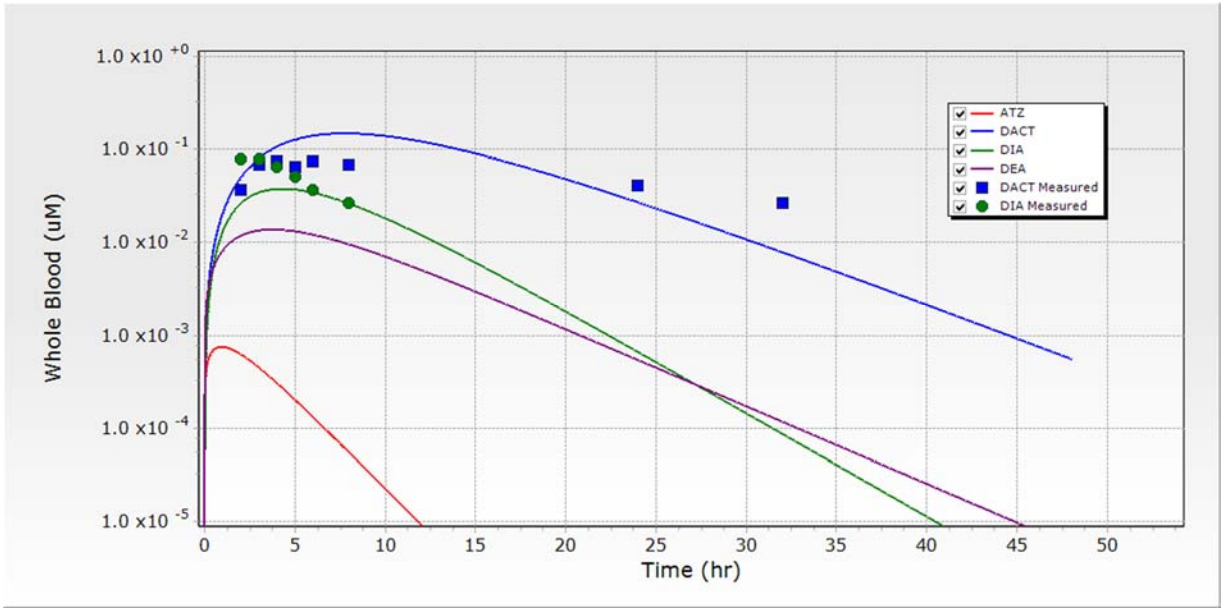

Figure A.3.7. Model simulations of atrazine, DIA, DEA, and DACT concentrations in the plasma of humans exposed to a single oral dose of 100 µg/kg atrazine.

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

Appendix B. New Epidemiology Literature on Atrazine since the 2011 FIFRA SAP Meeting

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 atrazine were the 13 epidemiology publications identified in the literature that reported a statistically significant estimate of effect for atrazine, emanated from a prospective cohort and/or were otherwise of a moderate or high quality study design[54] or were often referenced in the epidemiology literature, and that were unavailable at the time of the recent SAPs.

This appendix to the atrazine risk assessment briefly describes the methods and results from the epidemiology literature review of atrazine, simazine, and/or propazine, and describes the 13 studies of particular interest to the atrazine 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 meet the population, exposure, comparator, and outcome of interest (PECO)[55]. The population of interest was humans with no restrictions, including no restrictions on age, lifestage, 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 was all 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

[54] 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

[55] 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 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[56]. 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.[57,58]

[56] 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.

[57] 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.

[58] 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 B-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.

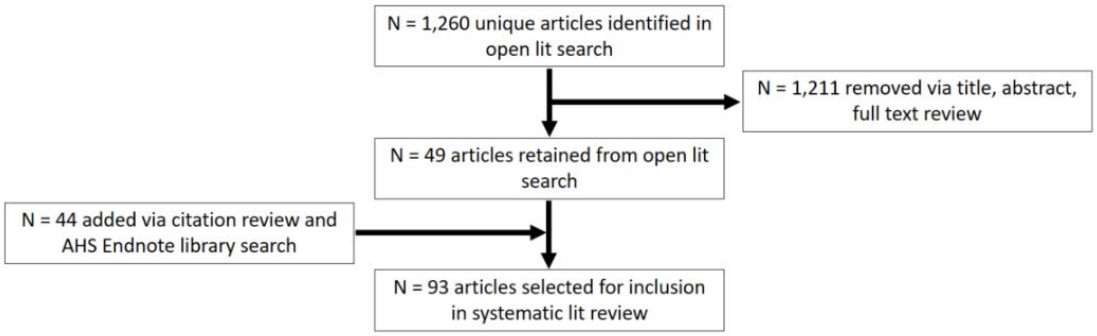

Figure B-1: Selection of studies for literature review of atrazine, simazine, and/or propazine (chlorotriazines) and carcinogenic and noncarcinogenic epidemiological effects.

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[59]. 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, and 12 of these recent studies[60] reported statistically significant[61] estimates of effect for atrazine and emanated from prospective cohorts and/or were of a moderate quality study design[62] or were often cited in the epidemiology literature. These 13 studies are summarized and reviewed below:

[59] 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

[60] It should be noted that three genetic modification studies (Koutros et al.2011, Karami et al. 2013, and Anreotti et al. 2012) for atrazine were reviewed and not summarized below since each study evaluated the genetic interaction data in regards to atrazine, instead of directly evaluating the association with atrazine.

[61] Critical value of significance was $p < 0.05$, unless otherwise noted. For odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant unless otherwise noted.

[62] 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. 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

Agopian et al. (2013a) assessed the relationship between maternal exposure to atrazine and the risk for choanal atresia or stenosis in offspring through a case-control study. Study participants were identified from the Texas (TX) Birth Defects Registry from 1999 through 2008, and included live, still, and terminated births to women living in Texas. Cases (n = 280) were defined as nonsyndromic[63] with postnatal diagnoses of choanal atresia or stenosis documented on the medical record. Controls (n = 3,720) were randomly selected from the population of births in TX during the study period and included births without major malformations. Maternal residential periconceptual exposure was estimated by linking county-level estimated atrazine application data with maternal county of residence at delivery. County-level atrazine application estimates were available from the United States Geological Survey (USGS) from 1997 – 2007; 2008 births were assigned the 2007 county-level atrazine estimates. (range: >0.00, 352.50 pounds per square mile; median = 3 pounds/square mile). County-level atrazine exposure estimates were categorically assigned to each subject based on the distribution among controls: low (below the 25th percentile: 0 to < 1.40 pounds/square mile), medium-low (between the 25th and the 75th percentile: 1.40 to < 15.03 pounds/square mile), medium (between the 75th and the 90th percentile: 15.03 to < 47.63 pounds/ square mile), or high (greater than 90th percentile: ≥ 47.63 pounds/ square mile). Logistic regression was used to estimate ORs and 95% CIs. In the unadjusted analyses, there was evidence of a positive association between maternal exposure and risk of choanal atresia/stenosis in the high exposure group compared to the low exposure group (OR = 1.65; 95% CI: 1.10, 2.48 with 42 exposed cases and 367 exposed controls), but not in the medium-low or medium exposure groups (OR = 0.93; 95% CI: 0.68, 1.27 with 120 cases and 1,856 controls in the medium-low exposure group; OR = 1.37; 95% CI: 0.94, 2.00 with 53 cases and 557 controls in the medium exposure group). When models were adjusted for season of conception, infant sex, birth year, maternal race/ethnicity, maternal education, maternal age, and maternal smoking, results were similar (high exposure: OR = 1.79; 95% CI: 1.17, 2.74; medium exposure: OR = 1.35; 95% CI: 0.90, 2.01; medium-low exposure: OR = 0.93; 95% CI: 0.68, 1.29). There was a significant linear trend identified (p-trend = 0.002).

Study strengths included the large, population-based sample for both cases and controls, including the TX Birth Defects Registry which utilizes active surveillance to identify cases. The inclusion of stillbirths and pregnancy terminations in the case population minimized selection bias, and the limitation to nonsyndromic cases may have reduced etiologic heterogeneity (the phenomena of cases with similar clinical features but differing exposure associations). The primary limitation of the study was in the exposure estimation, which relied on county-level data to estimate individual-level exposure, potentially introducing exposure misclassification. Authors utilized maternal residence at delivery to estimate exposure throughout pregnancy, another potential source of misclassification since it does not account for migration or relocation during pregnancy. Utilizing 2007 atrazine data to estimate 2008 exposures could also have introduced exposure misclassification if atrazine use differed between the years for some counties. Using

[63] Cases were limited to nonsyndromic to exclude those with possible diagnoses of chromosome abnormalities and/or malformation syndromes or sequences.

annual estimates of atrazine to assess exposure did not allow investigators to consider seasonal trends in atrazine application. Finally, atrazine was the only exposure considered in the analysis, and authors noted that they could not rule out the possibility that the observed associations were due to another, unmeasured exposure. Based on the study limitations, the overall quality of the study was ranked low.

Study 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.

Agopian et al. (2013b) investigated whether maternal residential atrazine exposure was association with gastroschisis in male offspring through a case-control study. Cases (n = 1,161) were identified from the Texas (TX) Birth Defects Registry from 1999 through 2008, and included live, still, and terminated births to women living in Texas. Only isolated cases were considered (those without comorbidities such as chromosome abnormalities, malformation syndromes, or other major birth defects). Case diagnoses were reviewed by clinical geneticists and linked to TX state birth and fetal death certificates. Controls (n = 8,390) were randomly selected from the population of all live born infants in TX during the study period (5 controls:1 case). Maternal residential periconceptual exposure was estimated by linking county-level estimated atrazine application data with maternal county of residence at delivery. Annual estimates of county-level atrazine application were available from the United States Geological Survey (USGS) from 1997 – 2007; 2008 births were assigned the 2007 county-level atrazine estimates. County-level atrazine exposure estimates were categorically assigned to each subject based on the distribution among controls: low (below the 25th percentile: 0 to <1.43 pounds/square mile), medium-low (between the 25th and the 75th percentile: 1.43 to <15.56 pounds/square mile), medium (between the 75th and the 90th percentile: 15.56 to <44.23 pounds/ square mile), or high (greater than 90th percentile: ≥44.23pounds/ square mile). Logistic regression was used to estimate ORs and 95% CIs. In the unadjusted analyses, there was no evidence of a positive association between maternal exposure and risk of gastroschisis for any exposure group, and a significant negative association was identified in the medium exposure group, compared to the low exposure group (medium-low exposure: OR = 1.01; 95% CI: 0.87, 1.18 with 590 cases and 4,154 controls exposed; medium exposure: OR = 0.73; 95% CI: 0.59, 0.91 with 129 cases and 1,266 controls exposed; high exposure: OR = 1.22; 95% CI: 0.98, 1.51 with 142 cases and 832 controls exposed). When models were adjusted for season of conception, infant sex, birth year, maternal race/ethnicity, maternal education, maternal age, maternal birthplace, history of previous lives births, and maternal smoking, results were similar, though the negative association identified in the medium exposure group failed to achieve significance (medium-low exposure: OR = 1.11; 95% CI: 0.94, 1.32; medium exposure: OR = 0.82; 95% CI: 0.64, 1.04; high exposure: OR = 1.22; 95% CI: 0.96, 1.56).

Since maternal age was a suspected risk factor for gastroschisis (with younger maternal age associated with higher risk), investigators analyzed data separately for females older than 25 years and 25 years old and younger. Among the older mothers, there was evidence of a significant positive association in the high exposure group compared to the low exposure group (adjusted OR = 1.97; 95% CI: 1.19, 3.26 with 33 cases and 466 controls exposed), but not in the medium-low or medium exposure group (medium-low exposure: adjusted OR = 0.96; 95% CI:

0.65, 1.42 with 83 cases and 2,462 controls exposed; medium exposure: adjusted OR = 0.74; 95% CI: 0.41, 1.32 with 18 cases and 774 controls exposed). Among the younger mothers, there was no evidence of a significant positive association in any exposure group (medium-low exposure: adjusted OR = 1.16; 95% CI: 0.96, 1.39 with 506 cases and 1,692 controls; medium exposure: adjusted OR = 0.84; 95% CI: 0.64, 1.09 with 110 cases and 492 controls; high exposure: adjusted OR = 1.06; 95% CI: 0.81, 1.40 with 109 cases and 366 controls; with 246 cases and 890 controls exposed in the low exposure reference group).

Study strengths included the large, population-based sample for both cases and controls, including the TX Birth Defects Registry which utilizes active surveillance to identify cases. The inclusion of stillbirths and pregnancy terminations in the case population minimized selection bias, and the limitation to isolated cases may have reduced etiologic heterogeneity (the phenomena of cases with similar clinical features but differing exposure associations). The primary limitation of the study was in the exposure estimation, which relied on county-level data to estimate individual-level exposure, potentially introducing exposure misclassification. Authors utilized maternal residence at delivery to estimate exposure throughout pregnancy, another potential source of misclassification since it does not account for migration or relocation during pregnancy. Utilizing 2007 atrazine data to estimate 2008 exposures could also have introduced exposure misclassification if atrazine use differed between the years for some counties. Using annual estimates of atrazine to assess exposure did not allow investigators to consider seasonal trends in atrazine application. Atrazine was the only exposure considered in the analysis, and authors noted that they could not rule out the possibility that the observed associations were due to another, unmeasured exposure. Finally, while the separate logistic regressions by age group is an adequate method to investigate differences in outcome by age, running a logistic regression with an interaction term utilizing the entire dataset together could have provided more information on the effect of age on the exposure-outcome relationship, and would have increased statistical power due to the increased sample size. Based on the study limitations, the overall quality of the study was ranked low.

Study 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

Agopian et al. (2013c) investigated whether maternal residential atrazine exposure was associated with genital malformations in male offspring through a case-control study. Genital malformations included hypospadias, cryptorchidism, and small penis, and cases (n = 16,433) were identified from the Texas (TX) Birth Defects Registry from 1999 through 2008, and included live, still, and terminated births to women living in Texas. Only isolated cases were considered (those without comorbidities such as chromosome abnormalities, malformation syndromes, or other major birth defects). Case diagnoses were reviewed by clinical geneticists and linked to TX state birth and fetal death certificates. Controls (n = 16,433) were randomly selected from the population of live male births in TX without major malformations. Maternal residential periconceptual exposure was estimated by linking county-level estimated atrazine application data with maternal county of residence at delivery. County-level atrazine application estimates were available from the United States Geological Survey (USGS) from 1997 – 2007; 2008 births were assigned the 2007 county-level atrazine estimates. County-level atrazine

exposure estimates were categorically assigned to each subject based on the distribution among controls: low (below the 25th percentile: 0 to <1.55 pounds/square mile), medium-low (between the 25th and the 75th percentile: 1.55 to <17.25 pounds/square mile), medium (between the 75th and the 90th percentile: 17.25 to <51.90 pounds/ square mile), or high (greater than 90th percentile: ≥51.90 pounds/ square mile). Separate unconditional logistic regressions were conducted to evaluate the relationship between estimated maternal periconceptual exposure to atrazine and each outcome of interest as well as all male genital malformations combined.

The table below is excerpted from Agopian et al. (2013c) and provides a summary of reported results on the association between atrazine ad isolated male genital malformations in Texas. Notable reported associations include:

- ***All Male Genital Malformations*** – Slight positive significant association between maternal exposure for the medium-low and medium exposure groups, but not for the high exposure group.
- ***Hypospadias*** – Slight positive significant association between maternal exposure for the medium-low and medium exposure groups, but not for the high exposure group. Adjusting the model for the covariates listed previously produced similar results, though no exposure group attained significance in the adjusted analysis
- ***Small Penis*** – Significant positive association between maternal exposure and for the medium exposure group, but not for the medium-low or high exposure groups.
- ***Cryptorchidism*** – Slight positive significant association between maternal exposure for the medium-low exposure group, but not for the medium or high exposure groups.

Table B-2: Association Between Atrazine and Isolated Male Genital Malformations in Texas, 1999–2008 (Excerpted from Agopian et al. (2013c))

Atrazine Levels[a]	Cases (%)	Controls (%) (N=16,433)	OR	95% CI	aOR[b]	95% CI
All male genital malformations (N=16,433)						
Low (reference)	3,546 (21.8)	3,918 (24.1)	1		1	
Medium-low	8,849 (54.4)	8,295 (51.0)	**1.18**	**1.12–1.25**	**1.19**	**1.12–1.26**
Medium	2,680 (16.5)	2,402 (14.8)	**1.23**	**1.15–1.32**	**1.2**	**1.11–1.29**
High	1,207 (7.4)	1,660 (10.2)	**0.8**	**0.74–0.88**	0.96	0.87–1.05
Hypospadias (N=8,909)						
Low (reference)	1,989 (22.5)	3,918 (24.1)	1		1	
Medium-low	4,659 (52.8)	8,295 (51.0)	**1.11**	**1.04–1.18**	1.07	1.00–1.15
Medium	1,485 (38.2)	2,402 (14.8)	**1.22**	**1.12–1.33**	1.09	1.00–1.20
High	691 (7.8)	1,660 (10.2)	**0.82**	**0.74–0.91**	1	0.89–1.11
Second or third degree hypospadias (N=738)						
Low (reference)	133 (18.2)	3,918 (24.1)	1		1	
Medium-low	428 (58.6)	8,295 (51.0)	**1.52**	**1.25–1.85**	**1.44**	**1.17–1.77**
Medium	117 (16.0)	2,402 (14.8)	**1.44**	**1.11–1.85**	1.18	0.90–1.55
High	53 (7.3)	1,660 (10.2)	0.94	0.68–1.30	1	0.71–1.41
Small penis (N = 670)						
Low (reference)	152 (23.1)	3,918 (24.1)	1		1	

Atrazine Levels[a]	Cases (%)	Controls (%) (N=16,433)	OR	95% CI	aOR[b]	95% CI
Medium-low	334 (50.8)	8,295 (51.0)	1.04	0.85–1.26	1.05	0.86–1.28
Medium	126 (19.2)	2,402 (14.8)	**1.35**	**1.06–1.72**	**1.38**	**1.07–1.77**
High	45 (6.9)	1,660 (10.2)	**0.7**	**0.50–0.98**	0.74	0.52–1.04
Cryptorchidism (N=4,324)						
Low (reference)	997 (22.8)	3,918 (24.1)	1		1	
Medium-low	2,331 (54.5)	8,295 (51.0)	**1.13**	**1.04–1.23**	**1.17**	**1.08–1.28**
Medium	621 (14.5)	2,402 (14.8)	1.04	0.93–1.16	**1.14**	**1.01–1.28**
High	348 (8.1)	1,660 (10.2)	**0.84**	**0.73–0.96**	0.93	0.80–1.07

Bold indicates statistical significance.
[a]Atrazine categories based on 25th, 75th, and 90th centiles in controls.
[b]Odds ratio adjusted for season of conception, birth year, and maternal race/ethnicity, education, age, history of previous live births, birthplace, and smoking.

Authors concluded that study results provided evidence of atrazine as a teratogen; however, the low number of associations, the few statistically significant associations, the lack of adjustment for multiple comparisons, and the lack of significant positive associations for the high exposure group potentially altered/influenced the evidence of any associations between maternal atrazine exposure and subsequent male genital malformations of offspring.

Strengths of Agopian et al. (2013c) included the large, population-based sample for both cases and controls. The inclusion of stillbirths and pregnancy terminations in the case population minimized selection bias, and the limitation to cases isolated from comorbidities may have reduced etiologic heterogeneity (the phenomena of cases with similar clinical features but differing exposure associations). The primary limitation of the study was in the exposure estimation, which relied on county-level data to estimate individual-level exposure, potentially introducing exposure misclassification. Authors utilized maternal residence at delivery to estimate exposure at conception, another potential source of misclassification. Finally, atrazine was the only exposure considered in the analysis, and authors noted that they could not rule out the possibility that the observed associations were due to another, unmeasured exposure, such as another pesticide.

EPA Evaluation of Agopian et al. (2013a, 2013b, 2013c)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is an association between maternal exposure to atrazine and birth effects in offpsring including male genital malformations, gatroschiss, and choanal atresia or stenosis among offspring. Two major study limitations observed in all three of the studies (Agopian et al. 2013a, 2013b, 2013c) included the semi-ecologic study design that used county-level data to estimate individual-level exposure, as well as the use of maternal residence at delivery to estimate exposure throughout pregnancy. While the Agopian et al. (2013a) study found evidence of a positive association between exposure to atrazine in mothers in (only) the high exposure group of mothers and there was evidence of a trend with increased exposure, the small number of exposed cases (n= 42) along with the primary design limitations of the study (mentioned above) led the agency to place less emphasis on this singular finding. In Agopian et al. (2013b), neither the unadjusted or adjusted analyses for any exposure group, reported evidence of a positive

association between maternal exposure and risk of gastroschisis for any exposure group. While the Agopian et al. (2013b) study in an extended analysis looking at younger vs. older mothers (age cut-off at 25 y.o.) did find evidence of a positive association between exposure to atrazine in older mothers in (only) the high exposure group, the small number of exposed cases (n=33) along with the primary design limitations of the study (mentioned above) leads the Agencyto place less emphasis on this singular finding. In Agopian et al. (2013c), the authors concluded that the study results provided evidence of atrazine as a teratogen; however, the low number of associations, the few statistically significant associations, the lack of adjustment for multiple comparisons, and the lack of significant positive associations for the high exposure group, potentially altered/influenced of any associations between maternal atrazine exposure and subsequent male genital malformations of offspring. These study limitations question the causal association of the study, and as a result, we are unable to conclude that a clear or casual associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of these three studies was ranked low.

Study 4. Chevrier, C., Limon, G., Monfort, C., Rouget, F., Garlantezec, R., Petit, C., . . . 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 atrazine 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 atrazine 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 atrazine and atrazine metabolites were quantified through liquid chromatography/triple-quadrupole mass spectrometry (LC/MS-MS). Mothers and fetuses were considered exposed if atrazine or at least one of its metabolites (atrazine mercapturate, desethylatrazine, hydroxyatrazine, or hydroxydesethylatrazine) was quantified in the maternal urine sample. Investigators further defined “direct exposure” as only atrazine or atrazine mercapturate quantified in maternal urine. Urine samples were also tested for potential confounding herbicides (simazine and simazine

mercapturate, alachlor and its metabolite 2,6-diethylaniline, metolachlor, and acetochlor) and for additional triazine metabolites (deisopropyl atrazine, 2-chlorodiaminoatrazine, hydroxysimazine, hydroxy-desisopropyl atrazine, and hydroxy-2-chlorodiaminoatrazine). 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. For study participants residing in municipalities in Ille-et-Vilaine (62% of the study population), exposure to atrazine via drinking water was estimated by multiplying self-reported average tap water consumption by average atrazine levels in public water supplies based on samples collected by the office of Social and Sanitary Affairs of Brittany from 2000 to 2002. 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[64]. 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 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 10 women with atrazine concentrations above the limit of quantification (LOQ) (median level = 0.12 µg/L; maximum = 0.52 µg/L), 24 with atrazine mercapturate above the LOQ (median = 0.05 µg/L, max = 0.68 µg/L), 60 with desethylatrazine above the LOQ (median = 0.10 µg/L; max = 14.0 µg/L), 57 with hydroxyatrazine above the LOQ (median = 0.10 µg/L; max = 4.00 µg/L), and 31 with hydroxydesethylatrazine above the LOQ (median = 0.60 µg/L; max = 2.50 µg/L) (urinalysis results not mutually exclusive; subjects could test positive for one or more markers of atrazine exposure). Analyses of FGR suggested a significant positive association between atrazine exposure and risk of FGR, adjusting for maternal smoking, blood pressure before and during pregnancy, thawing and refreezing of urine samples, and acetochlor exposure (OR = 1.50; 95% CI: >1, 2.20 with 61 cases exposed and 117 cases unexposed)[65]. Results also suggested a significant positive association between atrazine 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 = 1.70; 95% CI: >1, 2.70 with 38 cases exposed and 65 cases unexposed). There was no evidence of a significant positive association between atrazine exposure and major congenital anomalies, adjusting for year of enrollment, season at conception, maternal occupational exposure to solvents, gestational age at birth, and simazine exposure (OR = 1.20; 95% CI: 0.70, 2.10 with 26 cases exposed and 62 cases unexposed). There was no evidence of a significant positive association between atrazine exposure and male genital anomalies (OR = 1.40; 95% CI: 0.60, 3.20 with 5 cases exposed and 18 cases unexposed) and a positive but not significant association when the exposure definition was restricted to just atrazine or atrazine mercapturate (direct exposure) (OR = 2.30; 95% CI: 0.60, 8.40 with 3 cases exposed and 18 cases unexposed),

[64] 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.

[65] 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.

but small numbers altered/influenced the stability of these associations. Investigators reported that a 1 nmol/L increase in atrazine or atrazine mercapturate in maternal urine was associated with a positive but not significant association with male genital anomalies, but unreported numbers altered/influenced the impact of the finding (OR = 2.80; 95% CI: 0.90, 8.60 with n = 35 maternal samples analyzed but number of exposed and unexposed cases not reported). Linear analyses did not suggest that atrazine exposure was significantly associated with birth weight (atrazine coefficient p-value = 0.13), birth length (atrazine coefficient p-value = 0.20), or head circumference (atrazine coefficient p-value = 0.16), 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[66]. In contrast, linear analyses limited to direct exposure (atrazine and/or atrazine mercapturate in maternal urine sample) showed evidence of a positive association between direct exposure and decreased birthweight in grams (atrazine β = (-151), p-value = 0.04).

Investigators concluded that prenatal exposure to atrazine may impair fetal growth; however, the strength of the reported significant associations were potentially altered/influenced by CIs that nearly approximated the null value of 1.00. Investigators cautioned that results for male genital anomalies was based on small numbers.

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 intraindividual 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, and reported that stability tests on doped human urine samples showed a slight decrease in concentrations after 32 hours at ambient temperatures (-7% and -9% for atrazine and atrazine mercapturate, respectively). 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 between the samples and the calibration standards may have impacted the results of the urinalyses.

In addition to the limitations of the urinalysis, the role of fish consumption in the observed association between atrazine exposure and risk of adverse birth outcomes may not have been adequately explored[67]. Investigators noted that levels of atrazine and/or atrazine mercapturate

[66] Confounders were selected for final models following backwards selection of all covariates considered and retaining only those with $p < 0.20$.

[67] Investigators considered fish consumption in preliminary models but did not retain the variable in final models following backwards selection of covariates and retaining only those with $p < 0.20$.

were higher among women with higher fish intake[68], and in a separate publication, the same research group noted that PCBs and other seafood contaminants like mercury may have reproductive effects[69].

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[70]. 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 hypothesis generation[71].

The study identified atrazine biomarkers in urine samples up to 3 years after the banning of atrazine in France. Authors noted that in 2001, atrazine was widely used in Brittany, with 200 tons applied, mostly to corn, in the area. In 2002, the Ministry of Agriculture began banning products containing atrazine, and a complete ban on the use of atrazine began in October, 2003. Of the n = 579 mother/child study participants, half of the study participants were pregnant/prenatally exposed after a complete ban of atrazine was in effect[72]. While only 2% of study participants had atrazine quantified in urine, 10% had quantifiable hydroxyatrazine and/or desethylatrazine, biomarkers that investigators considered markers of atrazine exposure. It may be that these levels reflected exposure outside of France, exposure due to illicit use of atrazine despite the ban, environmental residue, or measurement error; only measurement error would lead to exposure misclassification and impact the study conclusions regarding the association between atrazine biomarkers and adverse birth outcomes. Other limitations of the study also did not necessarily impact study conclusions regarding associations between biomarker urinary concentrations and risk of adverse birth outcomes. Exposure through drinking water was assessed for a portion of the study population based on atrazine contamination data from 2000 to 2002, which may have been inappropriate to use for pregnancies that occurred after the atrazine ban in 2003, but the suitability of this data most likely did not affect the analyses of the biomarker-outcome association because this data was not used in either the logistic or the linear regression analyses reported above. Similarly, the authors concluded that corn agriculture activity in proximity to maternal residence was not a significant contributor to urinary biomarkers of herbicides, but the data used in this analysis was from 2000 and it was only estimated at the municipality level. However, the robustness of the agriculture data and the evidence linking agriculture activity to metabolite levels did not necessarily impact the biomarker-outcome study conclusions. Notably, investigators controlled for year of study enrollment (pregnancy) and for municipality of maternal residence in models where these variables were found to be significant, which may have captured the effect of annual changes in

[68] No test for trend or measure of association reported in text.
[69] Chevrier, C., Warembourg, C., Gaudreau, E., Monfort, C., Le Blanc, A., Guldner, L., & Cordier, S. (2013). Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. *Epidemiology*, *24*(2), 251-260.
[70] 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
[71] Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. EPA 2016
[72] 50% joined the study in 2002 and 2003 and 50% after the ban was implemented (2004 – 2006).

atrazine levels in drinking water due to the elimination of atrazine products and differences in agricultural practice across municipalities, respectively.

EPA Evaluation of Chevrier et al. (2011)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between maternal exposure to atrazine and adverse birth outcomes in offspring. Although Chevrier et al. (2011) reported a significant positive association between maternal atrazine exposure and risk of fetal growth restriction and small head circumference among offspring, 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. As a result, we are unable to conclude that a causal or clear associative relationship exists between maternal exposure to atrazine and adverse birth outcomes in offspring. Based on the study limitations, the overall quality of the study was ranked low.

Study 5. 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

Cragin et al. (2011) investigated the association between atrazine exposure in drinking water and menstrual cycle function among women through a hybrid retrospective and prospective cohort study. Study participants (n = 102) included women aged 18 to 40 years old, residing in agricultural communities in either Illinois (n = 53 from Mt. Olive, IL, an area with high atrazine concentrations in municipal drinking water) or Vermont (n = 49 from Waterbury and Fair Haven, VT, areas with low atrazine application). Women who took hormonal birth control or medication, who used an intrauterine device, who breast fed within the past 3 months or were pregnant within the past 6 months, and/or who had been diagnosed with reproduction or endocrine disorders were ineligible to participate in the study. Study participants answered a retrospective questionnaire at enrollment (n = 102), maintained a prospective menstrual diary (n = 67), and/or provided daily urine samples for hormone analysis (n = 35). Exposure was assessed in multiple ways, depending on the subject data available: state of residence (IL subjects were considered high exposed and VT subjects were considered low exposed, due to differences in state-wide application of atrazine), atrazine and chlorotriazine concentrations in tap water, atrazine/chlorotriazine concentrations in municipal water, atrazine/chlorotriazine and metabolite (atrazine mercapturate and desethylatrazine mercapturate) levels in urine, and estimated dose based on participant's water consumption. Water sample analyses aligned with the exposure estimation based on state, with none of the 20 tap water samples in VT exceeding the atrazine LOD and only 4 of the samples exceeding the chlorotriazine LOD, versus 15 of the 15 tap water samples exceeding the LOD for atrazine and 6 of the 15 tap water samples exceeding the LOD for chlorotriazine in IL. Average atrazine levels in tap water were higher in IL (0.70 µg/L) than in VT (0.40 µg/L) ($p < 0.01$), while chlorotriazine levels were higher in VT (2.50 vs. 3.30 µg/L, no p-value for test of significant difference reported), though the chlorotriazine analyses were affected by the low number of samples above the LOD. Cases were defined as menstrual cycle

length irregularity, and were assessed via retrospective questionnaire about cycle time and regularity over the year prior to enrollment. In addition to the questionnaire, cycle irregularity was assessed for 67 study participants via a prospective menstrual cycle diary for two complete menstrual cycles following enrollment, and for 35 participants through urinalysis. This subset of participants provided daily urine samples from study enrollment through two menstrual cycles.

ORs and 95% CIs were calculated by bivariate and multivariate unconditional logistic regression models, using the VT study participants as the reference group and adjusting for age, BMI, and smoking. Using the retrospective questionnaire data, results suggested a strong positive association between atrazine exposure and menstrual cycle length irregularity, when exposure was defined by state of residence comparing IL (high exposure) to VT (low exposure) (OR = 4.32; 95% CI 1.27, 14.63; p = 0.02; with 4 cases in VT and 18 cases in IL). Risk of menstrual cycle irregularity increased for IL residents who lived longer than 4 years in their homes (4 or less years in home: OR = 1.94; 95% CI: 0.41, 9.24; greater than 4 years in home: OR = 8.55; 95% CI: 2.15, 33.91, with 5 cases living 4 or less years and 11 cases living more than 4 years in their homes; with 4 VT (referent) cases; p-trend < 0.01). Risk of menstrual cycle irregularity also increased for IL residents who drank more than 2 cups of unfiltered water per day (2 or less cups: OR = 5.41; 95% CI: 1.34, 21.84; greater than 2 cups: OR = 6.73; 95% CI: 1.37, 33.07, with 10 cases drinking 2 or less cups and 8 cases drinking greater than 2 cups of unfiltered water per day, with 4 VT (referent) cases; p-trend = 0.01). Analyses of menstrual cycles longer than 6 weeks also indicated a strong positive association with atrazine exposure (unadjusted OR = 6.16; 95% CI: 1.29, 29.38 with 11 cases in IL and 2 cases in VT; p = 0.02). Notably, all of the logistic regression results were based on low numbers of exposed cases.

Multivariable linear regression models were also employed to assess the relationship between atrazine exposure and reproductive hormone levels, with log transformation applied to hormone data and inverse square transformation applied to the menstrual length continuous variable, and adjusting models for age and smoking status. Results of the linear regression analysis, which utilized the data from the population subset who submitted daily urinary samples (n = 35), indicated atrazine and chlorotriazine dose, calculated by multiplying the volume of unfiltered water ingested per day by the concentration in the residential tap water, was inversely associated to mean mid-luteal estradiol metabolite, adjusting models for age and smoking status (atrazine > 0.36 µg/L β = (-0.49), p = 0.01, with 23 participants exposed at this level; chlorotriazine > 2.50 µg/L β = (-0.49), p = 0.01, with 23 participants exposed at this level). Atrazine dose calculated by multiplying the volume of unfiltered residential tap water ingested per day by the concentration in the municipal water supply was inversely associated with mean mid-luteal progesterone metabolite levels (atrazine > 0.20 µg/L β = (-0.70), p = 0.01, with 9 participants exposed at this level) and with increased follicular phase length (β = -0.02; 95% CI (-0.04), 0.00; p value and number of exposed participants not reported[73]). Authors concluded that study results provided evidence that atrazine exposure in municipal drinking water was associated with reduced reproductive hormone levels and longer follicular phase in women; however, the low numbers of study participants in the urinary sample analyses (n = 35) potentially influenced these results. Authors also concluded that, based on inconsistent results in the analyses of luteinizing hormone, the study provided "no compelling evidence" of an association between atrazine exposure and altered LH secretion.

[73] Significance as reported by authors in text. Upper bound of β CI reported as 0.00.

Strengths of Cragin et al. (2011) included the retrospective and prospective study design, the consideration of different methods of exposure classification, and adjusting models for significant confounders. Study weaknesses included the overall participation rate, which was further reduced in the analyses that considered participant subsets which limited study precision and reduced statistical power. The use of the urinary metabolite desethylatrazine mercapturate may have introduced exposure misclassification, since desethylatrazine mercapturate may indicate exposure to the parent compound or to a breakdown product. Atrazine measurements were limited: in tap water, only 43% of samples were above the LOD, and in urine samples, only 2 women tested positive for measurable urinary atrazine levels, which may reflect both the half-life of atrazine in water and the limit of detection of the analysis methods. Atrazine measurements were similar between IL (0.70 µg/L) and VT (0.40 µg/L). The small number of cases may have affected the stability of the observed associations. Furthermore, authors noted that study findings may be related to unmeasured factors such as other water contaminants and not to atrazine exposure, and also that the generalizability of study results was limited by the predominantly white and middle class study participants.

EPA Evaluation of Cragin et al. (2011)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude there is a causal or clear associative relationship between atrazine exposure and menstrual cycle abnormalities as well as reproductive hormone level irregularities. Cragin et al. (2011) reported evidence of a positive association for menstrual cycle length irregularities and reduced reproductive hormone levels with a longer follicular phase in women relative to atrazine exposure; however, due to the small number of exposed cases ($n \leq 11$ cases), we hesitate to place much emphasis on these two findings. Furthermore, measured atrazine levels were limited in this study and authors noted that study findings may be related to unmeasured factors such as other water contaminants and not to atrazine exposure. These study limitations question the causal association of the study, and as a result, we are unable to conclude that a clear or casual associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 6. García-Pérez, Javier, López-Abente, Gonzalo, Gómez-Barroso, Diana, Morales-Piga, Antonio, Pardo Romaguera, Elena, Tamayo, Ibon, . . . Ramis, Rebeca. (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). 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 atrazine suggested a positive association between living within 2.5 km of a facility that released atrazine and risk of childhood leukemia (OR = 1.83; 95% CI: 1.20, 2.80 with 30 cases and 396 controls living within 2.5 km of a facility; 17 facilities reporting 5 kg atrazine released into water and no facilities reporting atrazine released into air).

Study strengths included the use of national registries to identify both cases and controls and the large number of controls[74]. 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[75,76]. 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 limited but insufficient to conclude there is a causal or clear associative relationship between residential proximity to urban pollutants such as atrazine 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 atrazine 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

[74] 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.)

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

[76] 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.

between residential proximity to urban pollutants including atrazine and childhood leukemia. Based on the study limitations, the overall quality of the study was ranked low.

Study 7. Hoppin, J. A., Umbach, D. M., Long, S., London, S. J., Henneberger, P. K., Blair, A., . . . 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)[77] 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, 28% (n ~ 367) reported current use of atrazine[78]. Among the 3,939 non-allergic wheeze cases, 33% (n ~ 1,300) reported current use of atrazine. Of the 16,885 non-case subjects, 27% (n ~ 4,559) reported current use of atrazine. 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 significant positive association between current atrazine use and both allergic and nonallergic wheeze (allergic: OR = 1.33; 95% CI: 1.09, 1.61; nonallergic: OR = 1.42; 95% CI: 1.26, 1.59). Atrazine exposure was further analyzed by frequency of current use (days per year used), with categories of exposure created by tertiles of the distribution of users' frequency of atrazine use, with the top tertile further divided into thirds, to create five days-per-year of use categories. For each category, ORs and 95% CIs were estimated, comparing the exposure category to subjects never exposed. Results suggested a significant positive association between atrazine exposure and allergic wheeze for the middle three exposure categories ($1.40 \leq OR \leq 1.81$; no 95% CIs encompassed the null value of 1.0 (average CI width: 0.42); with $2\% \leq n \leq 9\%$ cases in each exposure category; exposure categories 5 – 7, 8 – 10, 11 – 14 days per year of use), but not for the lowest or highest exposure categories (lowest: OR = 1.20; 95% CI: 0.94, 1.54, with 9% cases exposed 1 – 4 days per year of use; highest: OR = 1.20; 95% CI: 0.83, 1.74, with 3% cases exposed 15 – 122 days per year of use). For non-allergic wheeze, a significant positive association was observed in each exposure category relative to atrazine ($1.35 \leq OR \leq 1.72$; no 95% CIs encompassed the null value of 1.0; with $2\% \leq n \leq 12\%$ cases in each exposure category; exposure categories 1 – 4, 5 – 7, 8 – 10, 11 – 14, and 15 -122 days per year of use).

[77] 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.

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

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[79], 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[80].

EPA Evaluation of Hoppin et al. (2016)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between atrazine exposure and wheeze. Hoppin et al. (2016) reported evidence of a significant positive association between atrazine exposure and non-allergic and allergic wheeze in male pesticide applicators. Although this study benefited from the large AHS participant data collected on specific pesticide usage, the study was limited due to the small number of exposed cases observed in many of the exposure categories (n = 7 – 18 exposed cases (or n = 2 – 5%) at the three highest exposure categories; exposure categories 8 – 10, 11 – 14, and 15 – 122 days of use). Furthermore, the cross-sectional study design was considered a study limitation, as temporality could not be determined. These study limitations questioned the causal association observed in the study, and as a result, we are unable to conclude that a causal or clear associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 8. 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

James and Hall (2015) conducted an ecologic study to investigate the association between atrazine, simazine, and other pesticide levels in groundwater and the risk of Parkinson's disease (PD). The study population included n = 332,971 Medicare beneficiaries, living in Colorado in 2007, aged 65 and older. Prevalent cases of PD (n = 4,207) were identified through the 2007 Colorado Medicare Beneficiary Database. Age-standardized prevalence ratios for PD were calculated by zip code, and empirical Bayesian methods were used to smooth PD ratios across zip codes to account for the inflation potential of a single case in low population zip codes, using the ratios of adjacent zip codes to smooth the prevalence ratios. Exposure was defined as residential pesticide exposure and was estimated based on water samples taken from 286 wells, covering all the major aquifers in the state. Data on water quality from 2000 to 2007 was collected from the USGS National Water Quality Assessment Data Warehouse (NAWQA) and the Colorado Department of Public Health and Environment (CDPHE) Water Quality Division.

[79] 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.

[80] 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.

Ordinary kriging was used to predict groundwater pesticide levels across Colorado, and exposure levels were assigned based on nine-digit zip codes for each study participant. Logistic regression was used to estimate ORs and 95% CIs for atrazine, simazine, and other pesticides, combined and individually. Models were run first with pesticide levels as a continuous variable and second with pesticide levels analyzed categorically (low, medium, and high exposure). Results for all pesticides combined suggested that for every 1.00 µg/L of pesticides in groundwater, risk of PD increased 3% (OR = 1.03; 95% CI: 1.02, 1.04). Simazine was not analyzed independently. Mean measured atrazine levels in the water samples was 0.14 µg/L (range 0.0005 – 10.0 µg/L). Results from atrazine analyses suggested evidence of a slight positive significant association between groundwater atrazine levels and risk of PD (per 1.00 µg/L of atrazine in groundwater, OR = 1.04; 95% CI: 1.03, 1.06)[81]. When atrazine levels were assessed categorically, there was evidence of a significant positive association between high exposure (10 – 100 µg/L) and risk of PD (OR = 1.68; 95% CI: 1.36, 2.07), but not between medium exposure (1 – 10 µg/L) and risk of PD (OR = 1.08; 95% CI: 0.91, 1.28), compared to the low exposure group (< 1.00 µg/L); however, the robustness of the estimates for the high exposure group was hindered by the definition of high exposure (estimates of 10 – 100 µg/L), which extended to levels far above the maximum atrazine level measured in the well samples (10.0 µg/L).

The discrepancies between the measured and predicted atrazine levels greatly detracted from the weight of the evidence reported in James and Hall (2015). Study strengths included the use of a state database of a federal insurance program to identify cases, a large study population, the use of state and national sources for exposure assessment measurements of specific pesticides, the consideration of a small spatial areal unit (the nine-digit zip code, which typically encompasses several hundred yards) to aggregate the data, and appropriate statistical techniques, including Bayesian smoothing to manage the potential influence of small population zip codes and the use of spatial statistical techniques (kriging)[82] to predict spatially dependent data (groundwater pesticide levels) at unmeasured locations. However, the kriged outcome (predicted values) were the primary limitation of the study; the addition of a map of kriged standard errors of the predictions would have described the precision of the predictions across CO[83], an important and missing indication considering the disparity between the kriged predicted groundwater levels of pesticides (range 83 – 112 µg/L[84]) and the measured concentrations of pesticides (mean = 0.17 µg/L, range 0.0005 to 10.0 µg/L), and the difference between the high exposure category definition for atrazine based on kriged predictions (10 – 100 µg/L) and the atrazine measurements from the well samples (mean = 0.14 µg/L, range 0.0005 – 10.0 µg/L). Additional information on the spatial statistical analyses, such as the inclusion of a variogram to describe

[81] There was some confusion in the article on this topic. In the abstract, the authors refer to a 3% increase in the PD "per 1.0 ug/L", but in text (p. 268), they refer to it as "per 0.01 mg/L" (which = 10 ug/L). This represents a substantial difference with the former representing a 3% increase for every 1 ppb increase in atrazine concentation whereas the latter represents a 3% increase for every 10 ppb increase. In Figure 2 and Tables 1 and 2, the authors report in "mg/L", and Table 1 reports as "per 0.01 mg/L". They report the EPA MCL in ug/L in text (p. 270), and in the methods, they say data included contaminant levels in ug/L. They also report mean atrazine levels in ug/L (p. 268). Given these units issues and the discrepancies that appeared in the article, it is not clear what concentration units the authors were using when they report the 3% or 4% increase risk of PD.

[82] Cressie, N. (1989). Geostatistics. *The American Statistician*, *43*(4), 197-202.

[83] Notably, the publication text referenced a figure 1 (ordinary kriged spatial prediction map) and figure 2 (standard error map) that did not align with the printed figures (as printed, figure 1 showed prevalence rates of PD and figure 2 showed the ordinary kriged spatial prediction map for pesticide levels in groundwater).

[84] Reported in figure in mg/L: range = 0.083 – 0.112 mg/L.

residual spatial variation, would have further strengthened the descriptions of the spatial data and the results. Other weaknesses of the study included its cross-sectional design, with no assessment of the relative temporality between exposure and outcome and no assessment of exposure variability over time. Authors noted that collecting case definitions for a single year may have contributed to misclassification; verifying case status using multiple years of Medicare beneficiary information could have reduced the potential for misclassification. Authors noted that sensitivity analyses that removed cases with only 1 claim record in 2007 did not change the estimate of effect for all pesticides combined (OR = 1.03), though it did fail to attain significance (95% CI: 0.92, 1.16); no sensitivity analyses were reported for atrazine specifically.

EPA Evaluation of James and Hall (2015)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between atrazine in groundwater and PD. Although James and Hall (2015) reported a slight positive significant association between groundwater atrazine levels and risk of PD overall, and a significant positive association at the high exposure level compared to the low exposure level when the atrazine levels were assessed categorically, the study limitations mentioned above including the ecologic study design and the kriged outcome (predicted values) questioned the causal association observed in the study. As a result, we are unable to conclude that a causal or clear associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 9. 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

LaVerda et al. (2015) investigated the association between exposure to atrazine and other pesticides and weight gain through a prospective study of the AHS cohort. The study population (n = 8,365) included male pesticide applicators residing in Iowa or North Carolina, aged 20 years or older. Exposure information, including ever use of specific pesticides as well as duration and frequency of exposure, was assessed by self-administered questionnaires at study enrollment (1993 – 1997). During study enrollment, participants also self-reported body mass index (BMI) at age 20 and at study enrollment. At follow-up telephone interviews conducted 5 years after study enrollment, participants reported BMI and updated pesticide exposure. Also at follow-up, participants reported diet history through a self-administered questionnaire. Exposure was assessed by combining follow-up exposure data with enrollment exposure data to estimate lifetime exposure metrics. Of the 8,365 study participants, 6,407 reported ever exposure to atrazine, while 1,772 reported never exposure (186 subjects had missing atrazine exposure data). Analyses considered cumulated pesticide exposure days from age 20 to age at follow-up. The mean cumulated atrazine exposure days from age 20 to follow-up was 97.7 days (SD = 207.5). Multiple linear regression was used to assess the association between atrazine exposure as a continuous variable and unit change in BMI ($kg/m^2/d$; BMI associated with 100 cumulative exposure days between age 20 and age and follow-up). Results for atrazine indicated a significant positive association between cumulated atrazine exposure days and increased BMI, and results were similar for the unadjusted analysis ($\beta = 0.12$, $p < 0.01$) and for analysis adjusted

for BMI at age 20, age, smoking, daily kilocalories consumed, and daily hours of heavy lifting ($\beta = 0.10$, $p < 0.01$). To investigate the potential effect modification of weight-related health conditions diagnosed in 2,586 participants (cancer excluding nonmelanoma skin cancer, diabetes, heart disease, lupus, and/or amyotrophic lateral sclerosis (ALS)), these participants were excluded, and results from the medical exclusions analysis were similar to the overall analysis ($\beta = 0.11$, $p < 0.01$). To investigate the potential effect modification of state, a stratified analysis was conducted, and results indicated a significant positive association between cumulative atrazine exposure days and increased BMI in Iowa (adjusted analysis $\beta = 0.17$, $p < 0.01$), but not in North Carolina (adjusted analysis $\beta = 0.05$, $p = 0.05$; significance based on Bonferroni-adjusted p value = 0.003). Additional analyses used ordinal logistic regression (OLR) to assess the association between atrazine exposure and BMI, considering both variables categorically, with cut-points for atrazine at the 25th, 50th, and 75th percentiles and cut-points for BMI based on World Health Organization (WHO) categories for normal weight (18.5 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2), and found evidence of a significant positive association between atrazine exposure and BMI for the highest exposure group (OR = 1.41; 95% CI: 1.06, 1.87) but not in the lower exposure groups ($0.93 \leq OR \leq 1.25$; all 95% CIs encompassed the null value of 1.00 (average CI width: 0.11)) (number of participants in each exposure/BMI category not reported). The authors concluded that atrazine exposure was moderately associated with weight gain; however, they noted that the r-squared values for all models were small (R^2 range: 0.27 – 0.32 for adjusted multiple regression models for all participants, Iowa participants only, and North Carolina participants only), which indicated that BMI was not highly determined by atrazine exposure and that other, unmeasured factors may have greatly influenced the outcome.

Strengths of LaVerda et al. (2015) included the prospective cohort study design, questionnaires and interviews that assessed specific pesticide exposure including duration and frequency of exposure, adjusting for other pesticides in the models, and the use of the Bonferroni adjustment to minimize chance effects due to multiple comparisons and the chance of type I error. The study was limited by the self-reported outcome (BMI), including a retrospective report of BMI at age 20 collected during study enrollment (the mean age at follow-up was 56.4 years, indicating the mean age at enrollment was approximately 51 years old). This introduced the potential for outcome misclassification. The inclusion of variables for daily kilocalories consumed and daily hours of heavy lifting in the adjusted models attempted to control for the influence of physical activity and diet on BMI; however, the crude approximation for physical activity (defined as "heavy lifting" and based on participant responses to questions about hours of heavy lifting at time of interview and, retrospectively, 10 years prior to study enrollment) and the use of a diet history questionnaire may not have appropriately captured these critical influences on BMI. Additional limitations of this AHS cohort based study curbed the generalizability of the findings: the study population was predominantly white non-Hispanic (97%), strictly male, and drawn from a pool of farmers and professional applicators and therefore susceptible to the healthy worker effect[85]. The use of questionnaires to assess exposure and confounder information may have introduced the potential for recall bias and exposure misclassification. However, the AHS

[85] Potential confounding when study subjects are drawn from an occupational cohort, because healthy people are more likely to both gain and keep employment. See Pearce, N., Checkoway, H., & Kriebel, D. (2007). Bias in occupational epidemiology studies. Occupational and environmental medicine, 64(8), 562-568.

participant cohort has demonstrated high reliability for self-reported information for pesticide use, demographic, and lifestyle factors[86]. Finally, the medical exclusions list included diseases that may also be associated with exposure to pesticides investigated in this study; however, authors presented stratified results (with and without medical exclusions) to confront this effect modifier and the potential effect modification of state of residence, and found similar results for atrazine analyses across these stratifications.

EPA Evaluation of LaVerda et al. (2015)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between atrazine exposure and body weight gain among pesticide applicators within the AHS. Although LaVerda et al. (2015) reported a positive association for atrazine exposure, several study limitations (mentioned above) existed in this study including self-reported outcome (BMI) resulting in the potential for exposure misclassification, and the challenges associated with appropriately measuring BMI. These study limitations question the reliability of the study, and a result, we are unable to conclude that a causal or clear associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 10. 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

Lebov et al. (2016) evaluated the association of end-stage renal disease (ESRD) and pesticides including atrazine among men through a prospective cohort study. Study participants were male pesticide applicators living in Iowa and North Carolina and enrolled in the AHS (n = 55,580). Exposure information was collected from self-reported questionnaires at enrollment (1993 – 1997). ESRD cases (n = 320) were identified through linkage with the US Renal Data System (USRDS) and included cases diagnosed between study enrollment and December 31, 2011. The Cox proportional hazards model was used to calculate HRs for intensity-weighted lifetime days (IWLD) of use of specific pesticides (low, medium, and high exposure groups were created based on the distribution of pesticide use among cases) and risk of ESRD, adjusting for age and state and using participants who reported no use as the referent. Results provided evidence of a significant positive association between atrazine exposure and risk of ESRD for the high exposure group (high exposure ≥ 6,961.50 IWLD; HR = 1.52; 95% CI: 1.11, 2.09 with 69 cases and 8,630 non-cases exposed), but not for the low or medium exposure groups (low exposure ≤ 1,306.70 IWLD; HR = 1.13; CI: 0.82, 1.56 with 69 cases and 13,475 non-cases exposed; medium exposure 1306.71 to 6,961.49 IWLD; HR = 0.99; 95% CI: 0.72, 1.36 with 68 cases and 14,480 non-cases exposed). There was a significant linear trend identified (p-trend = 0.01).

Strengths of Lebov et al. (2016) included the prospective cohort study design, specific chemical exposure information, the use of a national database to identify cases, and the large cohort, with

[86] 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.

sufficient numbers of exposed and unexposed cases in each exposure category. The use of IWLD exposure allowed the researchers to evaluate the potential effects of exposure beyond the immediate effects of pesticide poisoning. Authors noted a potential for bias if cases modified their pesticide usage after enrollment. Additional limitations of this AHS cohort-based study curbed the generalizability of the findings: the study population was predominantly white non-Hispanic, strictly male, and drawn from a pool of farmers and commercial applicators and therefore susceptible to the healthy worker effect[87] The use of questionnaires to assess exposure and confounder information may have introduced 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[88].

EPA Evaluation of Lebov et al. (2016)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between atrazine exposure and end-stage renal disease (ESRD). Lebov et al. (2016) reported evidence of a significant positive association between atrazine exposure and risk of ESRD for the high exposure group only, along with a significant linear trend. Although an isolated association between atrazine exposure and ESRD in male applicators was reported in Lebov et al. (2016), there is insufficient weight of evidence to alter the Agency's conclusions regarding end-stage renal disease. Lebov et al. (2015) found no evidence of ESRD relative to atrazine exposure among wives of pesticide applicators. Study strengths included the prospective cohort study design and the specific chemical exposure information. The use of questionnaires to assess exposure and confounder information may have introduced the potential for recall bias and exposure misclassification were noted study limitations. Overall, the study quality was ranked high due to the AHS prospective cohort study design and large amount of data captured within the AHS.

Study 11. 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.

Rinsky et al. (2012) investigated the association between atrazine exposure in public drinking water and risk of preterm birth through an ecological study. The study population included residents living in Kentucky (KY) (approximately 4.2 million people), and considered n = 71,768 singleton, live births to women (90% white) in KY from 2004 to 2006, identified by reviewing birth certificate data from the KY Department for Public Health. Exposure was assessed by considering atrazine levels in public drinking water for the years 2000 to 2008. Atrazine concentration data was collected from the KY Division of Water for public community drinking water, and mean atrazine levels were calculated for each of the 120 counties in KY. Exposure was assigned based on the maternal county of residence as listed on the birth certificate using three methods: method 1 substituted 0 for all atrazine measurements below the limit of detection

[87] Potential confounding when study subjects are drawn from an occupational cohort, because healthy people are more likely to both gain and keep employment. See Pearce, N., Checkoway, H., & Kriebel, D. (2007). Bias in occupational epidemiology studies. Occupational and environmental medicine, 64(8), 562-568.
[88] 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.

(LOD), method 2 substituted a value equal to half the LOD based on the specific testing method for each measurements below the LOD, and method 3 substituted a value equal to half the LOD based on the lowest LOD among all testing methods used for each measurement below the LOD. Preterm cases (n = 8,915) were defined as births prior to 37 completed weeks of gestation, and were identified based on birth certificate data, using date of mother's last menstrual period and infant's date of birth to estimate gestational age. Individual-level confounding data including maternal age, race/ethnicity, education, smoking, and prenatal care, were also identified by birth certificates. Logistic regression was used to estimate ORs and 95% CIs to analyze the relationship between county-level atrazine exposure levels and risk of preterm birth, adjusting for these confounding covariates. Results suggested a slight positive association between high atrazine exposure and risk of preterm birth for the high exposure group compared to the low exposure group for all methods of exposure assessment (method 1: OR = 1.22; 95% CI: 1.16, 1.29 with 18,222 total births in the high exposure group (mean atrazine ≥ 0.08 µg/L) and 32,846 in the low exposure group (mean atrazine = 0 µg/L); method 2: OR = 1.20; 95% CI: 1.14, 1.27 with 17,615 total births in the high exposure group (mean atrazine ≥ 0.11 µg/L) and 37,886 in the low exposure group (mean atrazine ≤ 0.04 µg/L); method 3: OR = 1.26; 95% CI: 1.19, 1.32 with 17,825 total births in the high exposure group (mean atrazine ≥ 0.08 µg/L) and 26,824 in the low exposure group (mean atrazine ≤ 0.002 µg/L); the number of cases in each exposure category was not reported). There was no evidence of a significant positive association between moderate atrazine exposure and risk of preterm birth for any method of exposure assessment (0.90 ≤ OR ≤ 1.02; all 95% CIs encompassed the null value of 1.00 (average CI width: 0.01); with 16,267 ≤ n ≤ 27,119 total births in each method's moderate exposure category).

Strengths of Rinsky et al. (2012) included the use of a state birth registry to identify study participants, cases, and individual-level confounders, and the large sample size from diverse geographic areas derived from this method. Environmental samples with standardized testing methods added strength to the exposure method, though the assignment of individual-level exposures based on county-level atrazine concentrations may have led to exposure misclassification. The investigators noted this limitation of the study, and further noted that inconsistent monitoring of atrazine across water systems, including temporal differences in the data that was unaccounted for in statistical methods, may have lessened the quality of the exposure information. The use of maternal address at time of birth was another source of potential exposure misclassification in a study that endeavored to assess prenatal atrazine exposure, as mothers may have moved residences and thus been exposed to different public drinking water systems during pregnancy. Study investigators made no attempt to assess individual water consumption from these public drinking water supplies, further adding to the potential for exposure misclassification in this study.

EPA Evaluation of Rinsky et al. (2012)

Overall, the epidemiological evidence is limited but insufficient at this time to conclude that there is a causal or clear associative relationship between atrazine exposure in drinking water and the risk of preterm birth. Although Rinsky et al. (2012) reported a slight positive association between high atrazine exposure and risk of preterm birth for the high exposure group compared to the low exposure group based on separate methods, the ecologic study design and the inconsistent monitoring of atrazine across water systems within the study, led us to place less

emphasis on the observed study results. Due to these mentioned study limitations, we are unable to conclude that a causal or clear associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 12. 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.

Stayner et al. (2017) evaluated the association between atrazine exposure in drinking water and pre-term delivery and/or low birthweight at birth in an ecologic study. Using data from the EPA's atrazine water monitoring program (AMP) from 2003 – 2008, cases included full-term births (≥ 37 weeks) which occurred between 2004 – 2008 in 46 counties located within Ohio, Indiana, Iowa, or Missouri. Cases were identified from state birth registry databases. Exposure was assessed at the county-level, and estimates for each birth were based on the monthly average of atrazine concentrations found within the community water systems in each county between 2003 and 2008. The following outcomes were determined for each county: pre-term delivery (PTD), very pre-term delivery (VPTD), low birth weight (LBW), and very low birth weight (VLBW). Negative binomial models were fit for each birth outcome – PTD, VPTD, LBW, VLBW – and single exposure models were used to determine associations between atrazine exposure and each birth outcome, adjusting for race and ethnicity, state, season of birth, state, child's sex, median income, maternal education, smoking among women, and population density. A separate sensitivity analysis was also conducted to determine if a difference existed between community water systems and private well water usage, relative to atrazine exposure via drinking water and birth outcomes. For each of the four birth outcomes, all births were stratified by age (0 – 3 months, 4 – 6 months, 7 – 9 months, 9 months) and individual RRs with 95% CIs were calculated.

Among the total number of live-births in this study (n = 134,258), there were 13,875 PTD cases, 1,882 VPTD cases, 3,016 LBW cases, and 1,386 VLBW cases. Overall, no evidence of a significant positive association was observed between atrazine exposure and any of the following birth outcomes: PTD, VPTD, LBW, and VLBW, in the single exposure models ($0.98 < RRs < 1.07$; all 95% CIs encompass the null value of 1). For the sensitivity analysis, when the data was restricted to only looking at counties with private well water usage (< 10% or 20% private well usage), evidence of a slightly significant association was observed for atrazine restricted to < 10% of private well use among PTD cases at 4 - 6 months and 9 months of age (RR: 1.08; 95% CI: 1.05, 1.11 $p < 0.001$; RR: 1.10; 95% CI: 1.01, 1.20, $p < 0.05$). No evidence of a significant positive association was observed for atrazine exposure at < 10% well usage and PTD cases at 0 – 3 months and 7 – 9 months, and no evidence of a significant positive association was observed for atrazine exposure restricted to < 20% well usage among PTD cases in any age group. For VPTD, evidence of a slightly significant positive association was observed between atrazine exposure at < 10% private well water usage among cases at 7 – 9 months only (RR: 1.19; 1.04, 1.36, $p < 0.05$). No evidence of a significant positive association was observed between atrazine exposure restricted to < 20% private well usage among any of the VPTD cases. For LBW and VLBW, no evidence of a significant positive association was observed for < 10% and <2 0% private well water usage relative to atrazine in any age group ($0.88 < RRs < 1.10$; all 95% CIs encompass the null value of 1).

Although a strength of this study included the large study population, several significant study limitations also existed. Due to the ecologic study design, individual measurements for the exposure and outcome were not available; both were assessed at the county-level *only*. As a result, the associations observed are less reliable, due to the potential of misclassification. Furthermore, several concerns were noted in estimating the exposures of this study at the county-level and may have also contributed to exposure misclassification. First, the atrazine exposure estimates were obtained for regulatory instead of scientific purposes; second, some of the atrazine measurements were below the level of detection and as a result were potentially not included in the overall estimates; third, potential data from community wells not part of EPA's atrazine water monitoring program (AMP) involved in this study were not included; and fourth, the small amount of exposure data surrounding private well water usage (significantly more data was available regarding community well water use) may have led to misclassification. When the exposure data was restricted to counties using < 10% or 20% private well water use only, the number of cases and ultimately the amount of available data declined considerably, causing the statistical power to decline. Lastly, no information regarding personal drinking habits during pregnancy, maternal reproductive histories, and the time of conception were reported in this study.

EPA Evaluation of Stayner et al. (2017)

Overall, there is no epidemiological evidence at this time to conclude that there is a causal or clear associative relationship between atrazine exposure in drinking water and the risk of preterm birth and/or low birth weight at birth. Stayner et al. (2017) reported no evidence of a significant positive association between atrazine exposure and any of the following birth outcomes: PTD, VPTD, LBW, and VLBW, in the single exposure models (0.98 < RRs < 1.07; all 95% CIs encompass the null value of 1). Although evidence of a slightly significant association was observed for atrazine when restricted to < 10% of private well use among PTD and VPTD cases at 4 - 6 months and 9 months of age only, several study limitations discussed above caused the reported associations in this study to be less reliable. Due to these study limitations, we are unable to conclude that a causal or clear associative relationship exists relative to atrazine exposure at this time. Based on the study limitations, the overall quality of the study was ranked low.

Study 13. Koutros, S., Beane Freeman, L. E., Lubin, J. H., Heltshe, S. L., Andreotti, G., Barry, K. H., DellaVella, 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

In an update to the Alavanja et al. (2003) study, Koutros et al. (2013) investigated the potential association between prostate cancer and specific pesticides including atrazine through a prospective cohort study. The study population (n = 54,412) included male pesticide applicators participating in the AHS. Pesticide exposure information was obtained via self-administered questionnaires at study enrollment (1993 – 1997) and at follow-up 5 years after enrollment. Cumulative lifetime exposure was calculated as the product of lifetime days of use and a measure of exposure intensity based on application practices including mixing status, application method, equipment repair, and use of personal protective equipment. Incident prostate cancer cases were identified through cancer registry files in Iowa and North Carolina, and cases

diagnosed between study enrollment and December 31, 2007 were included in the analysis. Among the incident prostate cancer cases identified in the study population (n = 1,962 incident cases), there were 919 aggressive prostate cancer cases[89]. Poisson regression was used to calculate RRs, controlling for age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity. Exposure quartiles were constructed for prostate cancer and aggressive prostate cancer based on the distribution of exposed cases, and RRs were reported for each quartile. There was no evidence of a significant positive association for exposure to atrazine and either overall prostate cancer ($0.97 \leq RR \leq 1.05$; CIs encompassed the null value of 1.00 for all exposure quartiles (average CI width = 0.28), with 335 – 336 exposed total prostate cancer cases per quartile and 507 nonexposed cases of total prostate cancer) or aggressive prostate cancer ($0.93 \leq RR \leq 1.12$; CIs encompassed the null value of 1.00 for all exposure quartiles (average CI width = 0.45), with 162 – 163 exposed aggressive prostate cancer cases per quartile and 228 nonexposed cases of aggressive prostate cancer). Furthermore, there was no evidence of a linear trend across increasing exposure quartiles for total prostate cancer ($p = 0.68$) or aggressive prostate cancer ($p = 0.39$). Investigators considered the potential effect of a family history of prostate cancer on the association between atrazine exposure and prostate cancer by stratifying the total prostate cancer data by family history and found no evidence of a statistically significant interaction (likelihood ratio $p_{interaction} = 0.64$).

This study benefited from the large AHS participant cohort with data collected over time, including specific pesticide usage, demographics, and lifestyle factors, and the inclusion of a large number of prostate cancer cases. Weaknesses of the study included the potential for the healthy worker effect to bias observations towards the null,[90] the high percentage of white men compared to other demographic groups in the AHS cohort, potentially limiting the generalizability of results, 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,[91] and the restriction to within-cohort analyses may have minimized the healthy worker effect[92]. Another limitation of the study was that the Gleason score, used to assess aggressive prostate cancer, were not standardized (e.g., through a central review of all study subjects), and scores were missing from 30% of cases from North Carolina; thus, the aggressive prostate cancer analyses may not reflect the true risk.

EPA Evaluation of Koutros et al. (2013)
Overall, there is no epidemiological evidence at this time to conclude that there is a causal or clear associative relationship between atrazine exposure and prostate cancer. Koutros et al.

[89] Aggressive prostate cancer cases were defined as fatality due to prostate cancer and/or by tumor characteristics including distant stage, poorly differentiated grade, and/or a Gleason score of 7 or higher.
[90] Potential confounding when study subjects are drawn from an occupational cohort, because healthy people are more likely to both gain and keep employment. See Pearce, N., Checkoway, H., & Kriebel, D. (2007). Bias in occupational epidemiology studies. Occupational and environmental medicine, 64(8), 562-568.
[91] 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.
[92] 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

(2013) reported no evidence of a significant positive association between atrazine exposure and overall prostate cancer and aggressive prostate cancer. The prospective cohort design and the large size of the AHS cohort were study strengths, and inaccuracies in scoring aggressive prostate cancer using the Gleason score was considered a study weakness.. Based on the study limitations, the overall quality of the study was ranked moderate.

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

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spouses in the agricultural health study. *Environ Health Perspect, 119*(11), 1610-1615. doi:10.1289/ehp.1103413
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Appendix B.1:

Table B1. Publications full text reviewed. Articles that passed full text review are bolded in black; exclusion criteria specified for articles that failed full text review are not bolded. Articles that met additional inclusion criteria specific to this epidemiological assessment (see footnote)[93] are bolded in red.

Author	Year	Article Capture Method*			Passed full text review?		Exclusion criterion applied			
		Open literature search	AHS	Reference review			Specific chemical not quantified (ex., only triazine generally)	No original data	Not in English	Altered structure
Agopian, A. J., et al.	**2013a**	**X**			**YES**					
Agopian, A. J., et al.	**2013b**	**X**			**YES**					
Agopian, A. J., et al.	**2013c**	**X**			**YES**					
Alavanja, M. C., et al.	**2003**		**X**		**YES**					
Almberg, K. S., et al.	2014	X			No		X			
Andreotti, G., et al.	**2009**		**X**		**YES**					
Andreotti, G., et al.	**2010**		**X**		**YES**					
Andreotti, G., et al.	**2012**		**X**		**YES**					
Arbuckle, T. E., et al.	**2001**	**X**			**YES**					
Band, P. R., et al.	**2011**	**X**			**YES**					
Baris, D., et al.	1998	X			No		X			
Beard, J. D., et al.	**2011**		**X**		**YES**					
Beard, J. D., et al.	**2013**	**X**	**X**		**YES**					
Beard, J. D., et al.	**2014**		**X**		**YES**					
Birnbaum, L. S., et al.	2003	X			No			X		

[93] 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 atrazine were the 12 epidemiology publications identified in the literature that reported a statistically significant estimate of effect for atrazine, that emanated from a prospective cohort and/or were otherwise of a moderate or high quality study design[93] or were often referenced in the epidemiology literature, and that were unavailable at the time of the recent SAPs.

Author	Year	Article Capture Method*			Passed full text review?		Exclusion criterion applied			
		Open literature search	AHS	Reference review			Specific chemical not quantified (ex., only triazine generally)	No original data	Not in English	Altered structure
Blair, A., et al.	2005		X		No			X		
Boccolini, P. d. M. M., et al.	2013	X			No		X			
Brown, L. M. et al.	**1990**			**X**	**YES**					
Brown, L.M., et al.	**1993**			**X**	**YES**					
Burmeister et al.	1990			X	No			X		
Cantor, K.P., et al.	**1992**			**X**	**YES**					
Carreon, T., et al.	**2005**			**X**	**YES**					
Carter, C. J., et al.	2016	X			No					X
Chevrier, C., et al.	**2011**	**X**			**YES**					
Clark, R. M., et al.	1986	X			No		X	X		
Clavel, J., et al.	1996			X	No		X			
Clementi, M., et al.	2007	X			No		X			
Cockburn, M., et al.	2011	X			No					
Cragin, L. A., et al.	**2011**	**X**			**YES**					
Crawford, J. M., et al.	**2008**		**X**		**YES**					
Dabrowski, S., et al.	2003			X	No		X			
Dayton, S. B., et al.	**2010**		**X**		**YES**					
De Roos, A. J., et al.	**2003**	**X**			**YES**					
De Roos, A. J., et al.	**2005**	**X**	**X**		**YES**					
Donna, A., et al.	1989			X	No		X			
Engel, L. S., et al.	**2005**		**X**		**YES**					
Farr, S. L., et al.	**2006**		**X**		**YES**					
Farr, S.L., et al.	2004		X	X	No		X			
Flower, K. B., et al.	**2004**		**X**		**YES**					
Freeman, L. E., et al.	**2011**	**X**	**X**		**YES**					
García-Pérez, J., et al.	2016	X			No		X			
García-Pérez, J., et al.	**2017**	**X**			**YES**					
García-Pérez, J., et al.	**2015a**	**X**			**YES**					
García-Pérez, J., et al.	**2015b**	**X**			**YES**					
Goldner, W. S., et al.	**2010**		**X**		**YES**					
Goldner, W. S., et al.	**2013**		**X**		**YES**					
Henneberger, P. K., et al.	**2014**		**X**		**YES**					
Hessel, P. A., et al.	**2004**	**X**			**YES**					
Hoar Zahm, S., et al.	**1993**	**X**			**YES**					
Hoar, S.K., et al.	1985			X	No		X			

Author	Year	Article Capture Method*			Passed full text review?		Exclusion criterion applied			
		Open literature search	AHS	Reference review			Specific chemical not quantified (ex., only triazine generally)	No original data	Not in English	Altered structure
Hopenhayn-Rich, C., et al.	**2002**	**X**			**YES**					
Hoppin, J. A., et al.	**2002**	**X**	**X**		**YES**					
Hoppin, J. A., et al.	**2007**		**X**		**YES**					
Hoppin, J. A., et al.	**2008**		**X**		**YES**					
Hoppin, J. A., et al.	**2009**		**X**		**YES**					
Hoppin, J. A., et al.	**2016**		**X**		**YES**					
Hoppin, J. A., et al.	**2006a**		**X**		**YES**					
Hoppin, J. A., et al.	**2006b**		**X**		**YES**					
Hornemann, A., et al.	2009			X	No				X	
James, K. A., et al.	**2015**	**X**			**YES**					
Jones, R. R., et al.	2014	X			No		X			
Kamel, F., et al.	**2007**		**X**		**YES**					
Karami, S., et al.	**2013**		**X**		**YES**					
Kettles, M. A., et al.	1997	X			No		X			
Kirrane, E. F., et al.	**2005**		**X**		**YES**					
Klucinski, P., et al.	2001			X	No		X			
Kossman, S., et al.	1996			X	No		X			
Koutros, S., et al.	**2011**		**X**		**YES**					
Koutros, S., et al.	**2013**		**X**		**YES**					
Koutros, S., et al.	**2016**		**X**		**YES**					
Landgren, O., et al.	**2009**		**X**		**YES**					
LaVerda, N. L., et al.	**2015**	**X**	**X**		**YES**					
Lebov, J. F., et al.	**2015**	**X**	**X**		**YES**					
Lebov, J. F., et al.	**2016**	**X**	**X**		**YES**					
Lee, D.-H., et al.	2012	X			No		X			
Lee, W. J., et al.	**2007**		**X**		**YES**					
Lerro, C. C., et al.	**2015**	**X**	**X**		**YES**					
Limousi, F., et al.	**2014**	**X**			**YES**					
Lynch, S. M., et al.	2006	X			No		X			
Lynch, S. M., et al.	2009	X	X		No		X			
MacLennan, P. A., et al.	**2002**	**X**			**YES**					
MacLennan, P. A., et al.	**2003**	**X**			**YES**					
Malagoli, C., et al.	2016	X			No		X			
Mattix, K. D., et al.	**2007**	**X**			**YES**					
McElroy, J. A., et al.	**2007**	**X**			**YES**					

Author	Year	Article Capture Method*			Passed full text review?		Exclusion criterion applied			
		Open literature search	AHS	Reference review			Specific chemical not quantified (ex., only triazine generally)	No original data	Not in English	Altered structure
Metayer, C., et al.	2013	X			No					
Migeot, V., et al.	**2013**	**X**			**YES**					
Mills, K. T., et al.	**2009**		**X**		**YES**					
Mills, P. K.	**1998**	**X**			**YES**					
Mills, P. K., et al.	2003	X			No					
Mills, P. K., et al.	**2006**	**X**			**YES**					
Mills, P. K., et al.	2007	X			No					
Montgomery, M. P., et al.	**2008**		**X**		**YES**					
Muir, K., et al.	**2004**	**X**			**YES**					
Munger, R., et al.	**1997**	**X**			**YES**					
Ochoa- Acuña H., Carbajo C.	2009b			X	No		X			
Ochoa-Acuna, H., et al.	**2009**	**X**			**YES**					
Orsi, L., et al.	2009			X	No		X			
Parks, C. G., et al.	**2016**		**X**		**YES**					
Parrón, T., et al.	2011	X			No		X			
Reynolds, P., et al.	2004	X			No					
Rinsky, J. L., et al.	**2012**	**X**			**YES**					
Rinsky, J. L., et al.	**2013**		**X**		**YES**					
Rull, R. P., et al.	2009	X			No		X			
Rusiecki, J. A., et al.	**2004**	**X**	**X**		**YES**					
Rusiecki, J. A., et al.	2006	X			No		X			
Safi, J. M.	2002	X			No		X			
Saldana, T. M., et al.	**2007**	**X**	**X**		**YES**					
Sathiakumar, N. & Delzell, E.	1997			X	No			X		
Sathiakumar, N., et al.	1996	X			No		X			
Sathyanarayana, S., et al.	**2010**		**X**		**YES**					
Savitz, D. A., et al.	**1997**	**X**			**YES**					
Schroeder, J. C., et al.	**2001**	**X**			**YES**					
Slager, R. E., et al.	**2009**		**X**		**YES**					
Slager, R. E., et al.	2010		X		No		X			
Stallones, L., et al.	2002	X			No		X			
Starling, A. P., et al.	**2014**		**X**		**YES**					
Stayner, L. T., et al.	**2017**	**X**			**YES**					
Sturza, J., et al.	2016	X			No		X			
Swan, S. H.	2006	X			No			X		

Author	Year	Article Capture Method*			Passed full text review?		Exclusion criterion applied			
		Open literature search	AHS	Reference review			Specific chemical not quantified (ex., only triazine generally)	No original data	Not in English	Altered structure
Swan, S. H., et al.	**2003**	**X**			**YES**					
Thorpe, N., et al.	**2005**	**X**			**YES**					
Valcin, M., et al.	**2007**		**X**		**YES**					
Van Leeuwen, J. A., et al.	**1999**	**X**			**YES**					
Villanueva, C. M., et al.	**2005**	**X**			**YES**					
Waggoner, J. K., et al.	**2013**		**X**		**YES**					
Waller, S. A., et al.	**2010**	**X**			**YES**					
Weisenburger, D. D.	1990	X			No		X			
West, R. R., et al.	1995	X			No		X			
Wickerham, E. L., et al.	2012	X			No		X			
Winchester, P. D., et al.	**2009**	**X**			**YES**					
Yang, Y.	2013	X			No		X			
Young, H. A., et al.	**2005**	**X**			**YES**					
Zahm, S. H., et al.	1993	X			No					

Appendix C. Physical/Chemical Properties

Table C.1. Physicochemical Properties of Atrazine.		
Parameter	**Value**	**References**
Molecular weight	215.7	MRID 00142160, 00164822, 43337901, 00230302, Ciba Analytical Test #AG-87, Syngenta Study #1744-02
Molecular formula	$C_8H_{14}ClN_5$	
Melting point	176.0 °C	
pH	7.0 at 25º C	
Relative Density (20ºC)	0.37 g/cm^3	
Water solubility (20ºC)	33 mg/L	
Solvent solubility (g/100 mL at 20ºC)	Solvent grams/100 mL solvent Acetone 3.2 Octanol 0.92 Ethanol 1.11 Toluene 0.42 Hexane 0.01	
Vapor pressure	2.9 x 10^{-7} mm Hg	
Dissociation constant, pK_a	PKa = 1.60 @ 20º C	
Octanol/water partition coefficient	P = 481 Log P_{ow} = 2.68 at 25º C	

Appendix D. Tolerance/MRL Tables

Table D.1. Summary of US and International Tolerances and Maximum Residue Limits – Atrazine.				
Residue Definition:				
US		**Canada**	**Mexico[1]**	**Codex**
40 CFR § 180.220 (a) General: combined residues of the herbicide atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) and its chlorinated metabolites 2-amino-4-chloro-6-isopropylamino-s-triazine, 2-amino-4-chloro-6-ethylamino-s-triazine, and 2,4-diamino-6-chloro-s-triazine		6-chloro-*N*-ethyl-*N'*-(1-methylethyl)-1,3,5-triazine-2,4-diamine, including the metabolites 1,3,5-triazine-2,4-diamine, 6-chloro-; 1,3,5-triazine-2,4-diamine, 6-chloro-*N*-ethyl- and 1,3,5-triazine-2,4-diamine, 6-chloro-*N*-(1-methylethyl)-		None
Commodity	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[1]**	**Codex**
Cattle, fat	0.02	0.04		
Cattle, meat	0.02	0.04		
Cattle, meat byproducts	0.02	0.04		
Corn, field, forage	1.5			
Corn, field, grain	0.20	0.2		
Corn, field, stover	0.5			
Corn, pop, forage	1.5			
Corn, pop, grain	0.20	0.2		
Corn, pop, stover	0.5			
Corn, sweet, forage	15			
Corn, sweet, kernel plus cob with husks removed	0.20	0.2		
Corn, sweet, stover	2.0			
Goat, fat	0.02	0.04		
Goat, meat	0.02	0.04		
Goat, meat byproducts	0.02	0.04		
Grass, forage	4.0			
Grass, hay	4.0			
Guava	0.05			
Horse, fat	0.02	0.04		
Horse, meat	0.02	0.04		
Horse, meat byproducts	0.02	0.04		
Milk	0.02	0.04		
Nut, macadamia	0.20			
Sheep, fat	0.02	0.04		
Sheep, meat	0.02	0.04		
Sheep, meat byproducts	0.02	0.04		
Sorghum, forage, forage	0.25			
Sorghum, grain, forage	0.25			
Sorghum, grain, grain	0.20			
Sorghum, grain, stover	0.50			
Sugarcane, cane	0.20			
Wheat, forage	1.5			
Wheat, grain	0.10			
Wheat, hay	5.0			
Wheat, straw	0.50			
MRLs With No US Equivalent				
Eggs		0.04		
Fat of Hogs		0.04		
Meat of hogs		0.04		
Meat byproducts of hogs		0.04		
Fat of poultry		0.04		

Table D.1. Summary of US and International Tolerances and Maximum Residue Limits – Atrazine.				
Residue Definition:				
US		**Canada**	**Mexico[1]**	**Codex**
Meat of poultry		0.04		
Meat byproducts of poultry		0.04		
Completed: W. Donovan; 11/8/2017				

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

(d) Indirect or inadvertent residues. Tolerances are established for indirect or inadvertent residues of atrazine, 2-chloro-4-ethylamino-6-isopropylamino-s-triazine, in or on the following raw agricultural commodity when present therein as a result of application of atrazine to the growing crops in paragraph (a) of this section:

Commodity	Parts per million
Vegetable, leafy, except brassica, group 4	0.25

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

Table E.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 E.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 E.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 E-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
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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 PHED 1.1, the AHETF database, the ORETF, the ARTF database, the Residential SOPs (lawns/turf), and MRID 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). 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[94].

[94] 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. Atrazine Dermal PBPK Modeled External Doses (PODs) Corresponding to a $BMDL_{1SD}$ for LH Surge Attenuation Assuming a Shower Occurs 8 Hours After Initial Exposure

RA Type	Exposure Pathway (all triazines unless noted)	Young Children (1 - 2 years old)	Children (Residential: 6-11 years old)	Youths (Residential: 11-16 years old)	Females (13 – 49 years old)
		Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)	Steady State (4-day time to effect)
Residential Handlers	Dermal (mg/kg/day)				89.35
Residential (Golfers)	Dermal (mg/kg/day)		101.5	91	89.0
Residential (Mowing)	Dermal (mg/kg/day)			91.25	89.38
Residential (Other Turf Scenarios)	Dermal (mg/kg/day)	128.81			89.06
Non-Occupational Spray Drift	Dermal (mg/kg/day)	128.81			89.0
	Oral (mg/kg/day)	3.32			
Occupational	Dermal (mg/kg/day)				89.2

Table G.2. Residential Handler Non-cancer Exposure and Risk Estimates for Atrazine – Using PODs Derived Assuming 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[4]**	**Dose (mg/kg/day)[5]**	**MOE[6]**	**MOE[7]**
Mixer/Loader/Applicator										
Granular Formulations via Push Type Rotary Spreader	30	0.81	0.0026	2.2 lb ai/A	0.5 A	0.013	6,900	0.000041	110,000	6,500
Granular Formulations via Belly Grinder		360	0.039	0.000051 lb ai/ft^2	1200 ft^2	0.32	280	0.000035	140,000	280
Granular Formulations via Spoon		6.2	0.087	0.000051 lb ai/ft^2	100 ft^2	0.00046	190,000	0.0000064	730,000	150,000
Granular Formulations via Cup		0.11	0.013	0.000051 lb ai/ft^2	100 ft^2	0.0000081	11,000,000	0.00000096	4,900,000	3,400,000
Granular Formulations via Hand Dispersal		160	0.38	0.000046 lb ai/ft^2	100 ft^2	0.011	8,400	0.000025	180,000	8,000
Granular Formulations via Shaker Can		0.11	0.013	0.000051 lb ai/ft^2	100 ft^2	0.0000081	11,000,000	0.00000096	4,900,000	3,400,000

1 See Table 3.3. Based on the labels evaluated, the maximum single application rate to turf is 2.2 lb ai/A (0.000051 lb ai/ft^2). Most labels restrict application by hand; however some labels allow hand dispersal for spot applications up to 2.0 lb ai/A (0.000046 lb ai/ft^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 (89.35 mg/kg/day) ÷ Dermal Dose (mg/kg/day). LOC = 30.
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 (4.67 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). LOC = 30.
7 Total MOE = Total MOE = 1 ÷ [(1 / Dermal MOE) + (1 /Inhalation MOE)]. LOC = 30.

Table G.3. Residential Post-Application Non-cancer Exposure and Risk Estimates for Atrazine – 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[3]	Combined Routes (X indicates included in Combined MOE)	Combined MOEs
		Activity	Route of Exposure					
Adult	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0552	1,600		
		Golfing after Granular Application		2.2 lb ai/A	0.0324	2,700		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.0143	6,200		
		Mowing after Granular Application		2.2 lb ai/A	0.00842	11,000		
	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	0.703	130		
		High Contact Activities after Granular Application		2.2 lb ai/A	0.4591	190		
Children 11 to < 16 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0555	1,600		
		Golfing after Granular Application		2.2 lb ai/A	0.0326	2,800		
	Treated Turf	Mowing after Spray Application	Dermal	2.0 lb ai/A	0.0142	6,400		
		Mowing after Granular Application		2.2 lb ai/A	0.00834	11,000		
Children 6 to < 11 Years Old	Golf Course Fairways	Golfing after Spray Application	Dermal	2.0 lb ai/A	0.0651	1,600		
		Golfing after Granular Application		2.2 lb ai/A	0.0383	2,700		
Children 1 to < 2 Years Old	Treated Turf	High Contact Activities after Spray Application	Dermal	2.0 lb ai/A	1.20	110	X	60
			Hand-to-Mouth		0.0246	130	X	
			Object-to-Mouth		0.000747	4,4000		
			Soil Ingestion		0.0000677	49,000		
		High Contact Activities after Granular Application	Dermal	2.2 lb ai/A	0.778	170	X	120
			Hand-to-Mouth		0.0789	460	X	
			Object-to-Mouth		0.000439	7,600		
			Soil Ingestion		0.0000745	45,000		

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). LOC = 30. PODs are summarized in Table G.1 and Table 4.6.2.4.2.2.
4 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/incidental oral MOE)], where applicable. LOC = 30.

Table G.4. Recommendations for the Residential Exposures for the Atrazine 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	Post-Application High Contact Activities after Spray Applications	0.703	N/A	N/A	0.703	130	N/A	N/A	130
Children 11 to < 16 Years Old	Golfing after Spray Application	0.0555			0.0555	1,600			1,600

Table G.4. Recommendations for the Residential Exposures for the Atrazine 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
Children 6 to < 11 Years Old	Golfing after Spray Application	0.0651			0.0651	1,600			1,600
Children 1 to < 2 Years Old	High Contact Activities after Spray Application	1.20		0.0246	1.22	110		130	60

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/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

Table G.5. Atrazine 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	4-Day POD For Drinking Water[4] (ppb)	4-Day DWLOC[5] (ppb)
Infants <1 Year Old	NA	30	9100	NA	NA	NA	2.12E+04	700
Children 1 to < 2 Years Old	High Contact Activities after ***Spray*** Application	30	4000	110	130		5.14E+04	840
Children 6 to < 11 Years Old	Golfing after ***Spray*** Application	30	6800	1,600	NA		1.19E+05	3,900
Children 11 to < 16 Years Old	Golfing after ***Spray*** Application	30	11000	1,600			7.72E+04	2,500
Adult	High Contact Activities after ***Spray*** Applications	30	16000	130			9.22E+04	2,400

[1] **Food:** MOE_{food} = POD_{food} (from Table 4.6.2.4.2.2)/ *Background* Food Exposure (from Table 5.4.6.1).

[2] **Dermal:** MOE_{dermal} (from Table G.4).

[3] **Oral:** MOE_{oral} (from Table G.4).

[4] **POD** from Tables G.1 And Table 4.6.2.4.2.2.

[5] **DWLOC:** DWLOC ppb= POD_{water} ppb (from Table 4.6.2.4.2.2) /$MOE_{water;}$; Where MOE_{water} = 1/ [(1/MOE_{agg}) – ((1/MOE_{food}) + (1/MOE_{dermal}) + (1/MOE_{oral}))]; Where MOE_{agg} =LOC (30).

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
Mixer/Loader						
Water Soluble Packets for Backpack Sprayer and Mechanically Pressurized Handgun Application	Roadsides	0.1 lb ai/gal	1,000 gals	4,900 [EC]	480 [EC]	440 [EC]
Liquids for Backpack Sprayer and Mechanically Pressurized Handgun Application	Roadsides	0.2 lb ai/gal		820 [SL/G]	2,800 [No R]	630 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations for Backpack Sprayer or Mechanically Pressurized Handgun Application	Roadsides	0.2 lb ai/gal		600 [SL/G]	69 [No R]	62 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations for Aerial Applications	Sorghum, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	50 [SL/G] 62 [DL/G]	5.8 [No R] **29 [PF5]** 58 [PF10]	**5.2 [SL/G, No R]** **18 [SL/G, PF5]** **27 [SL/G, PF10]** 30 [DL/G, PF10]
	Fallow	0.5 lb ai/A	1,200 A	200 [SL/G]	**23 [No R]** 110 [PF5]	**21 [SL/G, No R]** 71 [SL/G, PF5]
Dry Flowable/Water Dispersible Granular Formulations for Groundboom Applications	Sod	4.0 lb ai/A	80 A	370 [SL/G]	43 [No R]	39 [SL/G, No R]
	Macadamia Nuts	4.0 lb ai/A	40 A	740 [SL/G]	87 [No R]	78 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	740 [SL/G]	87 [No R]	78 [SL/G, No R]
	Corn, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	300 [SL/G]	35 [No R]	31 [SL/G, No R]
	Winter Weed Control	1.0 lb ai/A	200 A	600 [SL/G]	69 [No R]	62 [SL/G, No R]
	Fallow	2.25 lb ai/A	200 A	270 [SL/G]	31 [No R] 150 [PF5]	**28 [SL/G, No R]** 96 [SL/G, PF5]
	Sugarcane	4.0 lb ai/A	200 A	150 [SL/G]	**17 [No R]** 87 [PF5]	**15 [SL/G, No R]** 55 [SL/G, PF5]
Liquids for Aerial Application	Guava	4.0 lb ai/A	350 A	120 [SL/G]	400 [No R]	92 [SL/G, No R]
	Sod	4.0 lb ai/A	350 A	120 [SL/G]	400 [No R]	92 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	350 A	230 [SL/G]	810 [No R]	180 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	68 [SL/G]	240 [No R]	53 [SL/G, No R]

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Fallow	2.25 lb ai/A	1,200 A	60 [SL/G]	210 [No R]	47 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	1,200 A	34 [SL/G] 44 [DL/G]	120 [No R] 590 [PF5]	**26 [SL/G, No R]** 32 [DL/G, No R] 32 [SL/G, PF5]
Liquids for Impregnated Dry Bulk Fertilizer Application – Commercial	Corn, Sorghum, Bioenergy Crops	20 lb ai/ton	500 tons	71 [EC]	150 [EC]	48 [EC]
Liquids for Groundboom Application	Sod	4.0 lb ai/A	80 A	510 [SL/G]	1,800 [No R]	400 [SL/G, No R]
	Macadamia Nuts, Guava	4.0 lb ai/A	40 A	1,000 [SL/G]	3,600 [No R]	780 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	1,000 [SL/G]	3,600 [No R]	780 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	410 [SL/G]	1,400 [No R]	320 [SL/G, No R]
	Fallow	2.25 lb ai/A	200 A	360 [SL/G]	1,300 [No R]	280 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	200 A	200 [SL/G]	710 [No R]	160 [SL/G, No R]
Water Soluble Packets for Aerial Application	Guava	4.0 lb ai/A	350 A	350 [EC]	34 [EC]	31 [EC]
	Sod	4.0 lb ai/A	350 A	350 [EC]	34 [EC]	31 [EC]
	Sweet Corn	2.0 lb ai/A	350 A	700 [EC]	68 [EC]	62 [EC]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	210 [EC]	**20 [EC]**	**18 [EC]**
	Fallow	2.25 lb ai/A	1,200 A	180 [EC]	**18 [EC]**	**16 [EC]**
	Sugarcane	4.0 lb ai/A	1,200 A	100 [EC]	**9.9 [EC]**	**9.0 [EC]**
Water Soluble Packets for Groundboom Application	Sod	4.0 lb ai/A	80 A	1,500 [EC]	150 [EC]	140 [EC]
	Guava	4.0 lb ai/A	40 A	3,100 [EC]	300 [EC]	270 [EC]
	Sweet Corn	2.0 lb ai/A	80 A	3,100 [EC]	300 [EC]	270 [EC]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	1,200 [EC]	120 [EC]	110 [EC]
	Fallow	2.25 lb ai/A	200 A	1,100 [EC]	110 [EC]	100 [EC]
	Sugarcane	4.0 lb ai/A	200 A	620 [EC]	60 [EC]	55 [EC]

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
Applicator						
Sprays via Aerial Equipment	Guava	4.0 lb ai/A	350 A	2,100 [EC]	18,000 [EC]	1,900 [EC]
	Sod	4.0 lb ai/A	350 A	2,100 [EC]	18,000 [EC]	1,900 [EC]
	Sweet Corn	2.0 lb ai/A	350 A	4,200 [EC]	36,000 [EC]	3,800 [EC]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	1,200 A	1,200 [EC]	11,000 [EC]	1,100 [EC]
	Fallow	2.25 lb ai/A	1,200 A	1,100 [EC]	9,400 [EC]	980 [EC]
	Sugarcane	4.0 lb ai/A	1,200 A	620 [EC]	5,300 [EC]	560 [EC]
Sprays via Groundboom Equipment	Sod	4.0 lb ai/A	80 A	1,200 [SL/G]	1,100 [No R]	570 [SL/G, No R]
	Macadamia Nuts, Guava	4.0 lb ai/A	40 A	2,400 [SL/G]	2,300 [No R]	1,200 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	80 A	2,400 [SL/G]	2,300 [No R]	1,200 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	200 A	960 [SL/G]	910 [No R]	470 [SL/G, No R]
	Sugarcane	4.0 lb ai/A	200 A	480 [SL/G]	460 [No R]	230 [SL/G, No R]
	Fallow	2.25 lb ai/A	200 A	850 [SL/G]	810 [No R]	410 [SL/G, No R]
Sprays via Mechanically Pressurized Handgun	Roadsides	0.2 lb ai/gal	1,000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
Sprays via Tractor Drawn Spreader – Commercial Application of Dry Bulk Fertilizer	Corn	2.0 lb ai/A	320 A	970 [SL]	160 [No R]	140 [SL, No R]
Flagger						
To Support Aerial Applications	Guava	4.0 lb ai/A	350 A	370 [SL/G]	250 [No R]	150 [SL/G, No R]
	Sod	4.0 lb ai/A	350 A	370 [SL/G]	250 [No R]	150 [SL/G, No R]
	Sweet Corn	2.0 lb ai/A	350 A	730 [SL/G]	510 [No R]	300 [SL/G, No R]
	Corn, Sorghum, Winter Weed Control, Conservation Reserve Program Areas	2.0 lb ai/A	350 A	730 [SL/G]	510 [No R]	300 [SL/G, No R]
	Fallow	2.25 lb ai/A	350 A	650 [SL/G]	450 [No R]	270 [SL/G, No R]

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Sugarcane	4.0 lb ai/A	350 A	370 [SL/G]	250 [No R]	150 [SL/G, No R]
Mixer/Loader/Applicator						
Dry Flowable/Water Dispersible Granular Formulations via Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Conifers [Ground Directed]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	38 [SL/G]	340 [No R]	34 [SL/G, No R]
	Landscape Turf [Spot]	0.133 lb ai/gal	40 gals	140 [SL/G]	9,000 [No R]	140 [SL/G, No R]
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	93 [SL/G]	6,000 [No R]	92 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations via Manually Pressurized Handwand Spray Equipment	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	2,700 [SL/G]	780 [No R]	610 [SL/G, No R]
Dry Flowable/Water Dispersible Granular Formulations via Mechanically Pressurized Handgun Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**7.5 [SL/G]** **11 [DL/G]**	36 [No R] 180 [PF5] 360 [PF10]	**6.2 [SL/G, No R]** **10 [DL/G, PF5]** **11 [DL/G, PF10]**
	Landscape Turf [Broadcast]	2.0 lb ai/A	5 A	440 [SL/G]	300 [No R]	180 [SL/G, No R]
	Sweet Corn [Ground Directed]	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
Liquid Formulations via Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Conifers [Broadcast]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	38 [SL/G]	340 [No R]	34 [SL/G, No R]
	Landscape Turf [Spot]	0.133 lb ai/gal	40 gals	140 [SL/G]	9,000 [No R]	140 [SL/G, No R]

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	93 [SL/G]	6,000 [No R]	92 [SL/G, No R]
Liquid Formulations for Manually Pressurized Spray Equipment	Landscape Turf [Broadcast]	0.133 lb ai/gal	40 gals	2,700 [SL/G]	780 [No R]	610 [SL/G, No R]
Liquid Formulations for Mechanically Pressurized Handgun Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**7.5 [SL/G]** **11 [DL/G]**	36 [No R] 180 [PF5] 360 [PF10]	**6.2 [SL/G, No R]** **10 [DL/PF5]** **11 [DL/PF10]**
	Landscape Turf [Broadcast]	2.0 lb ai/A	5 A	700 [SL/G]	6,500 [No R]	630 [SL/G, No R]
	Sweet Corn [Ground Directed	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
Water Soluble Packets for Backpack Spray Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Conifers [Ground Directed]	0.4 lb ai/gal	40 gals	47 [SL/G]	3,000 [No R]	46 [SL/G, No R]
	Landscape Turf [Broadcast]	0.067 lb ai/gal	40 gals	76 [SL/G]	670 [No R]	68 [SL/G, No R]
	Landscape Turf [Spot]	0.067 lb ai/gal	40 gals	280 [SL/G]	18,000 [No R]	280 [SL/G, No R]
	Guava [Ground Directed]	0.2 lb ai/gal	40 gals	93 [SL/G]	6,000 [No R]	92 [SL/G, No R]
Water Soluble Packets for Manually Pressurized Equipment	Landscape Turf [Broadcast]	0.067 lb ai/gal	40 gals	5,300 [SL/G]	1,500 [No R]	1,200 [SL/G, No R]
Water Soluble Packets for Mechanically Pressurized Handgun Equipment	Macadamia Nuts [Ground Directed]	0.4 lb ai/gal	1000 gals	**7.5 [SL/G]** **11 [DL/G]**	36 [No R] 180 [PF5] 360 [PF10]	**6.2 [SL/G, No R]** **10 [DL/G, PF5]** **11 [DL/G, PF10]**
	Landscape Turf [Broadcast]	1.0 lb ai/A	5 A	1,400 [SL/G]	1,400 [No R]	700 [SL/G, No R]
	Sweet Corn [Ground Directed]	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**

Table G.6. Occupational Handler Non-Cancer Exposure and Risk Estimates for Atrazine 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) [PPE/Mitigation]	**MOE[5] (LOC = 30) [PPE/Mitigation]**	**MOE[6] (LOC = 30) [PPE/Mitigation]**
	Guava [Ground Directed]	0.2 lb ai/gal	1000 gals	**15 [SL/G]** **23 [DL/G]**	71 [No R] 360 [PF5] 710 [PF10]	**12 [SL/G, No R]** **22 [DL/G, PF5]** **22 [DL/G, PF10]**
Loader/Applicator						
Dry Flowable/Water Dispersible Granular Formulations via Backpack Spray Equipment	Roadsides	0.2 lb ai/gal	40 gals	**25 [SL/G]** 46 [DL/G]	220 [No R]	**22 [SL/G, No R]** 38 [DL/G, No R]
Liquid Formulations via Backpack Spray Equipment	Roadsides [Broadcast]	0.2 lb ai/gal	40 gals	**25 [SL/G]** 46 [DL/G]	220 [No R]	**22 [SL/G, No R]** 38 [DL/G, No R]
Water Soluble Packets for Backpack Spray Application	Roadsides [Broadcast]	0.1 lb ai/gal	40 gals	50 [SL/G]	450 [No R]	45 [SL/G, No R]
Granular Formulations via Belly Grinder Equipment	Landscape Turf [Broadcast]	2.2 lb ai/A	1 A	300 [SL/G]	910 [No R]	230 [SL/G, No R]
Granular Formulations via Rotary Spreader	Landscape Turf [Broadcast]	2.2 lb ai/A	5 A	2,300 [SL/G]	1,100 [No R]	740 [SL/G, No R]

1 Results are presented assuming baseline attire unless otherwise specified. Applying via aerial application equipment is considered in a closed system/engineering control (EC). Risk estimates of concern are in bold.
2 Based on Table 3.3.
3 Based on Exposure Science Advisory Council Policy #9.1.
4 Dermal MOE = Dermal POD (89.2 mg/kg/day) ÷ Dermal Dose (mg/kg/day). LOC = 30. 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, EC = Engineering Control.
5 Inhalation MOE = Inhalation POD (1.8 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). LOC = 30. 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. EC = Engineering Control.
6 Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Table G.7. Occupational Post-Application Non-Cancer Exposure and Risk Estimates for Atrazine Using PODs that Assume a Shower Occurs 8 Hours After Initial Exposure.

Crop/Site	Activities	Application Rate (lb ai/A)	Transfer Coefficient (cm^2/hr)	DFR/TTR[1]	Dermal Dose (mg/kg/day)[2]	MOE (LOC = 30)[3]
Corn, Field; Corn, Pop; Corn, Sweet Grain; Corn, Sweet, Processing	Scouting	2.0	210	3.32	0.081	1,100
	Hand Set Irrigation		1900		0.731	120
	Hand Weeding		70		0.027	3,300
Golf Course	Maintenance	2.0	3700	0.231	0.099	900
Sod	Maintenance; Harvesting, Slab; Transplanting/Planting	4.0	6700	0.462	0.359	250
Sorghum, Grain	Scouting	2.0	210	3.32	0.081	1,100
	Hand Weeding		70		0.027	3,300

ii. 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 44958001: Day 0 residue: 0.226 ug/cm^2, study application rate = 1.96 lb ai/A.

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

3 MOE = POD (89.2 mg/kg/day) / Daily Dermal Dose. LOC = 30.