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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: March 28, 2006

Subject: **Triazine Cumulative Risk Assessment**. HED Human Health Risk Assessment In Support of the Reregistration Eligibility Decisions for Atrazine, Simazine and Propazine. PC Codes: 080808, 080803, 080807. DP 317976.

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Please find attached the triazine cumulative risk assessment and five supporting appendices.

APR 0 1 2006

Cumulative Risk From Triazine Pesticides

U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division
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CUMULATIVE RISK FROM TRIAZINE PESTICIDES

Executive Summary

As part of the tolerance reassessment process under the Food Quality Protection Act (FQPA) of 1996, EPA must consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity.

Identification of the Common Mechanism Group

A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group (CMG), that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body – that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events.

Certain triazine pesticides have been identified as a CMG by the Agency, and evaluated by the SAP (2000). After consideration of the SAP comments, OPP's own reviews, and the data underlying these reviews, as well as additional information received by the Agency from registrants or presented in the open literature since the 2000 SAP meeting, OPP published a paper in 2002 titled "The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity" (USEPA 2002). EPA concluded in that document that atrazine, simazine, propazine, and the metabolites desethyl-s-atrazine (DEA), desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT) should be considered as a CMG due to their ability to cause neuroendocrine and endocrine-related developmental, reproductive and carcinogenic effects. Other triazines, such as ametryn, prometryn, prometon, metsulfuron methyl, trisulfuron, chlorsulfuron, and DPX-M6316 were excluded because these triazines do not share the toxicity profile of the CMG triazines. Hydroxyatrazine was excluded based on the lack of mammary tumor induction and no compelling evidence of neuroendocrine-related toxicity.

Selection of the Cumulative Assessment Group

The Cumulative Assessment Group (CAG) is derived from the CMG, and includes those pesticides whose uses, routes, and pathways of exposure will present sufficient exposure and hazard potential to warrant inclusion in the quantitative estimates of risk.

Based on use patterns and the likelihood of exposure to atrazine, simazine, and propazine, only atrazine and simazine and their common metabolites (DEA, DIA and DACT) have been included in the CAG. These five compounds, referred to as "residues

of atrazine and simazine" or "triazine residues" from here on in this document, are the subject of this cumulative risk assessment. Although propazine is currently registered for indoor greenhouse use in the U.S., the only other use is an import tolerance for propazine on sorghum; this is expected to result in no exposures to the residues of propazine through drinking water and/or home uses. Even though residues of propazine from imported food (sorghum) could result in exposure, the single-chemical aggregate assessment conducted for propazine indicated that this exposure is negligible. Consequently, even though propazine is a member of the CMG for the triazine pesticides, propazine has been excluded from the CAG and thus from this cumulative assessment because exposures to propazine are not anticipated via any of the relevant exposure pathways.

A subsequent assessment will be conducted to address a proposed use of propazine on sorghum in the U.S. This subsequent assessment will include all six triazine compounds identified in the CMG. However, for the purposes of tolerance reassessment only currently registered uses have been considered and included in this cumulative risk assessment.

Identification of Exposure Scenarios to Include in the Quantitative Cumulative Risk Assessment

Following identification of the CAG, the cumulative risk assessment focuses on selecting the pesticides, pesticide uses, routes, and pathways, with exposure and hazard potential, to include in the quantitative estimates of risk.

Atrazine and simazine are registered for use in the U.S. on a variety of commodities, including: vegetables, grains, fruits, and nuts. Both compounds are also registered for use on turf grasses grown in the Southeastern U.S. (although most of the turf use occurs in Florida). These uses result in potential exposure to triazine residues through dietary ingestion via drinking water and/or food, as well as through residential activities on treated turf.

Initially, areas of high exposure were investigated and regions where triazine residues are likely to co-occur were identified through usage data for atrazine and simazine. As a result, three regions of likely high cumulative exposure to the triazine CAG chemicals were identified: the Midwest, California, and Florida. In the U.S., the Midwest receives the highest use of atrazine (in pounds of active ingredient per acre), California receives the highest use of simazine, and Florida receives equally high use of both. These three regions were determined to represent areas in the U.S. where the probability of residues of both compounds co-occurring is high, because in these states, atrazine and simazine uses overlap geographically, and both are used in high volumes.

After these regions of likely co-occurrence were selected, an analysis of the exposure scenarios that would be representative of high-end exposure (and therefore protective of human health) was conducted. To determine these likely pathways of exposure to triazine residues (*i.e.*, via drinking water, food and/or residential activities), available

monitoring data for atrazine and simazine in or on foods and in drinking water, and information on the home uses of pesticides were considered. As a result of this analysis, cumulative exposure to triazine residues in food is considered negligible (determined from monitoring data from USDA's Pesticide Data Program and Food Safety Inspection Service, and registrant supplied laboratory and field data), cumulative exposure to triazine residues in drinking water in the Midwest, California, and Florida is likely (determined from monitoring and usage data), and cumulative exposure to triazine residues across two exposure pathways, in drinking water and on lawns and golf courses, in Florida is possible (determined from usage data). Consequently, exposures to residues of atrazine and simazine and their common metabolites have been assessed for the following four exposure scenarios:

1. via drinking water in the Midwest (using monitoring data),
2. via drinking water in California (using modeled exposure estimates),
3. via drinking water in Florida (also using modeled exposure estimates), and
4. via combined drinking water and home lawn or golf course use in Florida (using modeled exposure estimates for drinking water and residential activities).

The first three exposure scenarios focus on a single exposure pathway: drinking water. The fourth exposure scenario focuses on multiple exposure pathways: drinking water and home lawns and/or golf courses.

Hazard and Dose-response Assessments and Toxicity Endpoint Selection

The underlying mechanism of the endocrine-related changes associated with atrazine and similar triazines is understood to involve a disruption of the hypothalamic-pituitary-gonadal (HPG) axis (USEPA 2000). In particular, the triazine-mediated changes in the HPG relating to neuroendocrine and neuroendocrine-related developmental and reproductive toxicity are considered relevant to humans, and these adverse effects were identified as endpoints for the exposure scenarios selected for consideration in the quantitative cumulative assessment.

For each exposure scenario, a no-observed-adverse-effect-level (NOAEL) based on a relevant adverse effect from a study in the triazine toxicology database was selected as a quantitative hazard estimate. These quantitative hazard estimates (with the application of relevant uncertainty factor(s)) were compared with the exposure estimates to assess the risk posed by each scenario. In addition to the traditional uncertainty factors applied to each risk assessment (10X for intraspecies variation and 10X for interspecies variability), a FQPA safety factor of 3X for hazard-based residual uncertainty related to the health consequences of exposure to the triazines on the developing young was applied to all cumulative risk assessments. An additional FQPA safety factor of 3X for exposure-based residual uncertainty related to deficiencies in monitoring data was applied to the cumulative risk assessment for drinking water exposures in the Midwest.

Although the endocrine-related induction of mammary tumor formation observed in rats was used as a parameter to group the CMG triazines, the SAP concluded that these chemicals are not likely to be carcinogenic to humans, and a cancer risk assessment was therefore not performed.

Risk Estimates

Based on the most appropriate combination of toxicity endpoint and period of highest concentrations of triazine residues in water, a 90-day average exposure was used for the cumulative risk assessments focusing on drinking water as the single exposure pathway in the Midwest, California, and Florida. Similarly -- to match an appropriate toxicity endpoint with the most likely period of exposure for the cumulative risk assessment focusing on multiple exposure pathways in Florida -- a 28-day average exposure to the triazine residues in drinking water and from lawns and golf courses was used.

Single Exposure Pathway - Drinking Water

For the Midwest drinking water exposure scenario, cumulative exposures to the triazine residues are not of concern. Monitoring data based on direct measurements for each of the five triazine compounds included in this assessment – atrazine, simazine, DEA, DIA, and DACT -- were available for 118 Community Water Systems (CWS) in the Midwest that were considered to be among those containing the highest levels of atrazine and potentially high levels of all five of the residues. Fifteen (15) of these 118 CWS were assessed as having the highest peak concentrations of combined triazine residues. All 15 of the CWS assessed are considered representative of high-end triazine residues in the Midwest. Risk estimates were above a Margin of Exposure (MOE) of 1000 at the 99.9th percentile of exposure for all 15 CWS. An analysis with the Cumulative and Aggregate Risk Evaluation System (CARES™ Model) using this monitoring data was conducted for each of these 15 CWS for four populations: infants (< 1 year old), children (1 to 2 years old), females (13 to 49 years old), and males (20 to 49 years old). These populations represent both the most vulnerable and sensitive groups relative to the endpoint and toxic effects of interest, *i.e.*, endocrine-related developmental and reproductive effects. Given that MOEs for the water pathway for these 15 CWS all exceeded 1000, the remaining CWS were not analyzed with the CARES™ model. The remaining CWS would be expected to have MOEs greater than 1000 as well. All 15 of these CWS are currently being monitored under the Memorandum of Agreement (MOA) developed as a part of the Interim Reregistration Eligibility Decision (IRED) for atrazine and EPA will continue to review and evaluate the triazine concentrations that are detected.

For the Florida and California drinking water exposure scenarios, cumulative exposures to the triazine residues are also not of concern. Minimal drinking water monitoring data were available for either locale; therefore, the Pesticide

Root Zone Model, linked to the Exposure Analysis Modeling System (PRZM/EXAMS) was used. A CARES™ analysis using residue files from the PRZM/EXAMS model was conducted for a Florida and a California drinking water exposure scenario for four populations: infants (< 1 year old), children (1 to 2 years old), females (13 to 49 years old), and males (20 to 49 years old). These populations represent both the most vulnerable and sensitive groups relative to the endpoint and toxic effects of interest, *i.e.*, endocrine-related developmental and reproductive effects. The scenario included typical use rates of atrazine and simazine. All risk estimates for the Florida and California drinking water scenarios are well above a MOE of 300.

Multiple Exposure Pathways - Drinking Water and Residential Activities

For the Florida scenario which combines exposures to the triazines across drinking water and residential activities on turf, the populations considered representative and vulnerable were assessed. They were: males (20 to 49 years old), females (13 to 49 years old), and two groups of children (1 to 2 and 3 to 5 years old). At the 99.9th percentile, the MOEs are 569 for toddlers (3 to 5 years old) and 510 for toddlers (1 to 2 years old). Exposure through the dermal route from residential activities on turf was the most significant contributor to the risk estimates. The MOEs for children at the 99.9th percentile do not exceed the level of concern (LOC) (which is an MOE of 300 or greater), and therefore these cumulative exposures are not of concern.

Conclusions

The risk estimates provided in this cumulative assessment are considered refined relative to the aggregate risk assessments conducted separately for atrazine and simazine, but protective. Refinements to the single chemical assessments for atrazine and simazine included the use of a probabilistic, aggregate model (CARES™) which allowed cumulative risk assessments based on 90-day and 28-day average exposures. In addition, the drinking water monitoring data used are based on direct measurement of the residues of interest. Although the assessment would be more robust if there had been 3 to 5 years of consecutive monitoring at all of the CWS considered in this assessment, the data used provide the most accurate assessment of exposures to triazine residues in CWS with high-end exposures that is possible at this time.

The PRZM/EXAMS model estimates have been refined by use of typical use rates (atrazine), typical timing of applications, and the Cumulative Adjustment Factor (CAF). The CAF was included to account for portions of the simulated watershed that are not treated by either atrazine or simazine. Chemical specific data and distributions of values for both exposure and contact factors were used to estimate exposures for residential turf uses of atrazine and simazine rather than strict reliance on default assumptions. Monitoring data from USDA's Pesticide Data Program and Food Safety Inspection Service, and registrant supplied laboratory and field data confirm that exposures to triazine residues in or on foods are negligible.

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I. Introduction

The passage of the Food Quality Protection Act (FQPA) in August 1996 led the Office of Pesticide Programs (OPP) to develop methodology to evaluate the risk from exposure to more than one pesticide acting through a common mechanism of toxicity. As defined in FQPA, those pesticides that induce adverse effects by a common mechanism of toxicity must be considered jointly. In other words, the exposures of concern are to include all relevant routes and sources based upon the use patterns of the pesticides in question. This multi-chemical, multi-pathway risk is referred to as cumulative risk.

The Agency's first step in developing a cumulative risk assessment was to develop methodologies and guidance on determining whether two or more chemicals share a common mechanism of toxicity. The reader is referred to the document, **Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity** (1/29/99) for additional information on this topic (see http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf).

Further guidance on conducting cumulative risk assessment was provided by EPA in 1999 and 2002. The **Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity** [1/14/02, see http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf, (USEPA 2002a)] and its precursor document **General Principles for Performing Aggregate Exposure and Risk Assessments** (10/29/99), see (http://www.epa.gov/pesticides/trac/science/aggregate.pdf) describe aspects of the exposure assessment that must be accounted for in developing an integrated cumulative risk assessment. Specifically, these guidance documents state that the cumulative assessment must account for temporal aspects of exposure such as those related to the time of year during which applications resulting in exposures are likely to occur, or co-occur, the frequency of application and period of re-application. In addition, these documents state that the assessment must appropriately consider demographic factors and patterns.

Based in part on the principles and suggested practices contained in the above guidance documents, the first cumulative risk assessment completed by the Agency was for the **organophosphorus (OP) class of pesticides**. EPA completed a revised cumulative risk assessment for these pesticides in June 2002 (USEPA 2002b). In this assessment, OPP developed and demonstrated in detail the methods, parameters, and issues that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. Various aspects of the hazard and dose-response assessment and the exposure analyses were presented to both the SAP and the public for comment numerous times over the course of several years. Both the SAP and the public provided helpful and insightful comments and ideas which were incorporated into the revised document.

Following completion of the Cumulative Risk Assessment for the OP pesticides and in accordance with the requirements of FQPA, OPP conducted a preliminary cumulative risk assessment for the **N-methyl carbamate pesticides**. *The results of* this effort appear in the document entitled, "Estimation of Cumulative Risk from N-Methyl Carbamates: Preliminary Assessment (USEPA, 2005a)". This assessment was presented to a FIFRA Science Advisory Panel (SAP) on August 2005.

II. The Cumulative Risk Assessment Process

As elaborated in the Cumulative Guidance document (USEPA 2002a), the cumulative risk assessment process unfolds in several steps. In brief, these include:

- ❑ Identification of the Common Mechanism Group (CMG)
- ❑ Determination of the Candidate Cumulative Assessment Group (CAG)
- ❑ Performance of a Dose Response Analysis
- ❑ Conduct of an Exposure Analysis (exposure scenarios for all routes and durations, establish exposure input parameters)
- ❑ Conduct of the final cumulative risk assessment
- ❑ Characterization of the cumulative risk assessment

The following sections will develop the process as applied to the triazine pesticides.

III. Performing the Cumulative Risk Assessment

A. Identification of the Common Mechanism Group (CMG)

A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group (CMG), that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body--that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events.

The triazine pesticides have been previously evaluated by the Agency to determine if some of them comprise a common mechanism group. In a thorough weight-of-evidence (WOE) analysis, the EPA examined the available data to determine the biological basis of the endocrine, reproductive and carcinogenic effects of triazines as a group. The WOE analysis focused on structural properties, toxicological effects, and metabolic, pharmacokinetic, and mechanistic considerations on triazines. The scientific evidence indicated that a common mechanism of toxicity exists among certain triazine-containing

pesticides. Details of the analysis appear in the document "The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity (USEPA 2002)." In brief,

- **Atrazine, Simazine, Propazine, and the metabolites Desethyl-s-atrazine (DEA), Desisopropyl-s-atrazine (DIA), and Diaminochlorotriazine (DACT)** may be grouped together based on a common end-point (neuroendocrine and neuroendocrine-related developmental, reproductive and carcinogenic effects) and a known mechanism of toxicity for this endpoint. All CMG triazines cause a disruption of the hypothalamic-pituitary-gonadal (HPG) axis in the rats by alteration of luteinizing hormone (LH).

The grouping of **Atrazine, Simazine, Propazine, and the metabolites Desethyl-s-atrazine (DEA), Desisopropyl-s-atrazine (DIA), and Diaminochlorotriazine (DACT)** based on a common mechanism of action was presented to the FIFRA Scientific Advisory Panel (SAP) in 2000. The SAP agreed with the Agency's conclusion that there is sufficient evidence to support the proposed grouping for the neuroendocrine and neuroendocrine-related effects (USEPA, 2000).

The FIFRA SAP noted in their report (USEPA 2000), additionally, that even though the evidence illustrated that a common mechanism could be used to group certain chemicals for the development of mammary tumors, it was recommended that this endpoint **was not relevant to humans**. This conclusion was based on the following considerations: though hypothalamic disruption of pituitary function (i.e., attenuation of LH surge) and resulting estrus cycle disruption may be occurring in humans following atrazine exposure, the hormonal environment resulting from these events would be expected to be much different from the hormonal environment seen in the rat. The prolonged/increased exposure to estrogen and prolactin (PRL) as seen in the rat would not be expected to occur in humans. The prolonged/increased exposure to estrogen and PRL in the rat is the basis of early-onset and increased mammary tumors in susceptible strains of rats. Additionally, the mutagenicity database is quite extensive and indicates that atrazine is not mutagenic. Consequently, in accordance with the *1999 Draft Guidelines for Carcinogen Risk Assessment*, the CARC classified atrazine "not likely to be carcinogenic to humans."

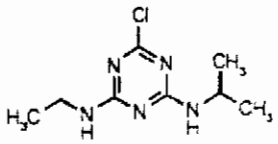
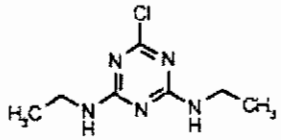
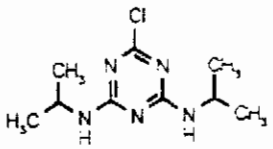
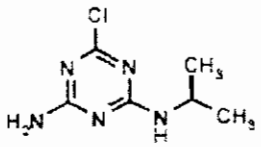
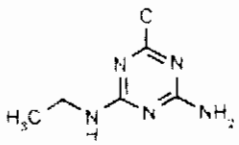
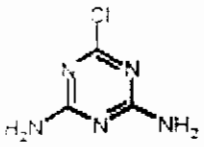
B. Determination of the Cumulative Assessment Group (CAG)

Once the CMG is defined, a subset of this group, the Cumulative Assessment Group (CAG) is selected, for which the cumulative risk assessment

will be performed. This final selection incorporates into the CAG those pesticides from the Common Mechanism Group whose uses, and pathways of exposure will present sufficient exposure and hazard potential to warrant inclusion in the quantitative estimates of risk. See Section D. Exposure Analysis and Methodology for a definition of the CAG used for the purposes of this triazine cumulative risk assessment.

The Common Mechanism Group (CMG) is comprised of atrazine, simazine, propazine, DACT, DEA and DIA (Figure 1).

Figure 1. Structures of Atrazine, Propazine, Simazine, DEA, DIA and DACT

Atrazine 	Simazine 
Propazine 	Desethyl-s- Atrazine (DEA) 
Desisopropyl-s- Atrazine (DIA) 	*Diaminochlorotriazine (DACT)* 

C. Dose Response Analysis and Determination of Toxicity Endpoints

1. Mode of Neuroendocrine Action

The underlying mechanism of the neuroendocrine and neuroendocrine-related changes associated with atrazine and similar triazines involves the disruption of the hypothalamic-pituitary-gonadal (HPG) axis (U.S. EPA 2000) (Figure 1). Specifically, several triazines can alter hypothalamic gonadotrophin-releasing hormone (GnRH) and catecholamine (dopamine and norepinephrine) levels. In both humans and rats, hypothalamic GnRH controls pituitary hormone secretion, i.e., LH and PRL. The result of changes in GnRH and catecholamines in turn leads to alterations in pituitary LH and PRL secretion. The hypothalamic-pituitary axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. Additionally, reproductive hormones modulate the function of numerous other metabolic processes (i.e., bone formation, and immune, central nervous system (CNS) and cardiovascular systems.

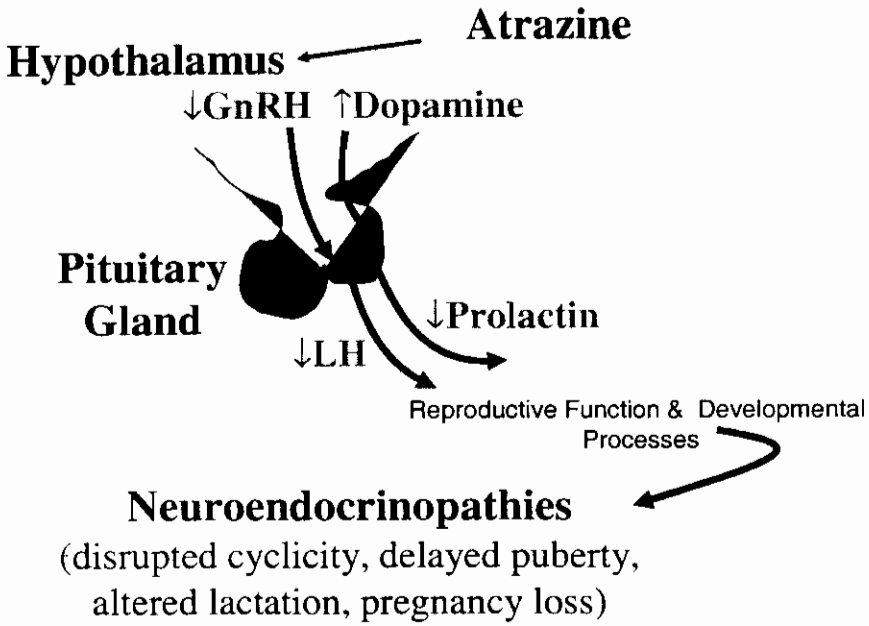
2. Overview of Neuroendocrine and Neuroendocrine-Related Effects

This section provides a succinct review of the critical neuroendocrine toxicity data that are available on the candidate CMG triazines. These data are most relevant to the evaluation of relative potency among the CMG triazines for the assessment of cumulative toxicity.

a. Attenuation of LH Surge

There is compelling evidence that atrazine attenuates the LH surge by a mechanism involving the hypothalamus. Attenuation of the LH surge can be considered a biomarker-indicative of atrazine's ability to alter hypothalamic-pituitary function; and estrus cycle disruptions in female rats. Table 1 summarizes the effects of several CMG triazines on LH surge. All of the CMG triazines examined for this effect caused an attenuation of the LH surge. Atrazine, in particular, has been well investigated. Atrazine was shown to attenuate the LH surge after single and multiple dosing regimens. The results demonstrate that atrazine can dramatically attenuate LH surge. The lowest LOAEL for atrazine was 3.65 mg/kg/day in a 6 month study; the corresponding NOAEL was 1.80 mg/kg/day.

Figure 2. Atrazine's Neuroendocrine MOA



Although less studied, simazine, propazine and DACT have also been shown to attenuate LH surge. The results of a special 4-week study on plasma LH concentration and peak LH effect demonstrated that atrazine, simazine and DACT at equimolar concentrations were equally effective at diminishing the LH surge in female rats (MRID 45471002). In this regard, the equimolar LOAEL for all 3 of these CMG triazines was 40 mg/kg/day, and the NOAEL was 5 mg/kg/day. This study suggests an equipotent effect on LH among these triazines. Only a 3-day exposure study is available for propazine; however, results also revealed an attenuation of LH surge in the rat.

Reductions in baseline serum LH levels were observed in pregnant female rats in a study designed to examine the effects of atrazine on implantation and early pregnancy in 4 strains of rats (Cummings *et. al.* 2000). Pregnant female Holtzman (HLZ), Sprague Dawley (SD), Long Evans (LE) and Fischer 344 (F344) rats were gavaged with 0, 50, 100, or 200 mg/kg/day atrazine on days 1-8 of gestation. The design of the study also included dosing prior to the diurnal and nocturnal surges of prolactin (PRL). PRL is important in the maintenance of the corpora lutea and progesterone secretion; PRL surges can lead to increased progesterone secretion necessary for implantation of the embryo in

the uterus. The results also revealed strain sensitivity to atrazine treatment. Reduced baseline serum LH was noted in all strains except for F344 rats during diurnal dosing. F344 rats were found to be most susceptible to the preimplantation effects of atrazine, while HLZ rats were most sensitive to the postimplantation effects. SD and LE rats appear insensitive to the effects of atrazine on implantation.

The preimplantation loss in F344 rats suggests the possibility that atrazine reduced PRL levels and interfered with implantation in this strain after nocturnal dosing. The role of PRL in regulating preimplantation development and implantation has been recognized. Besides postimplantation loss, HLZ rats were the only strain to exhibit a significant decrease in progesterone. This finding suggests that the decrease in serum progesterone may play a role in mediating the postimplantation loss. This assertion is supported by the observation in HLZ rats of reduced ovarian weights which may be related to decreased progesterone secretion. The authors also noted that the postimplantation loss is also likely to be mediated by LH. The authors concluded that atrazine's action on early pregnancy may be strain selective and is significant only in the sensitive strains.

TABLE 1. Summary of Endocrine Oral Toxicity Data on Common Mechanism Triazines[a]

Response	Chemical	Exposure Period	Rat Strain	NOAEL/LOAEL (mg/kg/day)	Reference
Attenuation of LH Surge	Atrazine	single dose	LE/adult	200/300	Cooper *et. al.* 2000; EPA 2000
		3 days	LE/adult	<25	Cooper -unpublished data
		4 days	LE intact cycling	3.25/6.25	Cooper 05 - SOT
		21 daily doses	LE/adult	<75/75	Cooper *et. al.* 2000; EPA 2000
		21 daily doses	SD	<75/75	Cooper *et. al.* 2000; EPA 2000
		30 daily doses	SD	5/40	Cooper *et. al.* 2000; EPA 2000
		GD 1-8 (dams)	LE & Holteman	50/100 (pregnancy outcome)	Cummings *et. al.* 2000
		4 week (once daily)	SD	5/40	MRID 45471002
		6 month	SD	1.80/3.65	MRID 44152102
	Simazine	4 week (once daily)	SD	5/40 (atrazine equimolar dose)	MRID 45471002
	Propazine	3 days	LE	<300/300	Cooper - unpublished
	DACT	3 days	LE	<37.5/37.5	Cooper - unpublished
		4 week (once daily)	SD	5/40(atrazine equimolar dose)	MRID 45471002
Disruption of estrous cycle/vaginal cytology	Atrazine	21 days	LE & SD/90d	<75/75	Cooper et a. 1996
		PND 35	Wistar	25/50	Laws *et. al.* 2000
	Simazine	21 days	LE/90d	<140/140	Cooper *et. al.* 2000
	DACT	21 days	LE/90d	12.67/25	Cooper *et. al.* 2000
	De-ethyl (DEA)	21 days	LE/90d	32.5/130	Cooper *et. al.* 2000
	De-isopropyl (DIA)	21 days	LE/90d	<15.05/15.05	Cooper *et. al.* 2000

Response	Chemical	Exposure Period	Rat Strain	NOAEL/LOAEL (mg/kg/day)	Reference
Pubertal delay - vaginal opening	Atrazine	PND 22-41	Wistar	25/50	Laws *et. al.* 2000
	Propazine	PND 22-41	Wistar	53/106.7 (equimolar dose: 50/100)	Laws *et. al.* 2003
	DACT	PND 22-41	Wistar	16.7/33.8 (equimolar: 25/50)	Laws *et. al.* 2003
	Simazine	no data			
	DEA	no data			
	DIA	no data			
Pubertal delay - pubertal separation	Atrazine	PND 23-53	Wistar	6.25/12.5	Stoker *et. al.* 2000
	Propazine	no data			Stoker *et. al.* 2002
	DACT	PND 23-53	Wistar	6.25	Stoker *et. al.* 2002
	DEA	PND 23-53	Wistar	12.5/25 (atrazine equimolar dose)	Stoker *et. al.* 2002
	DIA	PND 23-53	Wistar	12.5/25 (atrazine equimolar dose)	Stoker *et. al.* 2002
	Simazine	PND 23-53	Wistar	12.5/25 (Advanced puberty)	Stoker 2006 (manuscript in preparation)

[a]Doses are actual doses administered unless otherwise specified.

b. Disruption of Estrous Cycle

In the normal female SD rat, approximately 20-25% of the days of the estrous cycle are spent in estrus. Atrazine dose levels that lead to attenuation of the LH surge are also associated with disruption of the estrous cycle and an early development or increased incidence of mammary and pituitary gland tumors (U.S. EPA 2000). Estrus cycle (as evaluated by vaginal cytology) was disrupted in female Wistar rats administered (via gavage) 50 mg/kg/day atrazine (Laws *et. al.* 2000). A NOAEL of 25 mg/kg/day was identified.

Limited vaginal cytological evaluations have been performed on other triazines, including simazine, DACT, DEA and DIA (summarized in Table 1). Vaginal cycles were also disrupted in females administered DACT, DEA and DIA. Following Simazine treatment, disruption of estrous cycle in the rat was observed at 140 mg/kg/day but doses lower than this have not been tested.

c. Pubertal Development

Table 1 summarizes oral toxicity data on pubertal development. The onset of puberty in the female involves changes in the hormonal signaling within the hypothalamic-pituitary-ovarian axis (Laws *et. al.* 2003). Because pubertal development is under neuroendocrine control, it may be expected that administration of atrazine to young rats leads to delays in vaginal opening or preputial separation. Experiments on atrazine and other similar triazines support this notion. The results of experiments with the CMG triazines on several indicators of pubertal development (i.e., vaginal opening in females and preputial separation in males) are discussed in more detail below.

Pubertal Delay - Vaginal Opening

In addition to altered estrous cycle, atrazine exposure delayed vaginal opening in female Wistar rats following oral treatment during post-natal day (PND) 22 to 41 (Laws *et. al.* 2000). The LOAEL was 50 mg/kg/day and the NOAEL was 25 mg/kg/day. Confounders such as reduced food consumption and body weight were taken into account. The dose level of 50 mg/kg/day exceeds the dose reported to induce the premature development of mammary gland tumors in chronic feeding studies (Laws *et. al.* 2000). Exposure to this dose level has also been demonstrated to delay the timing of estrogen-induced LH and PRL surges in adult, ovariectomized females (Laws *et. al.* 2000; Cooper *et. al.* 2000).

Thus, the effect of atrazine on female pubertal development occurs at similar doses that have been reported to affect reproductive targets in other studies (Laws *et. al.* 2000). The findings of Laws *et. al.* (2000) are supported by a later study conducted by Ashby *et. al.* (2002). Ashby *et. al.* (2002) demonstrated that atrazine treatment can delay vaginal opening in the rat with a NOAEL between 10 and 30 mg/kg/day, consistent with the NOAEL of 25 mg/kg/day identified in the Laws *et. al.* (2000) study.

The atrazine dose levels that led to delays in vaginal opening also produced irregular ovarian cycles in offspring, which supports a role for disruption of neuroendocrine control in young animals treated with atrazine or its metabolites. The reductions in implantation sites and the full-litter absorptions reported following treatment of dams with atrazine during the LH-dependent phase of pregnancy are also consistent with an effect on neuroendocrine control (USEPA 2000).

In a recent study on pubertal development in female Wistar rats, propazine and DACT delayed the onset of puberty at doses equimolar to atrazine (Laws *et. al.* 2003). DACT delayed the onset of puberty at doses equimolar (i.e., 50 mg/kg/day) to the LOAEL observed for atrazine. The NOAEL was 25 mg/kg/day (atrazine equimolar dose). Propazine also delayed puberty but at the atrazine equimolar dose of 100 mg/kg/day; the NOAEL was 50 mg/kg/day. DACT is the active metabolite for atrazine, simazine, and propazine.

Pubertal Delay - Preputial Separation

A series of experiments in weanling male Wistar rats treated from PND day 23 to 53 with atrazine demonstrated delays in preputial separation (Stoker *et. al.*, 2000). The LOAEL for atrazine's effect on preputial separation was 12.5 mg/g/day. A NOAEL was not identified in this study, however, a NOAEL of 6.25 mg/kg/day was determined in a later study (Stoker *et. al.* 2002). Besides preputial separation, the male pubertal protocol also included assessments of thyroid synthesis, determination of the levels of LH, PRL, estradiol, estrone, and testosterone, analysis of LH-receptor number, and organ weight and histological examination of various male reproductive tissues (prostate gland, seminal vesicle, epididymis, testes). Dose-related increases in serum estrone and estradiol levels, decreased testicular testosterone levels, and reduced weights of the ventral prostate, seminal vesicle and epididymis were observed. Body weight change was not a cofounder.

Recent investigations from Stoker *et. al.* (2002) demonstrated that the three primary chlorinated metabolites of atrazine, i.e., desisopropylatrazine (DIA), desethylatrazine (DEA) and DACT, can also delay the onset of puberty in the male Wistar rat at doses similar to that of atrazine. Preputial separation was significantly delayed by DEA and DIA at an atrazine equimolar equivalent dose of 25 mg/kg/day; the NOAEL was 12.5 mg/kg/day. Similarly, all 3 metabolites also reduced the weights of various reproductive tissues, i.e., ventral prostate, seminal vesicle and epididymis. These data indicate that all 3 metabolites share a common mode of action with atrazine, one that involves Central Nervous System modulation of the hypothalamic-pituitary-gonadal axis and subsequent development of the reproductive tract. This finding impacts cumulative risk assessment of the triazines since atrazine and its chlorinated metabolites are persistent for extended periods in the environment and may potentially affect human and wildlife populations (Stoker *et. al.* 2002).

Like atrazine and the chlorinated metabolites, simazine can also disrupt pubertal progression in male rats. In a male rat pubertal protocol designed for the EPA Endocrine Disruptor Screening Program, simazine treatment altered the timing of puberty (Stoker *et. al.*, 2006 - manuscript in preparation). The LOAEL for advanced puberty was 25 mg/kg/day; the NOAEL was 12.5 mg/kg/day. Serum testosterone and androstenedione were significantly increased at 6.25 - 25 mg/kg/day dose levels. At higher dose levels, hormone levels begin to decrease. There was also a dose-dependent decrease in the seminal vesicle and prostate weights at the three highest doses (75 - 300 mg/kg).

d. Mammary Tumor Formation

Treatment of female SD rats with atrazine, but not male SD rats or Fischer 344 rats or CD-1 mice of either sex, results in neoplastic responses expressed as an increased incidence and/or an early onset of mammary carcinomas and adenomas, mammary fibroadenomas, and pituitary adenomas. The carcinogenicity of atrazine appears to be a consequence of the disruption of the normal secretory activity of the hypothalamic-pituitary-ovarian axis. Suppression of the LH surge in female SD rats is considered to be a necessary precursor for the development of atrazine-induced mammary gland tumors. This is because LH blood levels must reach a sufficient magnitude to induce ovulation and to maintain normal reproductive cycles. When atrazine reduces LH output to the critical point where there is not enough to trigger ovulation, a physiological state results which is characterized by prolonged or

persistent estrous. This state leads to continued stimulation of mammary tissue by estrogen. Evidence for an attenuation of the LH surge and an early onset of prolonged and/or persistent estrus is provided in several studies (Morseth 1996a,b; Thakur 1991a; Eldridge *et. al.*, 1993a; reviewed and cited in USEPA 2000). Removal of the estrogen stimulus by ovariectomy completely abolishes the formation of mammary tumors following chronic administration of atrazine (Morseth, 1998).

Treatment with the close structural analogues, simazine and propazine, also leads to the formation of mammary tumors in female SD rats. Dose responses for mammary tumor formation for these analogues are similar to that of atrazine. Treatment of male SD rats or CD-1 mice of either sex with these chemicals does not result in an increased incidence of tumors at any site.

However, it is now recognized that the hormonal environment conducive to tumor development (i.e., elevated or prolonged exposure to estrogen and PRL) that is found in SD rats is not expected to occur in humans. Instead, humans respond to reduced LH by having reductions in estrogen and PRL.

3. Study Selection and Toxicity Endpoint Determination

In the cumulative risk assessment presented here, simazine, propazine, and the chlorinated metabolites of these chemicals, are considered to be equivalent in toxicity to atrazine, *per se*. This consideration is based on the evaluation of endocrine-related data on the triazines demonstrating either equal potency or potency less than atrazine. This conservative approach is health protective and minimizes the possibility of underestimating risk.

a. Potential For Exposure To CMG Triazines

The Agency has considered the potential exposure pathways based on the use patterns of the CMG triazines. Based on use patterns, persistence and mobility in the environment, and frequent occurrence of atrazine and simazine in surface and groundwaters, the predominant exposure pathway for the CMG triazines is the oral route via drinking water. As will be discussed in more detail there is insignificant exposure via food.

Short - term (30 days) residential exposures to atrazine and simazine are also anticipated based on their registered use patterns. Intermediate-term and chronic exposures (greater than 30-days to greater than six months) to CMG triazines as a result of

residential uses are not anticipated.

In summary, the following exposure scenarios of concern have been identified:

i. Intermediate-term Drinking Water Exposure - 90 day period

ii. Short-term Residential Exposure - 30 day period

b. Critical Toxicological Effects Of CMG Triazines

Neuroendocrine effects are considered the critical endpoints for assessing the health effects of the CMG Triazines. The CMG triazines have been shown to lead to various endocrine-related changes as a result of an effect on the hypothalamic-pituitary-gonadal axis. The consequences of this action include a diminishment of hypothalamic gonadotrophin releasing hormone (GnRH) and norepinephrine levels. These triazines also increase dopamine level which can result in a diminished pituitary secretion of PRL. Therefore, the CMG triazines operate at the level of the hypothalamus. In both humans and rats, hypothalamic GnRH controls pituitary hormone secretion (e.g., luteinizing hormone and PRL).

The hypothalamic-pituitary axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. Additionally, reproductive hormones modulate the function of numerous other metabolic processes (i.e., bone formation, and immune, central nervous system, and cardiovascular functions). Therefore, altered hypothalamic-pituitary function can potentially broadly affect an individual's functional status and lead to a variety of health consequences.

c. Toxicology Endpoint Selection

Table 2 summarizes toxicity endpoint selection for the CMG triazines. The rationale for endpoint selection is discussed below.

Table 2. Summary of Toxicological Doses and Endpoints for CMG Triazines

Exposure Scenario	Dose used in Risk Assessment, Traditional UF	Special FQPA SF* for Risk Assessment	Study and Toxicological Effects
Dietary (drinking water only) 90-day Exposure	NOAEL = 1.8 mg/kg/day UF = 100	10X based on: 3X Hazard-based Factor 3X Exposure-based Factor **only** when monitoring data are used	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal Short-Term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X Hazard-based Factor	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Dermal Absorption	Dermal absorption factor = 6%	- -	**Human volunteer study with Atrazine**
Incidental Oral Short-Term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X Hazard-based Factor	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Inhalation Short-Term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X Hazard-based Factor	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = No Observed Adverse Effect Level. LOAEL = Lowest Observed Adverse Effect Level

Dietary (Drinking Water only) 90-day Exposure

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

MRID No.: 44152102

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

Body weight, body weight gain and food consumption were significantly ($p \leq 0.05$) decreased in the high-dose animals compared to controls (body weight decreased 8.5% at the end of the study and food consumption decreased 3.75% for the entire study). The percentage of days in estrus were significantly increased ($p \leq 0.01$) during the 21-22 and 25-26 week time periods at the high dose. Percent days in estrus were also increased during the 21-22 and 25-26 week time periods at the mid-dose level, but the increase was only significant ($p \leq 0.05$) for the 21-22 week time period. The proestrus afternoon LH surge was severely attenuated at the high dose (LH levels were actually decreased compared to baseline at most sampling time points) and less so at the mid dose (maximum increase over baseline was 157% compared to maximum increase over baseline in controls of 273%). Pituitary weights were increased at the high dose (absolute weight increased 22% and weight relative to body weight was increased 28%). Pituitary weights at the other two doses were not affected. There was a slight increase at the high dose of animals displaying enlarged pituitaries (0% in controls compared to 3.4% at 29.44 mg/kg/day) and thickened mammary glands (0% in controls compared to 6.7% at 29.44 mg/kg/day). There were no other gross necropsy findings in the high dose that could be attributed to compound exposure and there were no compound-related gross pathology findings at the mid or low dose. Selected tissues were saved for histopathology but those results have yet to be reported.

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

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

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

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

Comments about Study/Endpoint/Uncertainty Factor: This study was selected as the most appropriate study for endpoint selection for the structurally similar CMG triazines. The attenuation of the

LH surge is considered to be an indicator of the CMG triazine's neuroendocrine mode of action or its potential to alter hypothalamic-pituitary function. These biomarkers of the CMG triazine's neuroendocrine mode of action (i.e., LH surge attenuation and estrous cycle disruption) are considered to be applicable to the general population including infants and children given that they result from the CMG triazine's CNS mode of action. This dose is the lowest NOAEL available in the toxicology database on atrazine and therefore is protective of other adverse effects, including those occurring in males, infants, and children. Therefore, a separate endpoint is not needed for this population (i.e., males, infants, and children).

Short-Term (1-30 days) Residential Incidental Oral, Dermal, and Inhalation Exposure

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

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

Executive Summary: Since atrazine, a chlorotriazine herbicide, has been shown previously to alter the secretion of luteinizing hormone (LH) and PRL through a direct effect on the CNS, we hypothesized that exposure to atrazine in the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) male pubertal protocol (juvenile to peripubertal) would alter the development of the male rat reproductive system. We dosed intact male Wistar rats from postnatal day (PND) 23 to 53 and examined several reproductive endpoints. Atrazine (0, 6.25, 12.5, 25, 50, 100, 150 or 200 mg/kg) was administered by gavage and an additional pair-fed group was added to compare the effects of any decreased food consumption in the high dose group. Preputial separation was significantly delayed in the 12.5, 50, 100, 150 and 200 mg/kg atrazine dose groups. Preputial separation was also delayed in the pair-fed group, although significantly less than in the high dose atrazine group. The males were killed on PND 53 or 54 and pituitary, thyroid, testes, epididymides, seminal vesicles, ventral and lateral prostates were removed. Atrazine (50 to 200 mg/kg) treatment resulted in a significant reduction in ventral prostate weights, as did the pair-fed group. Testes weights were unaffected by atrazine treatment. Seminal vesicle and epididymal weights were decreased in the high dose atrazine group and the control pair-fed group. However, the difference in epididymal weights was no

longer significantly different when body weight was entered as a covariable. Intratesticular testosterone was significantly decreased in the high dose atrazine group on PND 45, but apparent decreases in serum testosterone were not statistically significantly on PND 53. There was a trend for a decrease in luteinizing hormone as the dose of atrazine increased, however, dose group mean LH were not different from controls. Due to the variability of serum PRL concentrations on PND 53, no significant difference was identified. Although PRL is involved in the maintenance of LH receptors prior to puberty, we observed no difference in LH receptor number at PND 45 or 53. Serum estrone and estradiol showed dose-related increases that were significant only in the 200 mg/kg atrazine group. No differences were observed in thyroid stimulating hormone (TSH) and thyroxine (T4) between the atrazine groups and the control, however tri-iodothyronine (T3) was elevated in the high dose atrazine group. No differences in hormone levels were observed in the pair-fed animals. These results indicate that atrazine delays puberty in the male rat and its mode of action appears to be altering the secretion of steroids and subsequent effects on the development of the reproductive tract, which appear to be due to atrazine's effects on the CNS. Thus, atrazine tested positive in the pubertal male screen that EDSTAC is considering as an optional screen for endocrine disruptors.

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

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

Comments about Study/Endpoint: This study was selected as the most appropriate study for endpoint selection for the structurally similar CMG triazines.

This study is appropriate for this scenario since it demonstrates an endpoint in the young animal that is consistent with the CMG triazine mode of action. The endpoint, delayed puberty, is relevant to the population of concern (infants and children), and delayed puberty also was demonstrated to occur in the female. Following exposure during PND 22-41, delayed puberty was observed in the female at 50 mg/kg/day [NOAEL of 25 mg/kg/day]. A possible explanation for a higher NOAEL in the female may be that the exposure duration in females [20 days] was shorter than in the males [31 days].

Dermal Absorption

Study selected: Human Dermal Absorption Guideline: 870.7600

MRID No.: 44152144

Executive Summary: The study selected is the same study which was used to derive the dermal absorption factor for atrazine. In this study, 10 human volunteers were exposed to a single topical dose of [triazine ring-U-^{14}C] atrazine (94.3-96.3% a.i., 98.0-98.4% radiochemical purity) at 6.7 (4 volunteers) or 79 ìg/cm^2 (6 volunteers) for 24 hours; equivalent to 0.1667 and 1.9751 mg of [14C] atrazine for the low and high doses, respectively. After 24 hours, the atrazine was removed and the percentage of atrazine absorbed was determined 168 hours (7 days) after the commencement of exposure. The maximum percent absorbed in this study was 5.6% of the dose in the lower dose group. Because the maximum percent absorbed is being used and because an ample amount of time (168 hours) was allowed for absorption to occur, 6% is deemed to be a protective estimate of dermal exposure.

Comments about Study: The dermal absorption factor derived from the human study is based on the most appropriate study in the data base to modify oral doses in terms of a dermal equivalent dose. It is route-specific for the species of interest, and of the appropriate duration of exposure for the short-term dermal risk assessments.

Dermal absorption Factor: 6% (Rounded off)

4. FQPA Safety Factor

a. Mode of Action Considerations

Recent research studies at EPA's National Health and Environmental Effects Laboratory (NHEERL) have provided evidence that atrazine alters the CNS (hypothalamic) control of pituitary-ovarian function (Cooper *et. al.*, 2000; Stoker *et.al.*, 2000; Laws *et. al.*, 2000; also see OPP Atrazine Health Assessment Document May 22, 2000). Atrazine has been shown by NHEERL to disrupt critical reproductive processes including puberty, ovarian cyclicity, pregnancy and lactation (milk quality/production) in treated rats. All of these effects are consistent with a CNS-hypothalamic mode of action. This CNS mode of action is operative in both adults and the young, and results in altered

pituitary hormone function, especially luteinizing hormone (LH) and PRL secretions. Atrazine has been shown to decrease the neurotransmitter, norepinephrine, which impairs the pulsatile release of gonadotropin releasing hormone (GnRH), thus leading to a suppression of the pituitary LH release. Atrazine also increases the neurotransmitter dopamine, which in turn leads to a decrease in pituitary PRL release.

Although the mode of action has been reasonably established for atrazine, the exact mechanism by which it changes neurotransmitters and neuropeptides within the CNS is not understood. Although atrazine alters hypothalamic norepinephrine and dopamine, these effects do not necessarily represent its primary site of action. These CNS alterations may be a signal of potential upstream effects on other neurotransmitters.

b. Implications of the Mode of Action on the Young & Relevance to Humans

Gonadal development and reproductive growth are dependent on the GnRH regulation of pituitary LH and PRL. Thus, it is not surprising that administration of atrazine during critical periods of development resulted in delayed puberty in both female and male rats, and in a decrease in suckling-induced PRL release in lactating dams that lead to prostatitis in adult male offspring. The pubertal and prostatitis effects are viewed as evidence consistent with atrazine's CNS mode of action. The health consequences in children of these hypothalamic changes are not known. Nevertheless, atrazine's CNS effect on the rat hypothalamic-pituitary-gonadal axis should be considered potentially serious. There is evidence in the literature that hypothalamic neurotransmitters and neuropeptides are involved in the modulation of GnRH during reproductive and pubertal development in primates. The primate GnRH pulse generator can be modulated by hypothalamic neuronal inputs like in the rat. For example, treatment of GnRH antagonists such as methyl aspartate can prevent the re-awakening of the pulsatile LH release in primates (Wu *et. al.*, 1996; Gay and Plant, 1987). Furthermore, neurotransmitters such as NE and dopamine play an important role in brain development. Thus, the rodent findings raise a concern for children if exposed to atrazine.

c. Completeness of the Toxicity Database

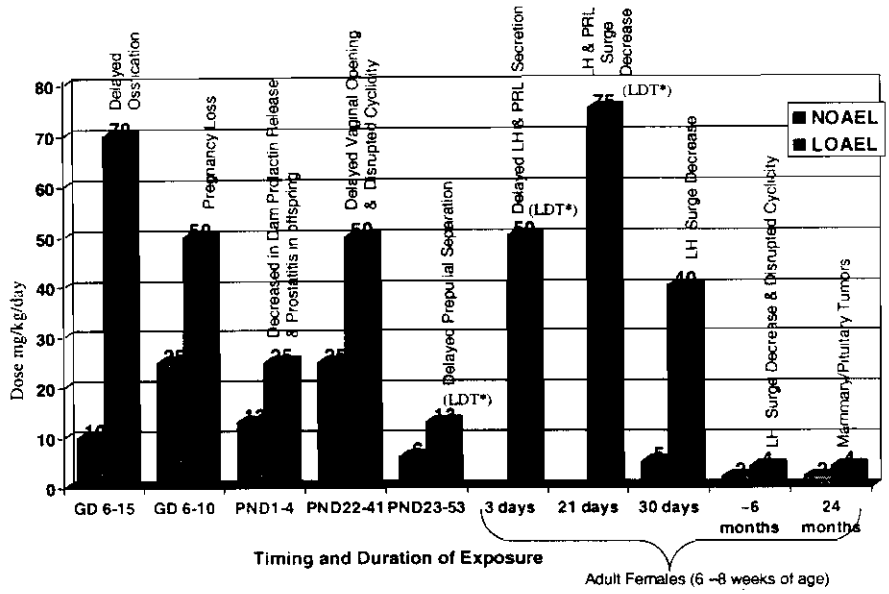
The toxicology database for atrazine was considered adequate for the consideration of potential health effects in infants

and children as a result of exposure to the CMG triazines under FQPA. Prenatal developmental toxicity in rabbits and rats are available. Although atrazine has been evaluated for potential reproductive effects, this was done under the old (*i.e.*, pre-1998) two-generation protocol in rats. Therefore, the lack of observed susceptibility in the atrazine guideline reproductive study is misleading because these pre-1998 guidelines did not include sensitive measures of endocrine disruption that are now included (e.g., estrous cyclicity, sperm measures, sexual maturation, expanded postmortem observations).

More recently, atrazine was evaluated under a study protocol designed for endocrine disruptors. It was evaluated by NHEERL in the rat pubertal assays where positive findings were observed for both males and females (Stoker *et. al.*, 2000 and Laws *et. al.*, 2000).

It should be noted that although atrazine has a CNS mode of action, it and its metabolites have not been evaluated in any standard guideline neurotoxicity assays. Below is a summary of the NOAELs and LOAELs for the developmental and reproductive effects of atrazine.

d. Data Base Issues



Key endocrine related effects following atrazine treatment of rats.
(A rat developmental study showed delayed ossification 10 mg/kg = NOAEL, 70 mg/kg = LOAEL)

*LDT = lowest dose tested

Although information has been developed on atrazine's mode of action and resulting neuroendocrinopathies (e.g., delayed puberty, prostatitis, pregnancy loss, altered lactation; refer to figure above), there are some issues and uncertainties that arise from the available data, as discussed below.

- *The focus of testing with atrazine in young rats has been limited to short term dosing of a specific developmental period (postnatal days ~20 - 50 in the rat pubertal assays).* This raises two issues: (1) the uncertainty associated with the apparent sensitivity during earlier developmental periods, and (2) the uncertainty of the consequence of a longer duration of dosing throughout development. From a review of the literature on endocrine disruptors (EPA 1997 Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis by Crisp *et. al.*, and the 1999 NAS Report on *Hormonally Active Agents in the Environment)*, an increased sensitivity can be found resulting from exposures during early developmental periods with other endocrine disruptors. Therefore, it is important for any chemical that is anti-estrogenic or anti-androgenic to evaluate critical periods throughout development. Although atrazine does not bind to estrogen or androgen receptors directly, it behaves like an anti- estrogenic or androgenic

chemical in studies done by NHEERL (Stoker et al 2000; Stoker *et. al.*, 2002; Laws *et. al.*2000; Laes et . al., 2003). Furthermore, it has been demonstrated in rats and mice that suppression of PRL in the lactating dam during postnatal days 1-10 will result in the disruption of neuronal development within the tuberoinfundibular dopaminergic neurons (TIDA). In the rat, this in turn will lead to the development of hyperprolactinemia prior to puberty (at ~PND 25-30) (Stoker et al 2000; Stoker *et. al.*, 2002). Evidence indicative of a loss of a specific population of hypothalamic neurons that play a key role in the regulation of PRL has been demonstrated for atrazine. Therefore, it is important to consider evaluation of earlier developmental periods for atrazine.

Data on atrazine suggest that the longer the duration of exposure to young animals, the lower the dose that is needed to produce effects. For example, a lower NOAEL is found in the male pubertal assay with a longer duration of exposure (30 days) compared to the female pubertal assay (20 days).

In summary, there is a reasonable basis to believe that atrazine longer term dosing that covered the critical developmental periods in gestation through puberty in both male and female rats could lead to lower NOAELs.

- ❑ Studies on the effects of norephinephrine (NE), Dopamine, and GnRH have been acute (3 day) treatments at high doses. Atrazine's effects on these neurotransmitters/peptides at longer exposures and longer doses are not known.

- ❑ The focus of testing has been on cancer and its endocrine reproductive effects: Atrazine's endocrine effects on reproduction are secondary to its CNS effects on hypothalamic neurotransmitters and neuropeptides. No evaluation of neurotoxicity has been conducted on atrazine or its metabolites. It is not known whether atrazine's CNS mode of action would lead to behavioral effects in the young or at what dose compared to its reproductive developmental effects given that these are generally gross measures. However, in addition to functional neurological evaluations, more sensitive CNS measures relevant to atrazine's mode of action should be discussed and considered, such as endpoints indicative of dopaminergic toxicity (e.g., striatal

cell counts) or measures of sexual differentiation in the brain.

Data on the neurological effects of hormonally active environmental contaminants are very limited. Unfortunately little is known about the neurological effects of endocrine disruptors. The EPA 1997 *Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis* (Crisp *et. al.*), and the 1999 NAS Report on Hormonally Active Agents in the Environment point out the major role played by the CNS in integrating hormonal and behavioral activity; disturbances in these finely coordinated mechanisms can impair normal adaptive behavior and reproduction.

e. Testing Recommendations

Although the Hazard Identification Assessment Review Committee (HIARC - August 28, 2000 report) determined that a standard developmental neurotoxicity study (DNT) is not required because atrazine's CNS mode of action affected pituitary endocrine function, HIARC did recommend that studies examining the specific CNS alterations described in the studies conducted by the registrant and the Agency's NHEERL labs, be performed.

Moreover, the more recent studies from the NHEERL indicate that any additional testing on atrazine should consider incorporation of hypothalamic neurotransmitter, hormone, and reproductive/developmental measures following developmental exposures (gestation through lactation, pre-weaning, up to day 60), as well as sensitive neurological evaluations.

f. Determination of Susceptibility

The HIARC (August 28, 2000) concluded that there was evidence of increased susceptibility given the delayed puberty found in rat studies consistent with atrazine's CNS mode of action.

g. Metabolites

DEA, DIA, and DACT are all considered toxicologically equivalent (equipotent) to atrazine. All are key metabolites that occur in drinking water and have been included in this cumulative risk assessment. Given their toxicologic equivalence to atrazine, it

is important to determine their potential effects on the young. There are more toxicity data available for DACT than for DEA or DIA. Some toxicological data are also available on hydroxyatrazine, and it is also addressed below.

- In a prenatal developmental toxicity study with DACT in rats, developmental effects were seen in the absence of maternal toxicity. The maternal NOAEL was 25 mg/kg/day based on statistically significant decrease in body weight gain at 75 mg/kg/day (LOAEL). The developmental NOAEL was 2.5 mg/kg/day based on increased incidence of incompletely ossified parietals, interparietals and unossified hyoids at 25 mg/kg/day (LOAEL). (See HIARC Report dated 8/28/0)

  It should be noted that very recently, NHEERL has generated data on the chlorinated metabolites of atrazine that demonstrate effects on male puberty similar to atrazine (Unpublished SOT Abstract - *The Effects of Atrazine Metabolites on Puberty in the Male Wistar Rat.* D L Guidici, R L Cooper and T E Stoker. Endocrinology Branch, NHEERL, U.S. Environmental Protection Agency, RTP, NC.). In the male pubertal assay, significant delay was found at the isomolar equivalents of 25 mg of atrazine/kg/day for all three metabolites, that is DIA (deisopropyl chlorotriazine), DEA (diethyl chlorotriazine), and DACT (diaminochlorotriazine).

- There was no evidence of increased susceptibility in the prenatal developmental toxicity study in rats, however there is more limited information to judge susceptibility to the chlorinated metabolites compared to atrazine. The pubertal assays conducted by NHEERL with hydroxyatrazine are incomplete at this time.

h. Placental Transfer and Lactational Exposure

Both atrazine and DACT are found in the milk. However, the percentage of administered dose is very small.

- In goats, 2% of the atrazine dose is transferred to milk. Qualitatively, the major metabolite in goats milk is DACT and it accounts for 45% of the residue found.

- In cows, 69% of the residue found in milk is DACT. Quantitatively, 2.7% of the administered dose comes out in the milk.

- R. Cooper's laboratory has done a study with tritiated atrazine using 2 and 4 mg/kg doses given to female rats (dam) and allowed the dam to nurse her pups for 30 minutes. One percent of those two doses were found in the stomach of the pups. Negligible concentrations were found in the pup brain.

- No studies have been identified that directly examine transplacental transfer of atrazine or its metabolites.

i. Magnitude of the Hazard-Based FQPA Factor

Based on the above-mentioned considerations and issues, there remains some degree of residual uncertainty as to the effects of triazines on the young. Although there are several specialized endocrine studies on the young (i.e., pubertal assays) available, and the most sensitive endpoints are utilized in the risk assessment, there are some limitations. In particular, exposures at all critical periods of development in the young have not been examined. Despite this shortcoming, a comparison of the available pubertal assay data with the adult studies indicate that a 3X hazard-based factor is sufficient and that the young are not likely to be an order of magnitude more sensitive than the adults. For instance, the most sensitive endpoint is the NOAEL of 1.8 mg/kg/day identified in a 6-month LH study in the adult rat. The most sensitive endpoint in the pubertal studies is the NOAEL of 6.25 mg/kg/day based on pubertal separation in young males. Application of a factor of 3X to the the NOAEL of 6.25 mg/kg/day yields an extrapolated NOAEL of 2.0 mg/kg/day.

j. Magnitude of the Exposure-Based FQPA Factor

Where models have been used to estimate drinking water exposure, no additional FQPA Exposure-based Factor is warranted. The model used (PRZM/EXAMS) provides exposure estimates that are conservative and protective. Where monitoring data are used that are limited in temporal scope or frequency of sampling, an additional 3X FQPA Exposure-based Factor is warranted. For the purposes of this assessment, an additional 3X FQPA Exposure-based Factor has been applied to the Midwest scenario which relies of monitoring data that are limited in temporal scope, i.e., less than 2 years of monitoring data. The Florida and California scenarios use the PRZM/EXAMS model and do not require an additional factor. The PRZM/EXAMS model is considered to be conservative and results from that model relating to drinking water exposure are considered protective. This is in

accordance with the single chemical assessments for the triazines of the CMG.

Because conservative assumptions based on HED's Residential SOPs were used to estimate residential exposures, no additional FQPA Exposure-based Factor is warranted. This is in accordance with the single chemical assessments for the triazines of the CMG.

D. Exposure Analysis and Methodology

1. Determination of Regions Where Atrazine, Simazine, and Propazine May Co-Occur

Initially all six CMG triazines (atrazine, simazine, propazine, and their common metabolites des-ethyl-s-atrazine (DEA), des-isopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT) were considered for inclusion in this cumulative risk assessment. The potential for all or some of these compounds to co-occur across different routes of exposure was determined. The following specific routes of exposure were considered: oral dietary intake via food and drinking water, incidental oral exposure via residential uses, and dermal and inhalation exposure via residential uses. For the purposes of this cumulative risk assessment, which is being conducted as a part of tolerance reassessment, only non-occupational exposures via these pathways have been considered. As a first step in this process, the registered uses of atrazine, simazine and propazine were considered to determine whether exposure to these compounds was anticipated, and if exposure was anticipated, through which pathways.

Atrazine is registered for agricultural use on a variety of grain crops (corn, wheat, and sorghum) and sugarcane with lesser use on macadamia nuts, and guava. Simazine is registered for agricultural use on a variety of fruit (pome, citrus, and stone), nut, and berry crops, corn, alfalfa, avocado, asparagus, artichoke, olives, and sugarcane. Atrazine and simazine are also registered for use on specific grasses: zoysia, Bermuda, and St. Augustine. This use results in residential exposures via home lawns and golf courses in the Southeast region of the US. Most of the use of atrazine and simazine products on turf in the Southeast occurs in Florida. Propazine is registered for use indoors on container-grown ornamentals in greenhouses. Propazine has no existing registered uses in the U.S. on agricultural crops. There is an import tolerance for propazine on sorghum. There are no registered residential uses of propazine in the U.S.

Based on these registered uses in the U.S., there is potential for

exposure to atrazine and simazine residues via food, drinking water, and home uses. Given their use patterns, however, it is more likely their residues will co-occur in drinking water. Atrazine, simazine, and their common metabolites (DEA, DIA, and DACT) have been included in this cumulative risk assessment. A more detailed analysis of the likelihood that atrazine and simazine residues may co-occur on the same foods follows in Section D. 2.

Based on existing uses, there is potential for propazine residues to occur in foods; there is no potential for propazine residues to occur in drinking water or the home environment. Based on the single chemical dietary assessment for propazine, exposures to propazine in the diet are not anticipated. The single-chemical risk assessment indicated that exposure to propazine in the diet, based on imported sorghum, is zero percent (0%) of the acute and chronic Population Adjusted Doses (aPAD and cPAD, respectively). As a result of this initial analysis of registered uses, propazine has been excluded from this cumulative analysis because there are no anticipated exposures to residues of propazine at this time.

With the exclusion of propazine, five of the six compounds included in the CMG have been included in this triazine cumulative risk assessment. They are: atrazine, simazine, DEA, DIA, and DACT. These five compounds comprise the Cumulative Assessment Group (CAG). The terms "residues of atrazine and simazine" or "triazine residues" as used in this document are taken to mean all five compounds.

a. Usage Data

Once the potential for exposures to residues of atrazine and simazine was established, usage data were used to identify where (in what regions of the U.S.) residues of atrazine and simazine might occur together (co-occur). OPP's Biological and Economic Analysis Division (BEAD) researched and collated usage data and prepared maps showing where atrazine and simazine use overlaps on a crop and state/county basis in the U.S. Usage data were available on a state basis, except for the State of California, which had some data on a county basis. Based on this analysis, regions where residues of atrazine and simazine may co-occur were determined. The maps in Appendix I indicate where atrazine and simazine are used in the U.S. and where this usage overlaps. Figures 1a and 1b show simazine and atrazine use in the U.S., respectively. Figure 2 shows atrazine and simazine usage in the U.S. combined. Figure 3 shows states where atrazine and simazine use overlaps.

The intensity of usage of the two compounds was considered as well. As can be seen by the maps and usage tables provided by BEAD in Appendix I, atrazine and simazine use overlaps in many states. Generally, there is usage overlap in the Northeast, the Mid-Atlantic, the Southeast, Texas, the Midwest, and along the West Coast. The intensity of usage by state is shown in Figures 1a and 1 b and indicates that the highest volume of use (as pounds applied of both atrazine and simazine) occurs in the Midwest, Florida, Texas, and California.

Based on the intensity of usage of both atrazine and simazine, the regions assessed in this cumulative risk assessment are: the Midwest (>50 million pounds), California (combined usage of ~1.5 million pounds), and Florida (combined usage of ~3 million pounds). For the purposes of this assessment, the Midwest assessment focuses on Indiana, Iowa, Illinois, Kansas, Nebraska, Missouri, and Ohio. Most of the combined usage in the Midwest can be attributed to atrazine (98%), while most of the usage in California (98%) can be attributed to simazine. In Florida, atrazine and simazine usage is similar, 54% and 46%, respectively.

Based on the usage information provided by BEAD, and considering use patterns and intensity of use defined as pounds applied, the Midwest presents as the region with the greatest atrazine use. California presents as the region with the greatest simazine use. There is no turf use in the Midwest or California. Florida presents as the region with approximately equal use of atrazine and simazine and the greatest likelihood of co-occurrence of atrazine and simazine residues across multiple exposure pathways: food, drinking water, and turf.

There are other regions with the potential for the co-occurrence of atrazine and simazine residues: Texas, the Northeast/Mid-Atlantic and the Northwest. Texas with 3.7 million pounds of combined atrazine (98%) and simazine (2%) usage will be the subject of a subsequent assessment to consider the impact on drinking water of a proposed domestic use of propazine on sorghum. Usage in the Northeast is estimated at 3 million pounds of atrazine and simazine and in the Mid-Atlantic usage is estimated at 2 million pounds. Although the combined usage in the Northeast/Mid-Atlantic region approximates 5 million pounds ai of atrazine and simazine, no single state estimates use at more than 1.5 million pounds, and most have much less usage than that. Usage in the Northwest is considered insignificant to the regions included in this assessment. Washington and Oregon account for only 382,000 pounds of atrazine and simazine usage. In general,

the intensity of usage for the currently registered uses of atrazine and simazine is greatest in the Midwest, California and Florida.

Once the general regions where atrazine and simazine may co-occur were determined, the likelihood of exposure to residues of both atrazine and simazine via the food, drinking water or turf pathways was investigated.

2. Determination of Likelihood of Exposure from Foods

For the purposes of this cumulative risk assessment it is assumed that food is distributed on a national basis. Therefore, if residues of atrazine and simazine are determined to co-occur on specific food commodities, or in general in the diet, exposure to their residues in the diet would be assumed regardless of region. However, residue data from the Pesticide Data Program (PDP) from 1994 to 2003 show no detectable residues of atrazine and simazine on foods. Because of their disparate use patterns, with the exception of corn, they are unlikely to co-occur on the same food commodities. USDA (FSIS) data and registrant-supplied metabolism and field trial data all show non-detectable residues of atrazine and simazine and their common metabolites under the CMG.

Based on the available residue data, dietary exposure assessments conducted for atrazine indicate that negligible exposure to atrazine and DEA, DIA, and DACT occurs through foods. The contribution of exposure to residues of atrazine in/on food to overall exposure and risk from registered uses of atrazine is insignificant. It represents < 1% of the aPAD and cPAD. Based on the estimated dietary exposure through food, exposure to atrazine residues on foods was assumed to be zero in this cumulative risk assessment. A similar situation exists for simazine. Based on the lack of potential dietary exposure through foods, exposure to simazine residues on food were assumed to be zero in its single chemical dietary assessment and in this cumulative risk assessment. A more detailed rationale and discussion of the available residue data for atrazine and simazine on foods follows. As previously stated, propazine has been excluded from this cumulative assessment based on a lack of anticipated exposure. Dietary exposure to propazine was estimated to be zero percent of the aPAD and cPAD.

a. Residue Data

Adequate residue data are available for atrazine in the following crops: corn, sorghum, sugarcane, wheat, macadamia nuts and guava. Adequate residue data are available for simazine in the following crops: apples, avocados, bananas, blueberries, caneberries, corn, grapes, olives, peaches, plums and pecans. An

adequate number of field trials have been conducted on these crops depicting residues of atrazine and simazine and its chlorinated metabolites resulting from application at the maximum labeled use rates. These residue data showed non-detectable residues, i.e., <0.05 ppm, the limit of detection (LOD) for the method for most of the crops. Available PDP monitoring data from 1994 to 2003 show no detectable residues for both chemicals. These data show that there is essentially no occurrence of atrazine and simazine on foods. Available FDA monitoring data show no detectable residues of atrazine and simazine.

Two corn metabolism studies conducted at different application rates of atrazine are available. One is based on a post-emergent application at 3.0 lbs ai/A (1.2 X the maximum pre-emergent/post-emergent 2.5 ai lbs/A), and the other is based on a pre-emergent application rate of 2.0 lbs ai/A (1.0X the maximum pre-emergent 2.0 lbs ai/A). Both studies resulted in non-detectable residues of atrazine and its chlorinated metabolites in corn grain.

Metabolism studies are available for simazine and its chlorinated metabolites on the following crops: apples, grapes, oranges, and field corn. These studies resulted in non-detectable (<0.001 ppm) residues of simazine and its chlorinated metabolites for: apples harvested 181 days after application at the maximum label rate (1X); for grapes harvested 131 days after application at the maximum label rate (1X); for oranges harvested at 105 days following the second of two applications at one-half the maximum label rate (0.5X) in FL and TX and at the maximum label rate (1X) in AZ and CA; and for corn forage, fodder and grain harvested at 30 days, 120 days, and 162 days, respectively, at the maximum label rate (1X).

After consultation with the Risk Assessment Review Committee (RARC), and review and extensive discussion of the available metabolism, field trial and PDP monitoring data for simazine and atrazine, HED has determined that food related exposures to atrazine and simazine residues are insignificant and set food residues to zero for the cumulative dietary exposure assessment. The rationale for this decision is based on the use patterns for atrazine and simazine, i.e., it is predominately used as a pre-emergent herbicide in soil directed sprays, rather than foliarly-applied, and the lack of detections in the monitoring, and metabolism and field trial databases. Consequently, for the purposes of this cumulative assessment, dietary exposure to residues of atrazine and simazine have been set to zero.

3. Determination of Likelihood of Exposure from Drinking Water

For the purposes of this cumulative risk assessment, drinking water exposures to atrazine, simazine, DEA, DIA, and DACT in the Midwest, California (CA), and Florida (FL) have been estimated. The rationale for the selection of these three exposure scenarios for drinking water is presented below.

Usage and monitoring data were used to determine the likelihood of exposure to triazine residues from drinking water. This assessment focuses on drinking water derived from surface water. Although the potential for atrazine and simazine residues to co-occur in groundwater exists, previous single-chemical assessments for atrazine and simazine determined that exposures to atrazine and simazine in drinking water via Community Water Systems (CWS) using groundwater were much less than from surface water, and not of concern.[1, 2]

The potential for atrazine and simazine to be used in the Midwest in the same area, watershed, county or state and to impact drinking water exists. This can be surmised based on registered uses, usage data and the maps presented in Appendix I. The same potential for atrazine and simazine to impact drinking water in California and Florida can be seen

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[1] Exposure to residues of atrazine and simazine in rural wells was considered in the single-chemical assessments and was noted as an uncertainty in each. Recommendations and requirements for rural wells were included in the single-chemical assessments for atrazine and simazine and are still under discussion with the registrant. In Florida in particular, groundwater, especially from private wells, is likely to be the primary source of drinking water for much of the population. However, given the historically-limited amount of reliable, available monitoring data on rural wells used for drinking water across the U.S., OPP reviewed the results of its modeling for both groundwater and surface water for the triazines and determined that surface water, which did not present levels of concern, is likely to result in higher concentrations of total chlorotriazines (TCT) than groundwater, even though groundwater may be the more prevalent source in many areas. Therefore, exposure from rural wells was not included in the scope of this cumulative assessment. OPP acknowledges that states and local entities have begun collecting new monitoring data through their pesticide management plans which could provide useful information for the triazine cumulative assessment. If new monitoring data from rural wells are likely to impact the conclusions presented in this assessment, then monitoring for rural wells could be considered.

[2] OPP acknowledges that the available water treatment data indicate that activated carbon (either as Powdered Activated Carbon (PAC) or Granulated Activated Carbon (GAC) is effective in removing atrazine from finished drinking water, while conventional water treatment processes (such as coagulation-flocculation, sedimentation, and conventional filtration) are not effective in removal or transformation of triazine pesticides. The incorporation of GAC and PAC treatment processes into the drinking water exposure assessment was not conducted because GAC is not a common treatment process among community systems and PAC usage coincides with taste and odor issues in drinking water (summer months) rather the time for atrazine occurrence (spring). Reverse osmosis water treatment was also not considered because it is not a common water treatment process. For the above reasons, the impact of water treatment processes on the removal of triazines and their degradates is not included in this triazine cumulative risk assessment.

from the maps located in Appendix I for these states. However, the maps also indicate that atrazine is likely to dominate drinking water exposures in the Midwest and simazine is likely to dominate drinking water exposures in California. Since the compounds have equal usage in Florida, either could be dominant in drinking water there.

In addition to usage data, monitoring data are very good at indicating areas of likely potential exposure to atrazine and simazine in drinking water. The PDP water monitoring program conducted by the USDA supports this. PDP monitoring data collected on specific CWS in California, New York, Colorado, Kansas, Texas, Michigan, North Carolina, Ohio, Oregon, Pennsylvania, and Washington State from 2001 to 2004 found that 37 to 52 percent of the finished drinking water samples analyzed contained atrazine, 12 to 44 percent contained simazine, and 5 to 42 percent contained both. Monitoring from 2001 to 2004 showed maximum concentrations of atrazine varied from 0.2 to 4.2 ppb, and maximum concentrations of simazine varied from 0.1 to 0.52 ppb. It is important to note that the PDP does not target CWS with high atrazine or simazine use to include in its program, nor does a history of high detections in a particular CWS factor into the selection process. The PDP also analyzes for the common metabolites: DEA, DIA, and DACT.

Additional databases also demonstrate that atrazine and simazine co-occur in finished drinking water in specific CWS. Extensive monitoring data on atrazine in finished drinking water exist in the following databases: the Safe Drinking Water Act (SDWA) which mandates the collection of drinking water data across the U.S. through the Safe Drinking Water Information System (SDWIS), the Acetochlor Registration Partnership (ARP) conducted by pesticide registrants focuses on the Midwest corn states, and the combined Atrazine Monitoring Program (AMP) and Voluntary Monitoring Program (VMP) conducted by the registrant. Under the SDWA, atrazine has been monitored and measured in CWS across the U.S since 1991.

Under the ARP, 175 CWS were monitored for atrazine for several years starting in 1995. And under the AMP, approximately 140 CWS have been monitored for atrazine since 2003, while its predecessor, the VMP, began in 1993. Since 2002, all five CAG compounds (atrazine, simazine, DEA, DIA, and DACT) have been monitored and measured during some periods in many CWS in the AMP. Both the ARP and the AMP/VMP monitoring programs are based in the Midwest where atrazine is most heavily used. The CWS included in both the ARP and the AMP/VMP have been targeted for monitoring as CWS with the highest measured concentrations of atrazine in the U.S. As such, the CWS included in these monitoring programs represent a set of CWS with high-end concentrations of residues of atrazine. Both the ARP and AMP/VMP

measure atrazine in finished drinking water.

Less monitoring data are available from these same databases on the common metabolites: DEA, DIA, and DACT. Monitoring data on simazine are likewise available, but to a lesser extent than for atrazine. In past single-chemical assessments for atrazine and simazine, linear regression equations based on measured atrazine and a limited set of monitoring data on the common metabolites have been used to estimate the total chlorotriazine (TCT) concentration of all five compounds. The use of linear regression equations in estimating the total concentration of all five compounds, its strengths and weaknesses, is discussed in Appendix V.

Because the AMP has specifically measured all five compounds included in this assessment for certain CWS during certain periods since 2002, these data were used to establish co-occurrence of residues of atrazine and simazine in specific CWS in the Midwest. This subset of CWS represents CWS with high residues of atrazine. All CWS monitored in the AMP/VMP are targeted for either high use of atrazine or a history of high detections of atrazine or both. Linear regression equations were not used to estimate concentrations of all five compounds (as TCT). Although this limits the years of data that could be used in the analysis, it ensures an assessment based on actual, directly measured concentrations of each of the five CAG compounds: atrazine, simazine, DEA, DIA, and DACT in finished drinking water in the Midwest.

For the purposes of this cumulative risk assessment, drinking water exposures to atrazine, simazine, DEA, DIA, and DACT in the Midwest, California (CA), and Florida (FL) have been estimated. The Midwest drinking water exposure estimates rely on monitoring data (described above, and described further, below). Because of the lack of monitoring data in California and Florida for atrazine and simazine compared to the Midwest, the computer simulation model PRZM/EXAMS was used to estimate residues of atrazine and simazine in drinking water derived from surface water. The scenarios modeled for each of the three regions are described below.

a. Inputs for the Midwest Drinking Water Exposure Scenario

Data from a pool of 118 CWS using surface water monitored from 2002 through 2004 for atrazine and simazine and their common chlorinated metabolites, DEA, DIA, and DACT were used for the cumulative drinking water risk assessment in the Midwest. These 118 CWS were identified as having been monitored for co-occurrence of one or more of the five compounds: atrazine,

simazine, DEA, DIA, and DACT. A total of 1,162 finished water samples were collected from these 118 CWS and used in this assessment. These samples were collected under either the Voluntary Monitoring Program (VMP), the Atrazine Monitoring Program (AMP/VMP), or a special VMP subgroup of 49 systems and used in the assessment. These data were submitted to EPA by Syngenta and collected as part of Syngenta's various monitoring programs.

Samples from these 118 CWS were measured with GC/MS and later LC/MS during the period of 2002 through 2004 for atrazine, simazine, DEA, DIA, and DACT. However, given the sporadic nature of the sampling in some CWS, at most there are 2 years of consistent monitoring for a given CWS, and as little as a few months. Measurements on each of the compounds were totaled for each sample for a given CWS. Measurements reflecting a concentration for a given compound of less than the LOQ were included as half the LOQ.

These 118 CWS do not represent an exclusive area where both compounds were always used together. Because the 118 CWS represent high-end atrazine detections and use in the Midwest, this subset of CWS is not necessarily considered to be representative of CWS in the Midwest with high simazine use. Rather, it represents high-end atrazine systems where simazine was often used. An examination of the overall data set used by EPA shows that simazine was detected in nearly two-thirds of the raw water samples, demonstrating its use in areas near many of the CWS in the subset. In general in the Midwest, usage statistics indicate an atrazine to simazine ratio of nearly ten to one in terms of pounds used. (See Appendix I). Simazine levels were higher in systems in Illinois, Indiana, Ohio, and Kentucky, and lower in systems from Kansas, Missouri, Texas, and Louisiana in this subset.

For many of these CWS, monitoring was carried out as specified by a weekly program during the season of use and biweekly during the remainder of the year. In other CWS, measurements of the five residues were taken only during the season of use, when levels were expected to be higher than at other times. Finally, for some CWS measurements were made only when initial results by immunoassay (IA) showed levels to be 3 ppb or above. Because the CARES™ model requires a daily water concentration input to run, daily concentrations had to be interpolated from the available weekly and biweekly, sometimes monthly samples. An algorithm built into the CARES™ model

interpolates daily concentration values linearly between measured values, and was used to estimate daily concentrations of triazine residues for each CWS assessed.

The 118 CWS showing co-occurrence of triazine residues were ranked from high to low for peak concentrations of triazine residues (all 5 compounds) in finished drinking water. Then the top 15 CWS with the highest maximum concentration values were selected initially for the cumulative assessment. These top CWS represent the 15 CWS out of the 118 with the highest peak total triazine residues (atrazine, simazine DEA, DIA, and DACT). In the 15 CWS with the highest triazine residues, concentration levels are contributed to most heavily by atrazine, rather than by simazine or any of the common metabolites. Data for each of these "high" 15 CWS were then entered into the aggregate CARES™ model. That is, 15 separate drinking water exposure assessments (one for each of the 15 "high" CWS) were conducted using the CARES™ model. Data were not combined across CWS. The data for the 15 "high" CWS entered into the CARES™ model are provided in Appendix II. The results of the CARES™ model analysis and risk estimates associated with drinking water exposures to the triazine residues are presented in Section E.

b. Inputs for the Florida and California Drinking water Exposure Scenarios

Monitoring data were submitted for the reregistration of atrazine and simazine. However, most of the data on finished drinking water target CWS in the Midwest and other areas where atrazine is heavily used. Very little data on finished drinking water in areas where simazine is heavily used (i.e., California and Florida) are available. For areas such as California and Florida where drinking water monitoring data are sparse and sporadic, the likelihood that peak simazine concentrations may have been missed is high. Therefore, for the purposes of this cumulative risk assessment on the triazines, the assessment of drinking water exposures to the triazine residues in California and Florida is based on the PRZM/EXAMS model.

As with previous cumulative assessments, for this triazine cumulative, the Environmental Fate and Effects Division (EFED) adapted its paired PRZM and EXAMS models for the Index Reservoir (PRZM/EXAMS IR) to estimate distributions of daily drinking water concentrations over a period of thirty years. The weather information, soil properties and site characteristics for each specific site of interest used in the modeling are chosen from

real world databases. The environmental fate properties for atrazine and simazine are extracted from acceptable studies submitted by the registrants for pesticide registration and reregistration. Detailed description, documentation, and direct links for running these models can be found in http://www.epa.gov/oppefed1/models/water/index.htm and also in the EPA EFED's pesticide science policy paper "Guidance for Use of the Index Reservoir in Drinking Water Exposure Assessments."

As mentioned earlier, a cumulative assessment estimates daily distributions of drinking water concentrations for use in the human health risk assessment as opposed to only the high end of the distribution (1-10 year upper 10th percentile concentration) for an individual chemical assessment. For atrazine, the daily drinking water concentrations were modeled based on typical application rates and patterns compiled by BEAD. Typical rates for atrazine are comparable to its labeled rates. For simazine, it was noted that typical application rates compiled by BEAD were substantially lower than the label rates assessed in the most current Simazine IRED. Therefore, the maximum rates and patterns specified on the current IRED are used in order to capture the most conservative runoff scenarios. Furthermore, to take into account the differences in cropping and pesticide use as well as the differences in runoff and leaching vulnerability of different regions, the selection of the modeling scenarios was performed on a regional basis and not on a national basis. Regional Percent Crop Area (PCA) factors are also used to adjust for the cropped area in a drinking watershed, since different regions in a pesticide use area will vary in vulnerability to surface water contamination due to variations in soil, weather, and agricultural practices. For this assessment, PCA factors of 0.56 and 0.38 were used for California and Florida, respectively. Lastly, since for a cumulative water assessment, multiple pesticides (atrazine and simazine in this case) were used on multiple crops in multiple fields in a watershed, a cumulative adjustment factor (CAF) for each watershed was also developed to account for the portion of the watershed that is treated by either atrazine or simazine on a particular crop. The steps and approaches taken to estimate the daily drinking water contributions to the cumulative human health risk assessment are described in more detail in Appendix III. The results of the model simulations estimating the risks associated with exposure to triazine residue in drinking water are presented in Section E.

4. **Determination of the Likelihood of Exposure from Residential Uses:**

Atrazine and simazine have registered uses on lawns and golf courses. Both atrazine and simazine are used to control a variety of weeds in grass varieties grown only in the Southeast region of the United States. Florida has the largest share of this market. These registered uses can lead to potential short-term exposure to triazine residues in the residential setting. Therefore, for the residential assessment, short-term (1 to 30 day) exposures to atrazine and simazine were assessed whereas intermediate- and long-term residential exposures (> 30 days) are not assessed (because they are not anticipated to occur). For the purposes of this cumulative risk assessment, risk estimates for residential exposures are based on a 28-day average exposure to residues of atrazine and simazine.

Residential applicator exposure via the dermal and inhalation routes is expected for adult homeowners treating their lawns with triazine products. Postapplication dermal exposure is expected for adults re-entering treated lawns or playing rounds of golf on treated courses. Also, postapplication exposure via the dermal and non-dietary (incidental oral ingestion) routes is expected for children playing on treated lawns.

The residential exposure assessment relied on assumptions and algorithms based on HED's Residential SOPs, which are conservative and protective.

a. Inputs for the Residential Exposure Scenarios

Three types of data were considered in the residential exposure assessment: pesticide use data, exposure factor data, and chemical-specific residue concentration data.

Pesticide Use Data

Based on the currently registered labels, it was assumed that a maximum of 6 applications would be made to residential lawns, and a maximum of 2 applications would be made to golf course greens, tees, and fairways. Additionally, each application would be effective for up to 30 days. The percent of households applying the various products was assumed to be 10 percent of the population. These assumptions are expected to provide a conservative assessment of residential exposure and risk.

Exposure Factor Data

Exposure factors such as the amount of time spent in an area, frequency of hand-to-mouth contacts, size of area treated, and location of residue source (lawn) are critical for estimating exposures to atrazine and simazine in lawn use products. These

data are described in detail in Appendix IV.

Chemical-specific Residue Concentration Data

Chemical-specific residue concentration data are available as turf transferable residues (TTR) for atrazine's granular and liquid products, and for simazine's liquid products. These data are described in detail in Appendix IV.

This assessment considered a variety of exposure scenarios for consumer applicator and postapplication exposures. Each of these is described in detail in Appendix IV. Since it is difficult to determine typical rates for homeowners, maximum labeled rates were used in this assessment: 2 lbs ai/A for granular atrazine, 1 lb ai/A liquid atrazine, 2 lb ai/A liquid simazine, and 1.8 lb ai/A granular simazine.

E. The Cumulative Risk Assessment Results

After the exposure scenarios and relevant endpoints are selected, and the inputs for the exposure estimates decided upon, the exposures are estimated, compared to the relevant quantitative hazard estimates, and the resulting risks are estimated. This section describes these risk assessment results for each exposure scenario considered quantitatively in the triazine cumulative risk assessment.

1. CARES™ Analysis of Drinking Water Exposures and Risks: Single Exposure Pathway Cumulative Assessments

a. Midwest

Risk estimates calculated by CARES™ for the Midwest scenario are based on exposure data from specific CWS considered representative of high-end triazine residues (15 CWS). More specifically, these risk estimates are based on monitoring data and 90-day rolling average exposures to the residues of atrazine and simazine, DEA, DIA, and DACT (discussed in more depth in Section D. 3. a.). Drinking water exposures have been shown through monitoring data to be highest in short- to intermediate-term exposure durations on the order of a few months. These 90-day rolling average exposures were compared to a quantitative hazard estimate of 0.0018 mg/kg/day, which is based on the endpoint of estrous cycle alterations and LH surge suppressions observed in a 6-month toxicity study with atrazine in the adult female rat (NOAEL = 1.8 mg/kg/day). This quantitative hazard estimate reflects a 100X uncertainty factor (10X for

interspecies variability and 10X for intraspecies variation) in addition to a 10X FQPA safety factor for residual hazard-based and exposure-based uncertainties. The exposure-based FQPA safety factor was applied because the monitoring data used in the assessment are limited in temporal scope; and the hazard-based FQPA safety factor was applied to account for residual uncertainties in the triazine toxicity database. Risk estimates with a Margin of Exposure (MOE) above 1000 are not of concern for the Midwest scenario.

Risk estimates are above a MOE of 1000 at the 99.9th percentile of exposure for all 15 of the CWS considered representative of high-end triazine residues in the Midwest. A CARES™ analysis using the monitoring data described above was conducted for each of these 15 CWS for 4 populations: infants (< 1 year old), children (1 to 2 years old), females (13 to 49 years old), and males 20-49 years old. These populations represent both the most vulnerable and sensitive groups relative to the endpoint and toxic effects of interest, i.e., endocrine, and developmental and reproductive effects. Given the results for these 15 CWS, the remaining CWS (out of the 118) were not analyzed with the CARES™ model. If these 15 CWS with the highest concentrations of triazine residues had MOEs above 1000, the remaining CWS would, as well. All 15 of these CWS are currently being monitored under the Memorandum of Agreement (MOA) developed as a part of the Interim Reregistration Eligibility Decision (IRED) for atrazine. Table 3 below provides these results.

Table 3. Atrazine and Simazine **Cumulative Risk Assessment: 90-Day Rolling Average In Drinking Water Assessment Using Monitoring Data From the Midwest**

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
Mt Olive, IL	Infants <1 yr	0	0	2.952E-4	6097	7.603E-4	2367
	Children 1-2 yrs	0	0	1.602E-4	11238	2.986E-4	6027
	Females 13-49 yrs	0	0	9.509E-5	18929	1.994E-4	9027
	Males 20- 49 yrs	0	0	1.052E-4	17113	1.869E-4	9631
Coulterville, IL	Infants <1 yr	0	0	2.466E-4	7300	9.190E-4	1959
	Children 1-2 yrs	0	0	1.330E-4	13534	3.529E-4	5101
	Females 13-49 yrs	0	0	8.138E-5	22120	2.430E-4	7408
	Males 20- 49 yrs	0	0	9.831E-5	18309	2.274E-4	7915
Waverly, IL	Infants <1 yr	0	0	3.619E-4	4974	6.176E-4	2914
	Children 1-2 yrs	0	0	1.492E-4	12068	2.527E-4	7124
	Females 13-49 yrs	0	0	9.687E-5	18582	1.617E-4	11129
	Males 20- 49 yrs	0	0	9.598E-5	18755	1.587E-4	11345
Aqua, IL	Infants <1 yr	0	0	5.124E-4	3513	1.129E-3	1595
	Children 1-2 yrs	0	0	2.205E-4	8163	4.232E-4	4254
	Females 13-49 yrs	0	0	1.480E-4	12163	2.983E-4	6034
	Males 20- 49 yrs	0	0	1.552E-4	11597	2.763E-4	6515
Westport, IN	Infants <1 yr	0	0	5.344E-4	3368	1.399E-3	1287
	Children 1-2 yrs	0	0	2.462E-4	7312	5.385E-4	3342
	Females 13-49 yrs	0	0	1.582E-4	11382	3.508E-4	5131
	Males 20- 49 yrs	0	0	1.790E-4	10058	3.427E-4	5253
Bedford, IN	Infants <1 yr	0	0	1.800E-4	9998	5.258E-4	3423
	Children 1-2 yrs	0	0	8.033E-5	22406	2.127E-4	8461
	Females 13-49 yrs	0	0	5.230E-5	34417	1.408E-4	12782
	Males 20- 49 yrs	0	0	5.894E-5	30541	1.396E-4	12893

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
Stucker Fork, IN	Infants <1 yr	0	0	8.237E-5	21854	2.999E-4	6001
	Children 1-2 yrs	0	0	3.122E-5	57663	1.121E-4	16062
	Females 13-49 yrs	0	0	2.167E-5	83083	7.613E-5	23643
	Males 20- 49 yrs	0	0	2.265E-5	79477	7.659E-5	23503
Versailles, IN	Infants <1 yr	0	0	3.073E-4	5858	9.054E-4	1988
	Children 1-2 yrs	0	0	1.344E-4	13383	3.346E-4	5380
	Females 13-49 yrs	0	0	9.105E-5	19769	2.274E-4	7915
	Males 20- 49 yrs	0	0	9.973E-5	18048	2.278E-4	7903
Leitchfield, KY	Infants <1 yr	0	0	2.553E-4	7051	6.448E-4	2792
	Children 1-2 yrs	0	0	1.080E-4	16670	2.571E-4	7000
	Females 13-49 yrs	0	0	6.833E-5	26344	1.707E-4	10545
	Males 20- 49 yrs	0	0	7.128E-5	25251	1.646E-4	10939
Iberville, LA	Infants <1 yr	0	0	3.453E-4	5213	7.790E-4	2311
	Children 1-2 yrs	0	0	1.419E-4	12682	2.818E-4	6388
	Females 13-49 yrs	0	0	9.256E-5	19448	2.001E-4	8995
	Males 20- 49 yrs	0	0	9.323E-5	19307	1.890E-4	9525
Piqua, OH	Infants <1 yr	0	0	4.523E-4	3980	1.177E-3	1529
	Children 1-2 yrs	0	0	2.179E-4	8262	4.396E-4	4095
	Females 13-49 yrs	0	0	1.411E-4	12755	3.130E-4	5751
	Males 20- 49 yrs	0	0	1.361E-4	13223	2.891E-4	6227
Hettick, IL	Infants <1 yr	0	0	3.132E-4	5748	9.378E-4	1919
	Children 1-2 yrs	0	0	1.492E-4	12064	3.884E-4	4634
	Females 13-49 yrs	0	0	9.766E-5	18431	2.495E-4	7213
	Males 20- 49 yrs	0	0	1.039E-4	17331	2.300E-4	7826

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
Lewisburg, KY	Infants <1 yr	0	0	1.862E-4	9668	5.238E-4	3437
	Children 1-2 yrs	0	0	8.621E-5	20879	1.854E-4	9710
	Females 13-49 yrs	0	0	5.558E-5	32384	1.223E-4	14713
	Males 20- 49 yrs	0	0	6.255E-5	28776	1.201E-4	14993
McClure, OH	Infants <1 yr	0	0	3.477E-4	5178	6.356E-4	2832
	Children 1-2 yrs	0	0	1.417E-4	12699	2.334E-4	7713
	Females 13-49 yrs	0	0	9.115E-5	19747	1.641E-4	10968
	Males 20- 49 yrs	0	0	9.396E-5	19158	1.600E-4	11250
Evansville, IL	Infants <1 yr (3,000 individuals)	0	0	2.284e-04	7880	9.140e-04	1969
	Infants <1 yr (10,000 individuals)	0	0	5.428e-05	33164	7.610e-04	2365
	Children 1-2 yrs	0	0	9.137e-05	19700	3.672e-04	4902
	Females 13-49 yrs	0	0	5.991e-05	30047	2.469e-04	7289
	Males 20- 49 yrs	0	0	5.994e-05	30030	2.419e-04	7440

b. Florida (FL) and California (CA)

Risk estimates for the CA and FL scenarios are based on modeling data and 90-day average exposures to the residues of atrazine and simazine, DEA, DIA, and DACT. These 90-day average exposures were compared to a quantitative hazard estimate of 0.006 mg/kg/day, which is based on the same endpoint used in the Midwest exposure scenario, with different uncertainty factors applied. The endpoint is based on the endpoint of estrous cycle alterations and LH surge suppressions observed in a 6-month toxicity study with atrazine in the adult female rat (NOAEL = 1.8 mg/kg/day), and the NOAEL was modified with the standard 100X uncertainty factor (10X for interspecies variability and 10X for intraspecies variation) in addition to a 3X FQPA safety factor for residual hazard-based uncertainties. Because a conservative simulation model was used to estimate drinking water exposures the additional exposure-based uncertainty factor under FQPA is not warranted. Risk estimates with a Margin of Exposure (MOE) above 300 are not of concern for the CA and FL scenarios.

A CARES™ analysis using residue files from the PRZM/EXAMS model was conducted for a FL drinking water exposure scenario for 4 populations: infants (< 1 year old), children (1 to 2 years old), females (13 to 49 years old), and males (20 to 49 years old). These populations represent both the most vulnerable and sensitive groups relative to the endpoint and toxic effects of interest, *i.e.*, endocrine, developmental and reproductive effects. The scenario included typical and maximum use rates of atrazine and simazine. All risk estimates are well above a MOE of 300. Table 4 below provides these results.

Table 4. Atrazine and Simazine Cumulative Risk Assessment: 90-Day Rolling Average In Drinking Water Assessment Using Modeling Data From Florida (Typical & Maximum)

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
FloridaTypical Rate	Infants <1 yr	0	0	6.741E-4	2670	2.367E-3	760
	Children 1-2 yrs	0	0	2.628E-4	6849	1.019E-3	1767
	Females 13-49 yrs	0	0	1.808E-4	9957	6.299E-4	2857
	Males 20- 49 yrs	0	0	1.794E-4	10035	5.430E-4	3315

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
Florida Maximum Rate	Infants <1 yr	0	0	6.812E-4	2642	2.369E-3	760
	Children 1-2 yrs	0	0	2.658E-4	6773	1.020E-3	1765
	Females 13-49 yrs	0	0	1.827E-4	9855	6.305E-4	2855
	Males 20- 49 yrs	0	0	1.808E-4	9958	5.436E-4	3311

As with the FL exposure scenario, a CARES™ analysis using residue files from the PRZM/EXAMS model was conducted for a CA drinking water exposure scenario for the same 4 populations: infants (< 1 year old), children (1 to 2 years old), females (13 to 49 years old), and males (20 to 49 years old). And again, these populations represent both the most vulnerable and sensitive groups relative to the endpoint and toxic effects of interest, *i.e.*, endocrine, developmental and reproductive effects. The scenario included typical use rates of atrazine and simazine. All risk estimates are well above a MOE of 300. Table 5 below provides these results.

Table 5. Atrazine and Simazine Cumulative Risk Assessment: 90-Day Rolling Average In Drinking Water Assessment Using PRZM/EXAMS Modeling Data From California

CWS	Population	CARES					
		95th % (mg/kg/day)	MOE	99th % (mg/kg/day)	MOE	99.9th % (mg/kg/day)	MOE
California Typical Rate	Infants <1 yr	0	0	3.840E-5	46870	9.189E-5	19589
	Children 1-2 yrs	0	0	1.682E-5	106985	3.639E-5	49461
	Females 13-49 yrs	0	0	1.215E-5	148165	2.456E-5	73300
	Males 20- 49 yrs	0	0	1.089E-5	165330	2.133E-5	84399

2. Analysis of Combined Drinking Water & Residential (Turf) Exposures and Risks for Florida: Multiple Exposure Pathway Cumulative Assessment

In this assessment, the combination of potential exposures across multiple pathways based on the use patterns of the triazines has been considered. This assessment sums the risk estimates resulting from residential (turf) and drinking water exposures to residues of atrazine and simazine. Residential exposures to the triazines are considered to be short-term, 30 days or less. As previously stated, drinking water exposures have been shown through monitoring data to be highest in short to intermediate-term exposure durations on the order of a few months. In order to match a toxic endpoint of interest (neuroendocrine and developmental effects) with the most appropriate duration of exposure for both residential and drinking water exposures, a 28-day rolling average was calculated for combined drinking water and residential exposure.

These combined exposure estimates, were then compared to a quantitative hazard estimate of 0.021 mg/kg/day, which is based on an endpoint of delayed preputial separation observed in a 28-day pubertal study conducted with developing male rats exposed orally to atrazine (NOAEL = 6.25 mg/kg/day), and reflects the standard uncertainty factor of 100X (10X for interspecies variability and 10X for intraspecies variation) in addition to a 3X uncertainty factor for hazard-based residual uncertainties associated with the potential health consequences on the development of the young. The additional 3X FQPA safety factor for exposure-based uncertainties was not applied because the assumptions and algorithms used in the residential portion of this assessment are based on HED's Residential SOPs which are conservative and protective and a conservative simulation model was used to estimate drinking water exposures, and therefore, the additional exposure-based uncertainty factor under FQPA is not warranted. Risk estimates with a MOE above 300 are not of concern for the combined drinking water and residential exposure scenario. For the residential portion of the assessment, the incidental oral and inhalation risk assessments assume 100% absorption. Whereas for the dermal risk assessment (an assessment where dermal exposure estimates are compared to a quantitative hazard estimate derived from an oral toxicity study), the assessment is modified by a dermal absorption factor of 6%.

The CARES™ model requires residential pesticide use inputs to aggregate exposure from multiple use scenarios. For the triazine cumulative residential assessment, it was assumed that pesticide application had equal likelihood of occurring on each day of the week, as well as each month of the year (and some form of drinking water was

assumed to be drunk daily).

The populations assessed for this multiple exposure pathway assessment were: males 20-49, females 13-49, and children 1-2 and 3-5 years old. These populations represent both the most vulnerable and sensitive groups relative to the exposure pathways and toxic effects of interest, *i.e.*, endocrine, developmental and reproductive effects. The table below (Table 6) summarizes the average daily exposure (over a 28-day duration) and risk estimates for the selected populations, at the upper percentiles of exposure. At the 95th, 99th, and 99.9th percentiles of exposure, the MOEs for all populations are above the level of concern. Risk estimates with a MOE above 300 are not of concern for the combined drinking water and residential exposure scenario.

Table 7 summarizes the average exposure (over a 28-day duration) and corresponding MOEs by source/route. From the table, it is evident that at the 99.9th %, the majority of the cumulative exposure is related to residential dermal exposure. Mouthing activities of toddlers and drinking water exposures do not contribute significantly to the risk estimate.

Table 6. Summary of Total Average Exposure (28-day duration) & MOEs for Triazines[a]

Subpopulation	Exposure (per capita)			MOE (per capita)		
	95% (mg/kg/day)	99% (mg/kg/day)	99.90% (mg/kg/day)	95%	99%	99.90%
1to2 yr olds	0.00110	0.00221	0.01226	5697	2822	510
3to5 yr olds	0.00104	0.00214	0.01098	6028	2917	569
Males 20-49 yrs old	0.00021	0.00096	0.00478	29,493	6511	1307
Females 13-49 yrs old	0.00022	0.00105	0.00637	28,325	5979	981

[a] The CARES software has only recently been upgraded to permit estimation of multipathway MOEs (MOE_T) on a rolling basis, and this multi-pathway, multi-day averaging capability is still undergoing testing by the Agency. Thus, the total 28-day average MOEs presented in this table represent MOE_Ts calculated by the Agency using the Statistical Analysis System (SAS) statistical software code designed and written to perform this specific averaging task per principles outlined in OPP's aggregate and cumulative guidance documents.

Table 7. Summary of Total Average Exposure (28-day duration) & MOEs for Triazines by Source/Route

Source\Route	Exposure (per capita)			MOE (per capita)		
	95% (mg/kg/day)	99% (mg/kg/day)	99.90% (mg/kg/day)	95%	99%	99.90%
1to2 yr olds						
Total MOE[a]	0.00110	0.00221	0.01226	5697	2822	510
Total Residential	0	0.00099	0.01182	$>10^6$	6311	529
Drinking Water	0.00098	0.00179	0.00266	6369	3490	2352
Residential: Dermal	0	0.00059	0.01146	$>10^6$	10,596	545
Residential: hand-to-mouth (H-T-M)	0	0.00021	0.00145	$>10^6$	29,949	4300
3to5 yr olds						
Total MOE[a]	0.00104	0.00214	0.01098	6028	2917	569
Total Residential	0	0.0008	0.01061	$>10^6$	7794	589
Drinking Water	0.00093	0.00176	0.00267	6713	3549	2342
Residential: Dermal	0	0.00052	0.01033	$>10^6$	11,996	605
Residential: H-T-M	0	0.00014	0.00103	$>10^6$	44,091	6065
Females 13-49 yrs old						
Total MOE[a]	0.00022	0.00105	0.00637	28,325	5979	981
Total Residential	0.00002	0.00073	0.00620	279,081	8585	1007
Drinking Water	0.00013	0.00039	0.00099	48,008	15,997	6311
Residential: Dermal	0.00002	0.00073	0.00620	27,908	8585	1007
Residential: Inhalation	0	0	0	$>10^6$	$>10^6$	$>10^6$
Males 20-49 yrs old						
Total MOE[a]	0.00021	0.00096	0.00478	29,493	6511	1307
Total Residential	0.00002	0.00055	0.00458	379,214	11,466	1365
Drinking Water	0.00013	0.00043	0.00112	48,703	14,580	5566
Residential: Dermal	0.00002	0.00055	0.00458	379,214	11,466	1365
Residential: Inhalation	0	0	0	$>10^6$	$>10^6$	$>10^6$

[a] The CARES software has only recently been upgraded to permit estimation of multipathway MOEs (MOE_T) on a rolling basis, and this multi-pathway, multi-day averaging capability is still undergoing testing by the Agency. Tus, the total 28-day average MOEs presented in this table represent MOE_Ts calculated by the Agency using the Statistical Analysis System (SAS) statistical software code designed and written to perform this specific averaging task per principles outlined in OPP's aggregate and cumulative guidance documents.

Of note when considering these residential exposure and risk estimates are data from the National Health and Nutrition Examination Survey III (NHANES) on the metabolite of atrazine (*i.e.*, atrazine mercapturate). The NHANES report provides the results of urinary analyses of a weighted probability sample of the non-institutionalized U.S. population, 1999-2002. The data identifies subjects with high serum and urinary levels of pesticide analytes who are at potential risk for pesticide-related illnesses. However, the urinary levels of atrazine mercapturate measured in a subsample of NHANES participants aged 6-59 years were below the level of detection. Although these data are not robust enough for use quantitatively in the residential exposure portion of the triazine cumulative assessment, they support the characterization of the risk estimates generated under this cumulative assessment for residential exposures to the triazines as conservative.

IV. Characterization and Conclusions of the Risk Assessment

As outlined in Section III, D, E, risk estimates for cumulative exposures to triazine residues for all exposure scenarios quantitatively assessed do not exceed HED's level of concern at the 99.9th percentile.

Single Exposure Pathway: Drinking Water

Risk estimates for cumulative exposures to triazine residues via drinking water based on currently registered uses of atrazine and simazine are not of concern.

The risk estimates provided for drinking water exposures in this assessment are based variously on: 1) chemical-specific monitoring data on finished drinking water in the case of the Midwest drinking water exposure scenario, and 2) a conservative simulation model for raw (unfinished) surface water that may serve as a source of drinking water for California and Florida drinking water exposure scenarios.

1. Midwest - Drinking Water

The Midwest scenario provides an assessment of high-end exposures to triazine residues from direct measurements made in finished drinking water. For many of the CWS in this assessment, the program of monitoring was fairly frequent with measured values for all 5 triazine residues, and the number of consecutive weeks of total chlorotriazines (TCT) measurements was high. Because of this, EPA believes that there is increased accuracy for those CWS used in its assessment. However, several of the "high" 15 CWS assessed had less than one full year of data or else a gap in monitoring for consecutive years. Where data gaps exist, and interpolated values fill in those gaps between measured values, overall estimates for 90-day averages could be either higher than "true" values or lower.

The Midwest assessment would have been more robust if multiple years

of consecutive monitoring data on each of the 5 compounds atrazine, simazine, DEA, DIA, and DACT had been available. It is recommended that this assessment be conducted again to confirm these results once 3 to 5 years of monitoring data are collected on each of the 5 compounds in the CWS currently enrolled in the AMP/VMP.

2. Florida - Drinking Water and 3. California - Drinking Water

The California and Florida drinking water exposure scenarios produced by the PRZM/EXAMS model have been modified by a cumulative adjustment factor (CAF) to account for portions of the simulated watershed that are not treated with atrazine and/or simazine. The model simulations are refined, but expected to be protective, and should be confirmed with monitoring data collected from CWS located in high simazine and atrazine use areas in those states. The monitoring program should include direct measurements on each of the 5 compounds: atrazine, simazine, DEA, DIA, and DACT.

Risk Estimates for the Drinking Water Exposure Pathway in the Single Chemical Assessments versus the Cumulative Assessment

Risk estimates for cumulative exposures to triazine residues via drinking water based on currently registered uses of atrazine and simazine are not of concern. The previous single-chemical risk assessment for atrazine identified drinking water exposures of potential concern. For atrazine, multiple CWS in the Midwest were identified for monitoring under the Memorandum of Agreement contained in the Interim Reregistration Eligibility Decision (IRED, 2002). This is likely a result of the inclusion of monitoring data for CWS in the Midwest from 1993 to 2001. Reductions to atrazine's maximum labeled use rate on corn negotiated in the early 1990s probably did not affect atrazine's impact on surface water until the mid to late 1990s. Most of the CWS identified in the single-chemical assessment had the highest concentrations of atrazine in 1993, 1994, 1996, and 1997. The drinking water monitoring data used for this cumulative assessment span 2002 to 2004 and likely do reflect the impact of previous mitigation and rate reductions for atrazine on surface water concentrations of atrazine. In addition, the linear regression equations that were used to estimate atrazine's chlorinated metabolites (DEA, DIA, and DACT), are considered conservative and likely to overestimate concentrations of the metabolites. The current cumulative assessment presents data from a more recent, although limited, period of exposure and relies on direct measurements of all 5 compounds.

For simazine, the previous single-chemical risk assessment identified 2 CWS in the Midwest as of potential concern. This is likely the result of using older data as described above for atrazine. The single-chemical assessment for simazine also identified potential drinking water exposure concerns and recommended monitoring in CWS located in high simazine use areas in California and Florida. The previous drinking water exposure assessment for simazine did not apply the CAF. In addition, the previous single-chemical risk assessments for atrazine and simazine relied on

linear regression equations to estimate total chlorotriazine residues in drinking water, rather than direct measurements. The previous model simulation used to estimate drinking water exposure to simazine is considered to be very conservative.

Although the linear regression equations used for the single chemical assessments for atrazine and simazine are considered conservative and likely to overestimate the chlorinated metabolites, there are no appropriate linear regression equations to accurately estimate total chlorotriazine residues for the 5 compounds considered in this cumulative assessment: atrazine, simazine, DEA, DIA, and DACT. Available linear regression equations used by the registrant to estimate to chlorotriazine concentrations in their own cumulative assessment of Midwest drinking water exposures may overestimate exposures where atrazine is present in highest concentrations, but may also underestimate exposures when simazine, DEA, DIA, or DACT are the dominant compounds in a drinking water sample. Therefore, EPA chose to base its refined exposure assessment on direct measurements of triazine residues in drinking water.

Multiple Exposure Pathway: Drinking Water and Residential Exposures

4. Florida - Drinking Water and Residential Exposures

Risk estimates for the portion of the cumulative assessment that combines exposures to the triazine residues across drinking water and residential pathways for adults and toddlers are not of concern. The risk estimates are driven largely by dermal exposures to triazine residues on lawns. The drinking water exposures are based on a model simulation that is considered more refined than that used for single-chemical assessments. Residential exposures are based on chemical-specific residue data, and distributions of various exposure factors such as of lawn size, body weight, and contact factors.

The application of pesticides is one of the more straight-forward activity patterns to measure since it represents easily defined activities. As a result, unit exposure data used to assess exposures during application of consumer-oriented pesticides are the most robust information used in the residential portion of this assessment. Recent data generated by the Outdoor Residential Exposure Task Force (ORETF) have been used to assess the use of hose-end sprayers and rotary granular spreaders (lawn care products) considered in this assessment. Short-sleeves and short pants were assumed for this assessment and may overestimate exposures as much of the homeowner applicator exposure comes from the legs. The distribution for lawn area used in this assessment ranged from 10,000 to 20,000 square feet. The range of lawn sizes used is reasonable given the application equipment used. Exposures from treated lawns larger than 20,000 square feet may be underestimated.

The current assessment also considers dermal post-application exposure

of adults contacting treated lawns and playing rounds of golf on treated courses. The liquid turf transferable residue (TTR) data available for atrazine and simazine and the granular TTR data available for atrazine were used to assess post-application exposure for the lawn care and golfer scenarios. Although atrazine data were used for assessments on granular simazine products; there is high confidence in these chemical-specific data. Since golf course turf is intensively maintained and typically watered and mowed every day, this residue data is likely to overestimate residues on treated golf course turf. The exposure duration for individuals playing golf was assumed to be 2 to 4 hours per day, based on information obtained from a 1992 survey conducted by the Center for Golf Course Management. These assumptions are expected to adequately estimate exposure for golfers.

Risk Estimates for the Residential & Drinking Water Exposure Pathways in the Single Chemical Assessments versus the Cumulative Assessment

Previous single-chemical assessments for atrazine and simazine identified residential exposures from lawns to be of concern when aggregated with drinking water exposures. However, in the single-chemical assessments, drinking water exposures were also a driver in the risk estimates of concern, and the refinements made to estimates of drinking water exposures in this cumulative assessment have been described above. Some refinements that have been made to the residential portion of this cumulative assessment include the reduction of maximum rates for liquid formulations of atrazine on turf. The rate was reduced from 2 lbs ai/A to 1 lb ai/A via mitigation and CWS of concern were placed in an intensive monitoring program under the IRED (2002) to achieve a reasonable finding of safety. In addition, it is likely that drinking water exposures are less of a risk driver when combined with residential exposures in this cumulative assessment, because in this assessment the drinking water exposure assessments rely on more recent monitoring data (for the Midwest scenario) which reflect the effects of past mitigation (rate reductions) and use of the CAF to modify the model simulation results (for the CA and FL scenarios).

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VI. List of Appendices

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Appendix III: Modeling Scenarios

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Chemical:	**Propazine** **Atrazine** **Simazine**
	PC Code: **080808** **080803** **080807**
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