UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Revised to Correct DWLOC Values

Date: January 12, 2006

MEMORANDUM

Simazine: Revised HED Chapter of the Reregistration Eligibility Decision Document (RED); Revised for Public Comments and to Correct DWLOC Values. PC Code: 080807, Case #: 0070, DP Barcode: D325433.

Regulatory Action: Phase II Reregistration Eligibility Decision
Risk Assessment Type: Single Chemical/Aggregate

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

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

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

Table of Contents

1.0 Executive Summary

Use Profile

Simazine is a chlorinated triazine herbicide. It acts by inhibiting photosynthesis and is considered to be a selective herbicide. It is usually applied as a pre-emergent herbicide to soil; it is absorbed through the roots and is translocated to other plant parts. It is systemic. Tolerances are expressed currently as simazine, per se and simazine plus des-ethyl simazine and diaminochlorotriazine. Under tolerance reassessment, it is recommended that tolerances be expressed as simazine plus des-ethyl simazine and diaminochlorotriazine. Simazine is used on a variety of agricultural crops, including fruit and nut crops as well as animal feeds such as alfalfa, corn, and range grasses (Syngenta notes that its products are not labeled for use on alfalfa and range grasses.) (Syngenta notes that its products do not currently allow for aerial application.) Simazine is formulated as granules, wettable powders, emulsifiable concentrates, and flowable concentrates.

Simazine has residential uses on turf. Simazine can be applied by professionals as well as homeowners to lawns. There is a granular and liquid formulation of the active ingredient.

Hazard Characterization

Simazine is not acutely toxic. Simazine shares a common mechanism of toxicity with atrazine and 4 other chlorinated triazine compounds. Simazine, atrazine, propazine, and the 3 chlorinated degradates common to these compounds all exhibit neuroendocrine effects seen across a variety of species. Simazine can alter hormone levels in rats that may result in developmental and reproductive consequences. These neuroendocrine effects are the primary toxicological effects of regulatory concern. These effects are time and dose dependent. In addition to this primary effect, exposure of animals to simazine has shown marginal blood effects and changes in body weight and organ weights. The neuroendocrine effects resulting in reproductive and developmental consequences seen in the test animals are believed to be relevant to humans.

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

Because of simazine’s similarity to atrazine, simazine is considered to be of equal potency to atrazine and the chlorinated degradates with respect to their common mechanism of toxicity, based on the available endocrine data (albeit limited to adult studies) on simazine, which indicate comparable effects to atrazine on LH surge (28-day study) and vaginal cytology. It was concluded that atrazine data can be used as bridging data for simazine because simazine and atrazine share a common mechanism of toxicity based on neuroendocrine effects, the database for simazine’s potential neuroendocrine effects is less robust than the atrazine database, particularly for the young, and neuroendocrine effects are the effects of primary regulatory concern.

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

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

Dietary Risk estimates

Residues of concern for dietary risk assessment are simazine plus des-ethyl simazine and diaminochlorotriazine. Existing field trial, and USDA's Pesticide Data Program (PDP), and FDA monitoring data on simazine residues in foods show non-detectable residues of simazine. Given that simazine is a pre-emergent herbicide applied mostly by soil-directed banding or broadcast applications, the lack of detections in edible portions of crops is not surprising. Exposures to simazine plus des-ethyl simazine and diaminochlorotriazine have been estimated to be zero (insignificant). Therefore, acute exposures to simazine in the diet (food only) represent 0% of the acute Population Adjusted Dose (aPAD). Similarly, chronic exposures to simazine in the diet (food only) represent 0% of the chronic Population Adjusted Dose (cPAD).

Drinking Water Risk Estimates

Residues of concern for drinking water risk assessment are simazine plus des-ethyl simazine and diaminochlorotriazine. Exposures to simazine residues in the diet may occur mainly through drinking water. Simazine is persistent and mobile and detected in surface and ground waters. It is not as prevalent as atrazine in water. Simazine is metabolized to des-ethyl simazine and diaminochlorotriazine (DACT) and hydroxy-simazine, and glutathione conjugates in plants, animals, soil, and water, and rats. Monitoring data on finished drinking water are available for simazine from compliance monitoring under the Safe Drinking Water Act (SDWA) and registrant-supported monitoring programs as well as USDA's PDP. Estimates of maximum concentrations of simazine plus the 2 chlorinated degradates detected in any sample from of finished drinking water from these monitoring programs reached ~ 25 ppb. The maximum average annual concentration of simazine plus its 2 chlorinated degradates in finished drinking water is ~6 to 7 ppb. Most monitoring programs on ambient water show simazine, per se, at 1 ppb, some with concentrations of a few ppb and a maximum concentration of 146 ppb in South Florida. Modeled estimates of maximum concentrations of simazine plus the 2 chlorinated degradates in surface water reached 200 ppb. The model estimates are considered upper bounds on concentrations of simazine residues in ambient water.

This risk assessment considers drinking water exposures to simazine based on its 5 major use areas: 1) the Midwest (use on corn), 2) California (use on fruits and nuts), 3) Florida (use on citrus), 4) Washington state (use on fruits), and 5) the Mid-Atlantic (use on fruits and corn). For the Midwest, Washington, and the Mid-Atlantic states, monitoring data on 23,000 finished drinking water from community water systems (CWS) sampled from 1993 to 2000 for simazine, and 18,000 CWS sampled from 2001 to 2003 for simazine was assessed and compared to drinking water levels of comparison (DWLOCs). Based on the frequency of monitoring (4 samples/year), a total of 185,459 samples were collected for simazine analysis over the eleven years. In addition, 1672 samples from 49 Midwest and South Central CWS were assessed for simazine from 2002 to the first quarter of 2003. Any CWS identified in this screening assessment with potential exceedences of a DWLOC were assessed using Lifeline in an attempt to refine the risk estimates. For California, Georgia, and Florida, a predictive model, PRZM/EXAMS, was used to estimate concentrations of simazine residues in surface water and compared to DWLOCs.

Drinking water risk estimates for populations in the Midwest , Washington, and the Mid-Atlantic states indicate that 2 CWS in the Midwest may have 90-day average concentrations of simazine plus its 2 chlorinated degradates that exceed HED's levels of concern for infants < 1 year old.

The 2 CWS with potential exceedences based on estimates of 90-day average concentrations are:

1) The Defiance City CWS of OHIO, serving 17,000 people, had a maximum quarterly concentration of 12.4 ppb simazine/17.5 ppb simazine + 2-chlorinated degradates in 2001, which exceeds the chronic DWLOC for infants and children. Chronic aggregate risk estimates for this CWS were estimated using Lifeline™. Drinking water exposures at the 99.9th percentile of exposure for infants (the most sensitive subpopulation) were 104% of the cPAD. Drinking water exposures for infants at the 50th percentile of exposure were 53 % of the cPAD.

2) The Hillsboro CWS of Illinois, serving 4,400, had a maximum quarterly concentration of 18.0 ppb simazine/25.2 ppb simazine + 2-chlorinated degradates in1994, which also exceeds the chronic DWLOC for infants and children, and toddlers. Chronic aggregate risk estimates for this CWS were estimated using Lifeline™. Drinking water exposures at the 99.9th percentile of exposure for infants (the most sensitive subpopulation) were 153% of the cPAD. Drinking water exposures for infants at the 50th percentile of exposure were 78 % of the cPAD.

Drinking water risk estimates for simazine uses in California, Georgia, and Florida exceed HED's levels of concern for the following use scenarios: almond uses (aerial application only) in California, Georgia peach and nut (aerial and ground applications), citrus uses in Florida (aerial and ground applications), and Hawaii (using a California PRZM-EXAMS site) macadamia and filbert nuts based on a comparison of 90-day average concentration estimates from PRZM/EXAMS with DWLOCs.

Residential Exposure Estimates

Homeowners who apply simazine for the control of weeds in recreational turf and lawns, fish aquariums, ornamental ponds, and fountains may be exposed for short-term durations via the dermal and inhalation routes. In addition, postapplication dermal exposures for adults and dermal and incidental oral exposures for children contacting treated turf can occur. Use rates for residential application of simazine range from 1.8 lb ai/acre for lawns to 6.8E-6 lb ai/gallon for fish aquariums, ornamental ponds, and fountains. Short-term dermal and inhalation risk was estimated using the NOAEL of 6.25 mg/kg/day, based on a delay in preputial separation seen in

a 28-day rat pubertal assay at the LOAEL of 12.5 mg/kg/day. HED's level of concern for simazine dermal and inhalation residential exposures is an MOE of 300 (10x inter-species extrapolation, 10x intra-species variation, 3x database uncertainty factor). One of four residential handler scenarios assessed had short-term risks of concern (i.e. an MOE less than 300).

The risk for postapplication dermal exposure for adults, youths, and toddlers were estimated using atrazine- and simazine-specific Turf Transferable Residue (TTR) Data (MRIDs 449588-01 and 449587-01, respectively). Of all scenarios estimated for adults, youth, and toddlers, none were of concern (i.e. MOEs are not less than 300). Oral exposures for toddlers were estimated using atrazine hand-press data, with the exception of acute oral exposure to granular pellets, for which there was no appropriate endpoint of concern. The risks for incidental ingestion of soil and from object-to-mouth activity on turf were not of concern.

Aggregate Risk Estimates

Simazine has agricultural uses that result in exposures to human through their diet and drinking water; it also has residential uses on turf that result in dermal and inhalation exposures to adults from handling home use products formulated with simazine, and postapplication dermal exposures to adults and children through recreational activities such as golfing and playing on lawns. All residential exposures are expected to be short-term in duration. Based on a common endpoint of toxicity, short-term dermal, oral, and inhalation risks may be aggregated.

Aggregate acute exposures to simazine and its 2 chlorinated degradates do not exceed HED's level of concern. Risk estimates for residential handlers using a push-type spreader and pouring ready-to-use liquid formulations do not exceed levels of concern; however, risk estimates associated with the use of belly-grinders alone exceed HED's level of concern. Risk estimates for aggregate short-term residential postapplication exposures for adults and youths do not exceed HED's level of concern. Short-term aggregate risk estimates for postapplication exposures of toddlers on turf exceed HED's level of concern for both granular and liquid formulations of simazine applied to residential turf.

Occupational Exposure Estimates

Simazine is currently registered for use on food/ feed crops, non-food crops, ornamental ponds, aquariums, and non-cropped industrial lands, primarily on select turf grasses and fairways, or other residential grass. The potential for occupational exposure to simazine exists in a variety of exposure scenarios. Such scenarios include the handling of simazine during the application process (i.e. mixer/ loaders, applicators, flaggers, and mixer/ loader/ applicators) and a potential for postapplication worker exposure from entering into areas previously treated with simazine. Use rates for the occupational application of simazine range from 0.8 lb ai/acre to 40 lb ai/acre. [The 9.6 lb ai/acre rate is not allowed on Syngenta products as a single application nor as a total annual rate on any crop.]

Short-term (up to 30 days) and intermediate-term exposures (1 to 6 months) to simazine may occur, however, long-term exposures (greater than 6 months) are not expected. Dermal and inhalation absorption rates used for this assessment are 6% and 100%, respectively. Daily dermal and inhalation risk was estimated using the short- and intermediate-term NOAEL of 6.25 mg/kg/day, based on a delay in preputial separation seen in a 28-day pubertal assay at the LOAEL of 12.5 mg/kg/day. HED's level of concern for simazine dermal and inhalation exposures is an MOE of 100 (10x inter-species extrapolation, 10x intra-species variation). In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate

Exposure Guide (8/98) were used with other HED default values for acres treated per day, body weight, and the level of personal protective equipment to assess the handler exposures.

Most occupational handler scenarios estimated for short-term risks (combined dermal + inhalation exposures) are not of concern at some level of risk mitigation. However some scenarios, particularly those with relatively high acres treated or high maximum application rates, remain a risk concern (i.e. MOEs are less than 100) at maximum risk mitigation. As for intermediate-term risks, many of the scenarios are a concern at maximum risk mitigation, particularly those with relatively high acres treated or high maximum application rates.

Handler exposures were based on the maximum label rates using typical daily area treated values (e.g. acres per day) by one handler for given application methods (e.g. 350 acres per day for aerial application). HED acknowledges that some of the scenarios assessed may not reflect real-life practices in some cases. For example, application of a granular formulation at the maximum label rate for rights-of-way areas to 350 acres for aerial application or 80 acres using a ground boom may not be likely occurrence for simazine products. Nevertheless, handler exposure was estimated using these inputs based on a lack of more specific use information. Handler exposure estimates can be refined with data regarding typical application rates and daily area treated.

Most short- and intermediate-term postapplication estimates resulted in risks that were not of concern (after 12 hours of exposure). However, for tasks with higher transfer coefficients, such as pruning, training, topping, or staking Christmas trees, dermal risks are a concern until 2 days after application.

Uncertainties

All risk estimates presented in this document are considered conservative and protective. Uncertainties associated with this assessment include the use of predictive models (PRZM/EXAMS) to estimate drinking water concentrations of simazine plus its 2 chlorinated degradates for fruit and nut uses of simazine in California and Florida. Additional monitoring of finished drinking water in high use areas of those states would help to refine risk estimates.

Estimated occupational and residential exposures in this assessment represent central to high-end values. Average daily exposures were estimated based on maximum label rates with average values for handler unit exposures, foliage/turf residues, foliage/turf postapplication contact rates, exposure duration, area treated, and other exposure factor inputs.

2.0 Ingredient Profile

Simazine is a triazine herbicide. Simazine acts by inhibiting photosynthesis and is considered to be a selective herbicide. Simazine is usually applied to the soil, absorbed through leaves and roots, is translocated via the xylem and concentrates in the meristem, so it is a systemic herbicide. Simazine is formulated as ~42% Flowable Concentrates (FlC), 6- ~42% suspension concentrates, 80% wettable powders (WP), ~43 - 90% water dissolvable granules, 0.76 - ~ 4% pellets. It is applied by broadcast or banded ground application or can be applied to corn with aerial equipment.

2.1 Summary of Registered/Proposed Uses (for Food uses Only)

Table 2.1. Summary of Directions for Use of Simazine.

Site Application Type [a] Application Timing Application Equipment	Formulation [EPA Reg. No.]	Max. Single Application Rate (lb ai/A)	Max. # Apps./season	Minimum Retreatment Interval/PHI (Days)	Max. Seasonal Application Rate (lb ai/A)	Use Limitations [b, c]
Almonds (CA only)						
Banded ground application in late fall or early winter Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	2	1	NA		Use is restricted to CA. Make only one application per year, and do not apply to trees established for <3 years.
Avocados (FL and CA only)						
Broadcast or banded ground application after grove preparation Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	Not applicable (NA)		Use is restricted to CA and FL. Do not make more than one application per year.
Bananas						
Soil-directed application	40% WP	1.6	4	30		A 0-day PHI and a maximum seasonal use rate of 6.4 lb ai/A are specified. (Syngenta notes that their labels in the U.S. do not support use on bananas.)
Blueberries						

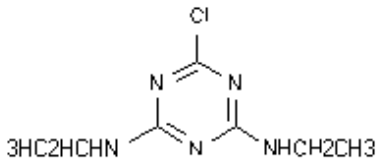
Site Application Type [a] Application Timing Application Equipment	Formulation [EPA Reg. No.]	Max. Single Application Rate (lb ai/A)	Max. # Apps./season	Minimum Retreatment Interval/PHI (Days)	Max. Seasonal Application Rate (lb ai/A)	Use Limitations [b, c]
Broadcast or banded ground application in fall and/or spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4 (2+2) [d]	1 (2)	Not specified (NS)		Apply one application in spring or a split application in spring and fall. Do not apply when fruit is present. Apply in a minimum of 40 gal/A.
Caneberries (blackberries, boysenberries, loganberries, and raspberries)						
Broadcast or banded ground application in fall and/or spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4 (2+2) [d]	1 (2)	NS		Apply one application in spring or a split application in spring and fall. Do not apply when fruit is present. Apply in a minimum of 40 gal/A.
Cherries						
Broadcast or banded ground application Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Apply only once per year. For sweet cherries, apply in late fall or early spring. Use on sweet cherries is restricted to MO and states East of the Mississippi River, except TN.
Citrus Fruit						
AZ (Lemons and Oranges only)						
Broadcast or banded ground application in spring and fall Ground Equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	1.6 + 1.6 [d]	2	NS		Do not apply to bedded citrus trees.
CA (Grapefruit, Lemons and Oranges)						
Broadcast or banded ground application in spring and/or fall Ground Equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4 (2+2) [d]	1 (2)	NS		Do not use in the Imperial, Coachella, or Palo Verde Valleys. Do not apply to bedded citrus trees.
FL and TX (Grapefruit and Oranges only)						

Site Application Type [a] Application Timing Application Equipment	Formulation [EPA Reg. No.]	Max. Single Application Rate (lb ai/A)	Max. # Apps./season	Minimum Retreatment Interval/PHI (Days)	Max. Seasonal Application Rate (lb ai/A)	Use Limitations [b, c]
Broadcast or banded ground application in spring and/or fall Ground Equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4 (FL) 4.8 (TX)	2 (FL) 1 (TX)	NS		In FL, do not exceed 8 lb ai/A during any one growing season. Do not apply to bedded citrus trees, except in FL.
Cranberries						
Broadcast or banded ground application in fall after harvest or spring before growth Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	2 4 (MA only)	1	NA		Use of 4 lb ai/A rate is restricted to MA only. Apply only once per year.
Corn [e]						
Broadcast or banded preemergence, preplant, or preplant-incorporated application Ground or aerial equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	2 (coarse soil) 2.5 (medium soil) 3 (fine soil) 4 (organic soil)	1	NA		Do not apply more than 4 lb ai/A/year. Do not graze treated areas. Do not rotate to any crop except corn until the following year, and do not plant sugar beets, tobacco, vegetables (including dry beans), spring-seeded small grains, or small-seeded legumes and grasses the year after an application. For applications >3 lb ai/A, follow with an untreated crop of corn the next year. For the High Plains and intermountain areas of the West, follow with an untreated crop of corn prior to rotation to other crops. In western MN and eastern ND, SD, NE and KS, do not rotate to soybeans the year following an application at >2 lb ai/A.
Filberts						
Broadcast or banded ground application in fall or a split application in fall and spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4 (2+2) [d]	1 (2)	NS		Do not apply when nuts are on the ground during the harvest period.

Site Application Type [a] Application Timing Application Equipment	Formulation [EPA Reg. No.]	Max. Single Application Rate (lb ai/A)	Max. # Apps./season	Minimum Retreatment Interval/PHI (Days)	Max. Seasonal Application Rate (lb ai/A)	Use Limitations [b, c]
Grapes						
Broadcast or banded ground application anytime after harvest to early spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4.8	1	NA		Do not use on vineyards established less than 3 years. Apply only once per year.
Macadamia Nuts						
Broadcast or banded ground application before harvest Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	NS	NA		Apply in 50 gal of water/A. Repeat application as necessary. Do not apply when nuts are on the ground during harvest period.
Olives						
Broadcast or banded ground application in fall or midwinter Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Apply only once per year.
Peaches						
Banded ground application in late fall or early winter Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	2	1	NA		Use is restricted to CA. Apply only once per year.
Broadcast or banded ground application in late fall or early spring Ground equipment		4				Use is restricted to AR, LA, MO, OK, TX, and states East of the Mississippi River. Apply only one application per year.
Pecans						
Broadcast or banded ground application in spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Apply only once per year, and do not apply when nuts are on the ground. Do not use in AZ, CA, or NM, or in TX (West of Pecos River). Do not apply to trees established <2 years. Do not allow animals to graze in treated areas.

Site Application Type [a] Application Timing Application Equipment	Formulation [EPA Reg. No.]	Max. Single Application Rate (lb ai/A)	Max. # Apps./season	Minimum Retreatment Interval/PHI (Days)	Max. Seasonal Application Rate (lb ai/A)	Use Limitations [b, c]
Plums (only in MO and states East of Mississippi River, excluding TN)						
Broadcast or banded ground application in late fall or early spring Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Use is restricted to MO and states East of the Mississippi River (except TN). Make only one application per year.
Pome Fruit (apples and pears)						
Broadcast or banded ground application Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Apply only once per year.
Strawberries (OR and WA only)						
Broadcast ground application at time of bed renovation or October through November. Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	1	1	NA		Use is restricted to OR and WA. Make only one application per year. Do not apply within 4 months after transplanting.
Walnuts						
Broadcast or banded ground application. Ground equipment	4 lb/gal FlC [100-526] 90% DF [100-603]	4	1	NA		Make only one application per year, and do not apply when nuts are on the ground.

2.2 Structure and Nomenclature

TABLE 2.2. Test Compound Nomenclature - Simazine	
Chemical Structure	
Empirical Formula	$C_7N_5H_{12}Cl$
Common name	Simazine
Company experimental name	G27692
IUPAC name	6-chloro-N^2,N^4-diethyl-1,3,5-triazine-2,4-diamine
Other Systematic	2-chloro-4,6-bis(ethylamino)-*s*-triazine
CAS name	6-chloro-N,N'-diethyl-1,3,5-Triazine-2,4-diamine
CAS Registry Number	122-34-9
End-use product/EP	Amizine, Gesapun, Primatol S, Princep,
Chemical Class	triazine herbicide
Known Impurities of Concern	

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	201.7	
Melting point/range	225-227 C	Simazine Registration Standard 1989
pH	6 - 7	Simazine Registration Standard 1989
Density (specific gravity)	1.21 at 20 C	Simazine Registration Standard 1989
Water solubility (20 C)	5 ug/g	Simazine Registration Standard 1989
Solvent solubility (temperature not specified)	400 ppm in methanol at 20 C 3 ppm in n-pentane at 25 C 300 ppm in diethyl ether at 25 C 900 ppm in chloroform at 20 C 100 mg/20 mL in tetrahydrofuran	Simazine Registration Standard 1989
Vapor pressure (25 C)	6.1 10^{-9} mm Hg at 20 C, 3.1 x 10^{-8} at 30 C	Simazine Registration Standard 1989
Dissociation constant, pKa	pKa = 1.65 in water at 22 C	Simazine Registration Standard 1989
Octanol/water partition coefficient, $logP_{OW}$ (25 C)	log P o/w = 2.1 K=18.30	Simazine Registration Standard 1989
UV/visible absorption spectrum	– (white)	Simazine Registration Standard 1989

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Simazine is metabolized and excreted in the rat within 72 hours of dosing. Most of the excreted simazine residues were detected in the urine (49%) and feces (41%) with minor amounts respired as CO_2. Simazine is metabolized in the rat through the removal of alkyl side chains and conjugation of the triazine ring with glutathione-S-transferase. The mono- and di-dealkylated compounds, 2-chloro-4-ethylamino- 6-amino-s-triazine and diaminochlorotriazine (DACT), respectively, are the major rat degradates. Conjugated mercapturates of hydroxy simazine were also detected.

The metabolic pathway in plants is similar to that in rats. Plant metabolism occurs via several competing routes. In one major route the N-ethyl groups are cleaved leaving the bare amine attached to the ring. First one ethyl group is lost, then both are lost, ultimately leaving diaminochlorotriazine (DACT). DACT can subsequently proceed to replacement of the chlorine with a proline group, which is attached to the triazine via the proline nitrogen. In a second major route of metabolism, the chloro group on simazine is replaced by a hydroxy group to hydroxy-simazine, which can proceed by loss of the ethyl groups to diaminohydroxytriazine, the hydroxy equivalent of DACT. The diaminohydroxytriazine can then under go replacement of one or both amines by hydroxy groups ultimately leading to cyanuric acid. Alternatively, the chlorine in simazine can be replaced by glutathione and through a variety of intermediate conjugates can be eventually lysed to NH2-simazine, and then presumably loss of one or both ethyl groups.

The metabolic pathway in livestock is also similar to that in plants and rats with one exception; animals do not metabolize simazine directly to hydroxy-simazine, but animals may receive hydroxy simazine through feeds. Several studies have been performed on the metabolism of simazine in livestock and poultry. In animals, in general, simazine residues tend to lose one or both ethyl groups to form the chloro-metabolites or to replace the chloro- group with a hydroxy-group and then to lose one of both ethyl groups. Feeding with hydroxy-simazine leads to formation, through loss of one or both ethyl groups of hydroxy-metabolites only. A glutathione conjugate is also formed from the hydroxy-simazine.

The team concluded that based on the above descriptions of plant, animal, and rat metabolism, the residues of concern are similar across all these metabolic pathways, i.e., simazine and the chlorinated metabolites. The metabolic pathway for simazine is also similar to that for atrazine.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

In apples the principle metabolites are the free hydroxy-metabolites (31% TRR) with about 16% as the proline conjugate. Only minor amounts of one chlorometabolite, DACT (1.1% TRR, <0.001 ppm), were detected in the apples; simazine and desethylsimazine were not detected. The TRR in apples were 0.02 ppm. In grapes, 81% of the TRR (TRR = 0.10 ppm) are the free hydroxy metabolites. Simazine and its chlorometabolites were not detected (<1% TRR, <0.001 ppm) in mature grapes. In oranges, 50 -75% of the TRR is the proline conjugate. Simazine and its chlorometabolites were not detected (<1% TRR) in any of the orange fractions. Although

TRR was not reported for whole oranges, rather oranges were divided into peel, pulp and juice, the cumulative TRR is between 0.06 - 0.27 ppm..

In field corn, TRRs were 0.158 ppm in forage harvested 30 DAT, 0.209 ppm in silage harvested 120 DAT, and 0.493 and 0.044 ppm in/on fodder and grain harvested at 162 DAT following a single preemergence application of [^{14}C]simazine (4 lb/gal FlC) at 1.7 lb ai/A to a silty clay loam soil (0.6x maximum label rate for this soil type; 0.4x the maximum rate for any soil type). In silage, fodder and grain, simazine accounted for 0.1% of the TRR and its chloro-metabolites each accounted for up to 6.9% of the TRR (see table below). The most abundant hydroxy-metabolites were GS-17792 in silage (27.9% TRR) and fodder (15.6% TRR), and GS-17791 in grain (11.9% TRR). Total triazine-ring containing compounds released by acid hydrolysis accounted for 73.0% of the TRR in silage, 58.7% of the TRR in fodder, and 56.8% of the TRR in grain.

As is discussed more fully below, although in many cases simazine and its chloro-metabolites are not the highest residues in these crops, HED has concluded that they are the residues of interest and the residues to be used in the tolerance expression. This decision is based largely upon toxicological considerations.

3.2.2 Description of Livestock Metabolism

Ruminants. Several studies (40614431, 40614432, 40614435, 40431350,) and a metabolism review (40614428) have been evaluated pertaining to the metabolism of simazine in goats. In a goat dosed for 10 days with [^{14}C]simazine at a dose equivalent of 5 ppm [12x the maximum theoretical dietary burden (MTDB)], TRR in milk plateaued by Day 5 at 0.10 ppm. TRR in tissue samples collected 48 hours after the final dose ranged from 0.02 ppm in fat to 0.93 ppm in liver. After residues plateaued in milk (at 2% of the administered dose), the major metabolite in milk (23.5% TRR) was identified as DACT, along with minor amounts (0.25% TRR) of simazine and of desethylsimazine (1.3% TRR). Metabolites in the aqueous fraction and the hydrolysate of the casein fraction were characterized as amino acid and peptide conjugates of simazine.

In another study, a goat was dosed for 7 days with [^{14}C]simazine at a dose equivalent to 50 ppm in the diet (119x). TRR in milk ranged from 0.71-1.07 ppm during the 7-day dosing period. TRR in tissues collected within 24 hours of the final dose were 0.06-0.10 ppm in fat, 0.69-0.71 ppm in muscle, 3.03 ppm in kidneys, 2.59 ppm in brain, 0.78 ppm in heart, and 3.24 ppm in liver. Components of the TRR identified in milk and tissues are listed in the table below. Simazine accounted for 3.8-10.8% of the TRR in tissues, but was not detected in milk. DACT was the major metabolite in milk (30.3% TRR) and accounted for 4.2-5.2% TRR in liver and kidney, and 13.8% TRR in muscle. Desethylsimazine was detected in liver and kidney at 10.7-16.9% TRR, but was not detected in muscle and milk. A glutathione conjugate of desethylsimazine was also tentatively identified in kidney (18.7% TRR) and milk (14.9% TRR). Desethylhydroxy-simazine constituted up to 32.9% of the TRR in liver, but may have been an artifact of proteolysis.

Table 3.2.2.1. Residues in tissues and milk of a goat dosed for 7 days with [14C]simazine at a level equivalent to 50 ppm in the diet.

Residues	% Total Radioactive Residues

	Liver (3.24 ppm)		Kidney (3.03 ppm)		Muscle (0.71 ppm)		Milk (1.07 ppm)	
	%TRR	ppm	TRR	ppm	%TRR	ppm	% TRR	ppm
Simazine	6.96	0.23	3.84	0.12	10.79	0.08	--	--
DACT (G-28273)	5.20	0.17	4.20	0.13	13.78	0.10	28.94	0.31
G-28279[a]	10.70	0.35	16.93	0.51	--	--	--	--
GS-17792 [b]	32.94	1.06	12.73	0.39	6.52	0.05	--	--
Glutathione conjugate of desethylsimazine[c]	--	--	18.70	0.57	--	--	14.90	0.16

[a] Desethylsimazine
[b] Desethylhydroxy-simazine. Possible artifact of proteolysis.
[C] Identification was tentative.

In addition to the above simazine metabolism studies, there is a study on the metabolism of hydroxy-simazine in goats (MRID 43506801). Two diary goats were dosed for 4 days with [^{14}C]hydroxy-simazine at an average dose equivalent to 78 ppm (185x) in the diet. Maximum ^{14}C-residues in milk for both goats occurred on Day 3 and averaged 0.50 ppm. TRR in tissues collected within 6 hours of the final dose averaged 0.019 ppm in fat, 0.149 ppm in muscle, 0.788 ppm in liver, and 1.9 ppm in kidneys. Components of the TRR identified in milk and tissues are listed in the table below. Hydroxy-simazine (G-30414) was the principal component identified in milk, kidney, muscle, and fat, accounting for 47.7-61.9% TRR; and it also accounted for 15.1% of the TRR in liver. The main component in liver was a ring methylated hydroxy-simazine (Metabolite A) (35.5% TRR). Desethylhydroxy-simazine accounted for 5.6-20.5% of the TRR in milk and tissues.

Table 3.2.2.2.. Residues in tissues and milk of goats dosed for 4 days with hydroxy-simazine at a level equivalent to 78 ppm in the diet.

Residues	% Total Radioactive Residues									
	Liver (0.789 ppm)		Kidney (1.898 ppm)		Muscle (0.149 ppm)		Fat (0.019 ppm)		Milk (0.479 ppm)	
	%TRR	ppm	TRR	ppm	%TRR	ppm	% TRR	ppm	% TRR	ppm
G-30414	15.1	0.12	61.9	1.11	53.6	0.08	47.7	0.01	58.7	0.28
GS-17792	5.6	0.04	10.0	0.18	20.5	0.03	8.9	0.002	10.7	0.05
Combined free hydroxy metabolites	**20.7**	**0.16**	**71.9**	**1.29**	**74.1**	**0.11**	**56.6**	**0.01**	**69.4**	**0.33**
Metabolite A	35.5	0.28	6.9	0.12	5.0	0.01	8.9	0.002	7.5	0.04
Metabolite B	5.2	0.04	1.7	0.03	2.6	0.004	4.2	0.001	6.1	0.03
Metabolite C	7.3	0.06	4.3	0.08	6.6	0.01	3.8	0.001	8.2	0.04
Metabolite H	--	--	2.7	0.05	--	--	1.4	<0.001	--	--
Total identified	**68.7**	**0.54**	**87.5**	**1.57**	**88.3**	**0.13**	**74.9**	**0.02**	**91.2**	**0.44**

Poultry. Two studies (40614429, 40614431) are available on the metabolism of simazine in poultry. In the earlier study, two laying hens were dosed orally via capsule with [^{14}C]simazine for 20 consecutive days at a dose equivalent to 50 ppm (313x) in the diet. TRR plateaued by

Day 2 in egg whites at 0.5 ppm and by Days 12-14 in egg yolks at 1.1 ppm. TRR in tissues collected at sacrifice were <0.1 ppm in fat, and 1-3 ppm in skin/fat, muscle, kidney, and liver. Analyses were limited, but DACT (24.1-43.5% TRR) and desethylsimazine (7.4-15.6% TRR) were detected in eggs.

In the second study, four laying hens were dosed daily for 7 days with [^{14}C]simazine at 50 ppm (313x). TRR levels in egg whites and yolks did not plateau but both increased in parallel from 0.02 ppm on Day 1 to 1.2 ppm on Day 7. TRR levels in tissues after sacrifice were 0.09 ppm in fat, 1.57 ppm in skin/fat, 1.98 ppm in muscle, 3.00 ppm in liver, and 3.65 ppm in kidney. Treatment of tissue and egg samples with protease solubilized 96-100% of the radioactivity. Components of the TRR identified in the protease filtrates are listed in the table below. Simazine was identified in each tissue at 6.7-16.9% of the TRR and in egg yolks at 14.9% of the TRR. DACT accounted for 11.2-12.7% of the TRR in muscle and liver, and 28.9% of the TRR in egg yolk, and desethylsimazine was detected in liver (14.7% TRR) and muscle (7.8% TRR), but not in egg yolks. A glutathione conjugate of desethylsimazine was also tentatively identified in liver (29.7% TRR), muscle (6.5% TRR), and egg yolks (28.7% TRR).

Residues in tissues and eggs of poultry dosed for 7 days with simazine at a level equivalent to 50 ppm in the diet.

Residues	% Total Radioactive Residues							
	Liver (3.00 ppm)		Muscle (1.98 ppm)		Skin/fat (1.57 ppm)		Egg yolk (1.2 ppm)	
	%TRR	ppm	TRR	ppm	%TRR	ppm	% TRR	ppm
Simazine	6.79	0.20	16.93	0.34	15.68	0.25	14.89	0.18
G-28273 (DACT)	12.68	0.38	11.23	0.22	--	--	28.94	0.35
G-28279 (desethylsimazine)	14.72	0.44	7.78	0.15	--	--	--	--
GS-17792 [a]	10.05	0.30	--	--	--	--	--	--
Glutathione conjugate of G-18279 [b]	29.70	0.89	6.46	0.13	--	--	28.68	0.34

[a] Desethylhydroxy-simazine. Possible artifact of proteolysis.
[b] Identification was tentative.

Simazine and its chloro-metabolites are the residues of interest and are to be used in the tolerance expression for animals. The reasoning is similar to that used for plants and is discussed more fully below.

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

The registrant is supporting uses on two crops that are normally rotated: corn and strawberry. Rotational crop restrictions do not exist for strawberries, but extensive restrictions are listed for corn. The maximum use rate on strawberries is 1 lb ai/A. The maximum use rate on corn is 4 lb ai/A. For applications >3.0 lb ai/A, a 2-year rotational crop restriction would apply to all crops except corn based on current label restrictions.

The metabolism of simazine is similar in primary and rotational crops but concentrations of simazine and its chloro-metabolites are much higher in rotational crops than in primary crops.

Levels of simazine and its chlorometabolites in confined rotational crops planted 4 months (wheat) or 1 year (spinach and beets) following a soil application of simazine at 1.7 lb ai/A (0.6x) were 0.083 ppm in wheat forage, 0.018 ppm in wheat straw, 0.059 ppm in spinach, 0.068 ppm in beet tops, and 0.011 ppm in beet roots. Because these residues were >0.01 ppm, limited field rotational crop studies (OPPTS GLN 860.1900) are required for simazine.

[^{14}C]Simazine (4 lb/gal FlC) was applied preemergence at 1.72 lb (0.6x) to a primary crop of field corn growing on a silty clay loam soil. One-third of the treated plot was replanted with winter wheat at 137 days (4.5 months) post-treatment. The remainder of the corn was harvested at maturity, 162 days after planting and the following spring (362 days post-treatment) this portion was planted with spinach and garden beets. Immature and mature samples of wheat, spinach, and beets were collected for analysis. The TRR in each rotational crop commodity is presented in the table below:

Table 3.2.3.1.. TRR in rotated crops

Crop/commodity	growth stage	Planting interval, PBI (days)	Sampling interval, DAP (days)	Total radioactive residues (ppm)
Wheat forage	immature	137	61	0.145
	immature		239	0.029
Wheat straw	mature		300	0.135
Wheat grain	mature		300	0.020
Spinach	immature	362	46	0.071
	mature		60	0.130
Beet tops	immature		60	0.101
	mature		73	0.182
Beet roots	immature		60	0.297
	mature		73	0.126

In wheat RACs from the 4 month PBI, simazine and its chloro-metabolites together accounted for 57% TRR in forage, 13% TRR in straw, and 2% TRR in grain; free hydroxy-triazine metabolites accounted for another 4 - 16% of the TRR. For spinach and beets planted at a 1-year PBI, simazine and its chloro-metabolites accounted for 45.7% TRR in mature spinach, 37.1% TRR in mature beet tops, and 9.1% TRR in mature beet roots, and free hydroxy-triazine metabolites accounted for another 6.7-56.6% of the TRR in these RACs.

Table 3.2.3.2.. Identity and distribution of metabolites in the confined rotational crop study

	% Total Radioactive Residue					
	Wheat (137-day PBI)			Spinach (362-day PBI)	Beet (362-day PBI)	
Residue	Forage (0.145 ppm) [a]	Straw (0.135 ppm)	Grain (0.020ppm)	Leaves (0.130 ppm)	Tops (0.182 ppm)	Root (0.126 ppm)
Simazine	30.2	0.5	--	3.2	20.4	6.1
G-28279	20.7	1.6	--	23.5	6.9	1.0
G-28273	6.5	11.0	2.1	19.0	9.8	2.0

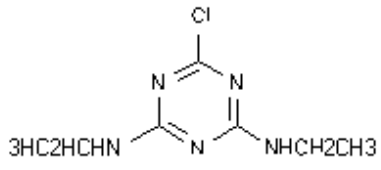
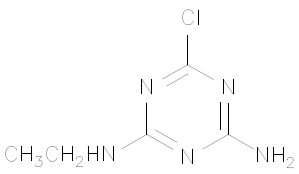
Total chlorinated triazine compounds	57.4 (0.083 ppm)	13.1 (0.018 ppm)	2.1 (<0.001 ppm)	45.7 (0.059 ppm)	37.1 (0.068 ppm)	9.1 (0.011 ppm)
G-30414	0.5	2.2	--	1.4	2.2	18.3
GS-17792	0.7	3.8	8.4	1.8	2.3	6.2
GS-17791	2.8	--	0.5	3.5	2.9	--
Total free hydroxy-triazine compounds	4.0 (0.006 ppm)	2.0 (0.003 ppm)	8.9 (0.002 ppm)	6.7 (0.009 ppm)	7.4 (0.013 ppm)	24.5 (0.031 ppm)
Total detected triazine-ring compounds	61.4 (0.089 ppm)	26.1 (0.035 ppm)	18.6 (0.004 ppm)	52.6 (0.068 ppm)	44.5 (0.081 ppm)	67.0 (0.084 ppm)

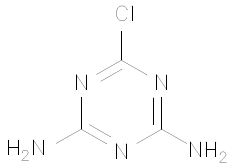
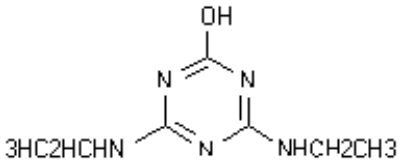
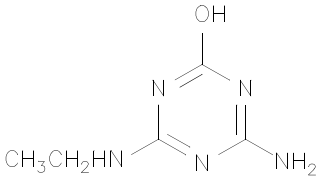
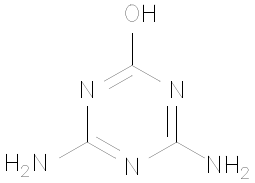
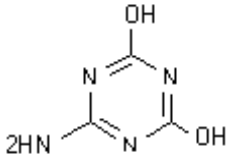
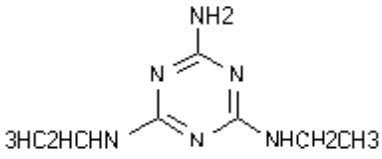
3.3 Environmental Degradation

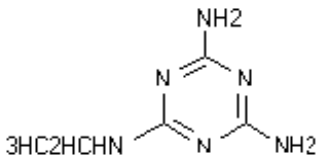
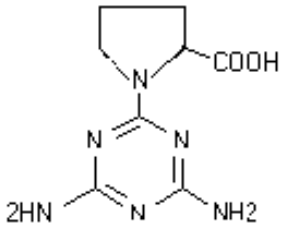
Simazine is a mobile and persistent compound. Simazine is stable to abiotic hydrolysis at pH 5, 7, and 9 over a 28-day period. It degrades under aerobic conditions in soil at various rates depending on soil moisture and temperature. Typically, simazine has a half-life in soil of weeks to months. Simazine is persistent under aquatic aerobic conditions such as lakes or ponds, persisting for 50 to 700 days. Simazine degrades to 2 chlorinated compounds, diamino chlorotriazine and monodesethylated simazine that can reach concentrations >10% of the parent compound; it shares these degradates in common with atrazine. Simazine and its degradates are moderately to very mobile in soils depending on the percentage organic matter present. In sandy loam soils with low percentage of organic matter, simazine is very mobile. Once simazine and its degradates reach water they persist. Hydroxy simazine compounds also occur, but in lesser amounts. Primary drinking water treatment systems do not remove simazine or its degradates efficiently from drinking water. Simazine has been detected in surface and ground water in federal and state monitoring programs. It is not as commonly detected as atrazine in water.

3.4 Tabular Summary of Metabolites and Degradates

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

Common Name/Chemical Name	Chemical Structure
Simazine 2-chloro-4,6-bis(ethylamino)-*s*-triazine	
G-28279 2-amino-4-chloro-6-ethylamino-*s*-triazine	

Common Name/Chemical Name	Chemical Structure
G-28273 2,4-diamino-6-chloro-*s*-triazine	
G-30414; hydroxy-simazine 2-hydroxy-4,6-bis(ethylamino)-*s*-triazine	
GS-17792 2-amino-4-hydroxy-6-ethylamino-*s*-triazine	
GS-17791 2,4-diamino-6-hydroxy-*s*-triazine	
GS-35713	
G-30705	

Common Name/Chemical Name	Chemical Structure
CGA-74650	
Proline-diamino conjugate	

3.5 Toxicity Profile of Major Metabolites and Degradates

Simazine toxicity has been bridged to atrazine toxicity and the toxicity of desethylsimazine (GS-28279) and DACT (GS-28273) are taken to be the same as the parent, as they are for atrazine. Specific toxicity information exists for DACT allowing it to be bridged to atrazine, and hence to simazine. Although no toxicity information exists for the hydroxy simazine metabolites, it does exist for the hydroxy-atrazine metabolites, and the hydroxy-simazine metabolites are likewise taken to have the same toxic properties as the hydroxy-atrazine metabolites. Toxicity studies conducted in the rat were submitted for sub chronic, chronic/carcinogenic, and developmental effects of hydroxy atrazine. Results indicate that the kidney is the primary target organ associated with hydroxy atrazine toxicity. Hydroxy atrazine crystals appeared in the kidney. This crystallization phenomenon has not been observed with atrazine or any of the chlorinated metabolites of atrazine. Hydroxy atrazine is not a chlorinated metabolite of atrazine and is not expected to be associated with any of the effects attributed to atrazine or its chlorinated metabolites.

The proline conjugate of diamino-s-triazine is the largest portion of the simazine TRR in citrus (prolinediaminotriazine is estimated at 0.036 - 0.11 ppm following a 0.5x treatment), it is a significant part of the TRR only in citrus. While no toxicological data is available for this proline conjugate, the proline conjugate is not likely to be more toxic than the parent (personal communication with Leonard Kiefer), so HED concludes that this metabolite need not be included in either the tolerance expressions for plants and animals or the dietary risk assessment. Because reliable field trial data for citrus are not available, new citrus field trials will be needed to confirm the assumption, but all existing evidence suggests that overall exposure to simazine residues through citrus is not likely to be significant. HED does recognize that, based on the metabolism study, the proline-conjugate is likely to be present in these citrus trials at concentrations above the concentrations of the chloro-metabolites. HED, however, is not requiring analysis for the proline conjugates because the toxicity of the proline conjugate is expected to be no greater than and likely much less than the parent compound. Because HED is not including the proline conjugate in the dietary exposure assessment there is no need to

measure it in the field trials. Presumably because fruit trees were not tested, no proline conjugate of atrazine was detected in the atrazine metabolism studies.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

3.6.1 Tabular Summary

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

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

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

Tolerances have been reassessed for simazine; the reassessment table can be found in Appendix 4.0.

3.6.2 Rationale for Inclusion of Metabolites and Degradates

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

Hydroxy-atrazine has a different toxicological profile from atrazine (see Tables 4.1.b & c), and although no toxicological data are available for hydroxy-simazine, by analogy, the hydroxy-

simazine metabolites are expected to have a different toxicological profile from simazine and the chlorinated degradates. Although hydroxy-simazine residues are present in plants, exposure to hydroxy-simazine metabolites is mainly expected to be through livestock products from eating feed items made of the stems and leaves of treated plants. Only the use of simazine on corn is likely to lead to such residues in any significant animal feed commodities. Other uses are on tree and bushes that do not leave byproducts behind after the crop is harvested to be used in animal feeds . Furthermore <1%, on average, and <5% maximum, of the corn crop is treated with simazine. (Note that <1% average, and <5% maximum, are also default lower limit results currently used by BEAD for percent crop treated values and may be conservative compared to the actual percent of the crop that is treated.) An assessment for hydroxy-atrazine based upon similar transfer of residues to animal feed items, but with the much wider use of atrazine on corn (>75% crop-treated), led to exposures and risk estimates that were <1% of the cPAD for hydroxy-atrazine. From this it is anticipated that the exposure to hydroxy-simazine in the diet would be very small, and of very low risk. In addition, the team notes that analytical methods exist for determining simazine and the chlorinated metabolites, but no analytical methods exist for the determination of the hydroxy-metabolites of simazine. Therefore the simazine team recommends against risk assessments, or tolerance expressions including the hydroxy-simazine metabolites.

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

Simazine has been grouped with several structurally-related, chlorinated triazines (e.g., atrazine, propazine, and 3 chlorotriazine degradates common to atrazine, simazine and propazine) on the basis of a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis. As a result of their common mechanism of toxicity, exposure to simazine, like exposure to atrazine, results in reproductive and developmental effects and consequences that are considered relevant to humans. These effects form the basis of the regulatory endpoint selection for both compounds. This mechanism involves a central nervous system (CNS) toxicity, specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus, which cause cascading changes to hormone levels, e.g., suppression of the luteinizing hormone surge prior to ovulation resulting in prolonged estrus in adult female rats (demonstrated with atrazine and simazine), and developmental delays, i.e., delayed vaginal opening and preputial separation in developing rats (studied in atrazine but not simazine). These neuroendocrine effects are considered the primary toxicological effects of regulatory concern. Body weight changes and blood chemistry effects are also noted as a result of long-term exposures of animals to atrazine and simazine. However, the blood effects are not considered to be robust, but marginal. Dose selection or dose spacing may also account for differences in NOAELS and LOAELs between atrazine and simazine in studies where changes in body weight and blood effects occur. Further, they are not part of the primary mechanism of neuroendocrine toxicity. The NOAEL for endocrine changes are protective of systemic toxicity.

This CNS mechanism of toxicity also results in mammary tumors specific to female Sprague-Dawley rats exposed to simazine and atrazine; however, the particular cascade of events leading to tumor formation in this specific strain of rat is not considered to be operative in humans. Consequently, atrazine has been classified as “Not Likely to be Carcinogenic to Humans”, as per the June 2000 Scientific Advisory Panel (SAP) report. Although currently classified as a Group C (possible human carcinogen), simazine has been reclassified as “Not Likely to be Carcinogenic to Humans”.

Simazine is considered to be of equal potency to atrazine and the chlorinated degradates with respect to their common mechanism of toxicity, based on the available endocrine data (albeit limited to adult studies) on simazine, which indicate comparable effects to atrazine on LH surge (28-day study) and vaginal cytology. It was concluded that atrazine data can be used as bridging data for simazine because simazine and atrazine share a common mechanism of toxicity based on neuroendocrine effects, the database for simazine's potential neuroendocrine effects is less robust than the atrazine database, particularly for the young, and neuroendocrine effects are the effects of primary regulatory concern.

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

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

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

Table 4.1 a Acute Toxicity Profile - Simazine				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.11	Acute Oral	148897	LD_{50} > 5 g/kg (M&F combined)	IV
870.12	Acute Dermal	148898	LD_{50} > 2 g/kg (M&F combined)	III
870.13	Acute Inhalation	148899	LC_{50} > 1.71 mg/L	III
870.24	Primary Eye Irritation	148900	Slight irritant	IV
870.25	Primary Dermal Irritation	148901	PIS = 0.2	IV
870.26	Dermal Sensitization	41184501	Negative	N/A

Sub-chronic Toxicity: In rats, decreased body weight gain, reduced food consumption, and decreased white blood cell count (males) and blood urea nitrogen (females) were noted in rats administered simazine in the diet for 90 days (LOAEL = 14.25 mg/kg/day; NOAEL = not identified). Effects overall were similar to atrazine. Differences in LOAELs and NOAELs may be attributed to dose spacing.

Dogs administered simazine (65.2/64.3 mg/kg/day, males/females) in the diet for 90 days exhibited decreased body weight/body weight gain, decreased food consumption, increased relative brain and liver weights, decreased heart weight, decreased testes weight (males), decreased serum glutamate oxaloacetate (SGOT) and reduced alkaline phosphatase activities (females). The NOAEL was 6.9/8.2 mg/kg/day in males/females.

Chronic Toxicity:

In a 12-month dietary study in the dog, decreased body weight gains were noted in males administered 42.9 mg/kg/day (HDT) simazine, and in females administered 3.64 mg/kg/day (MDT) and 44.9 mg/kg/day (HDT). Mid- and high-dose females displayed decreased levels of red blood cell counts, hemoglobin, and hematocrit. Platelet counts were increased in high-dose males and females. Adrenal weight , adrenal/brain weight ratio, and adrenal/body weight ratio were significantly increased in the high-dose females, whereas adrenal/brain ratio was increased in the high-dose males. The LOAEL in males is 42.9 mg/kg/day based on decreased body weight gains, increased platelet counts, and increased adrenal/brain weight ratio; the NOAEL is 3.41 mg/kg/day. The LOAEL in females is 3.64 mg/kg/day based on decreased body weight gain, hematological effects (decreased levels of red blood cell counts, hemoglobin and hematocrit) and increased adrenal weight, adrenal/brain weight ratio, and adrenal/body weight ratio. The NOAEL in females is 0.76 mg/kg/day.

In a 104-week dietary study in rats treated with simazine, decreased body weights and body weight gains were evident in mid-dose females (5.3 mg/kg/day), high-dose females (63.1 mg/kg/day), and high-dose males (45.8 mg/kg/day). Food consumption was reduced in the high-dose animals. Mortality was increased in the high-dose females. Treatment-related hematological effects observed in the mid- and high-dose females included decreased red blood cell counts, decreased hemoglobin and hematocrit levels, increased mean corpuscular hemoglobin, increased mean corpuscular hemoglobin concentration, increased white blood cell counts, increased percent neutrophils, and decreased lymphocyte count. Hematological changes

in males included increased mean corpuscular hemoglobin concentration (high-dose) and decreased leukocyte counts (mid-and high-dose). Females receiving the high dose exhibited decreased glucose levels and increased alkaline phosphatase activity. Organ weight changes in high-dose females included increased heart, kidney and liver weights. In high-dose males, increased liver and testes weights and decreased heart weights were noted. No non-neoplastic lesions were observed in males. In the high-dose females, liver hematopoiesis, splenic hematopoiesis and cystic mammary glandular hyperplasia were significantly increased. A re-evaluation of selected tissues subsequent to the original study revealed a significant increase after 24 months exposure to the high dose in ovarian atrophy and Sertoli cell hyperplasia. The LOAEL in females is 5.3 mg/kg/day based on hematological changes and decreased body weight gain. The NOAEL in females is 0.5 mg/kg/day. The LOAEL in males is 4.2 mg/kg/day based on decreased leukocyte counts. The NOAEL in males is 0.41 mg/kg/day. Effects overall were similar to atrazine. Differences in LOAELs and NOAELs may be attributed to dose spacing.

In a carcinogenicity study, male and female mice administered simazine (131.5 mg/kg/day - males; 160 mg/kg/day - females) in the diet exhibited decreased body weights and body weight gains. Food consumption was decreased in the high-dose males (542 mg/kg/day) and females (652.1 mg/kg/day), and in the mid-dose males. Water consumption tended to be decreased in the mid- and high-dose males and females. There were no apparent treatment-related effects on hematology, clinical chemistry, organ weights and pathology. The LOAEL (131.5 mg/kg/day - males; 160 mg/kg/day - females) is based on decreased body weights and body weight gains. The NOAEL is 5.3 mg/kg/day for males, and 6.2 mg/kg/day for females.

Developmental/Reproductive Toxicity: Available developmental toxicity data provided no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits to *in utero* and/or postnatal exposure to simazine. Developmental effects (skeletal variations) in the rat were observed in the presence of maternal toxicity (decreased body weight/body weight gain and food utilization at 300 mg/kg/day). No malformations were reported . In the rabbit, maternal effects occurred at doses (75 mg/kg/day) lower than those associated with developmental effects (decreased fetal weight and increased skeletal variations at 200 mg/kg/day).

No treatment-related offspring toxicity was reported in a two-generation reproduction study in the rat. The parental LOAEL is 100 ppm (5.61 and 7.04 mg/kg/day for males and females, respectively), based on decreased body weight and body weight gain. The NOAEL is 10 ppm (0.56 and 0.7 mg/kg/day for males and females, respectively). The NOAEL for offspring toxicity is 500 ppm (HDT - 28.9 and 35.0 mg/kg/day for males and females).

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

Simazine	Atrazine
Special Study - LH surge in rats (SD) (gavage - 4 weeks) **MRID 45471002**	**Special Study - LH surge in rats (SD) (gavage - 4 weeks)** **MRID 45471002**
LOAEL for systemic toxicity: 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects.	LOAEL for systemic toxicity: 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects.
NOAEL for all three compounds is 5 mg/kg/day.	NOAEL for all three compounds is 5 mg/kg/day.
LOAEL for endocrine effects : 40 mg/kg/day for simazine, atrazine, and DACT, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels).	LOAEL for endocrine effects : 40 mg/kg/day for simazine, atrazine, and DACT, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels).
NOAEL for endocrine effects: 5.0 mg/kg/day for simazine, atrazine, and DACT.	NOAEL for endocrine effects: 5.0 mg/kg/day for simazine, atrazine, and DACT.
Special Study - 6-month LH surge study in the rat (SD) **MRID XXXXX**	**Special Study - 6-month LH surge study in the rat (SD)** **MRID 44152102**
An unacceptable study was available, and not useful for risk assessment.	LOAEL: 3.65 mg/kg/day, based on estrous cycle alterations and LH surge attenuation. NOAEL: 1.8 mg/kg/day.
Special Study - in vivo endocrine effects in rats (SD). (14-23 days) MRID 43598614	**Special Study - in vivo endocrine effects in rats (SD). (14-23 days) MRID 43598614**
LOAEL for systemic toxicity: 100 mg/kg/day for both atrazine and simazine, based on body weight effects and organ weight effects for atrazine.	LOAEL for systemic toxicity: 100 mg/kg/day for both atrazine and simazine, based on body weight effects and organ weight effects for atrazine.
NOAEL for toxicity: cannot be determined.	NOAEL for toxicity: cannot be determined.
LOAEL for endocrine effects : 300 mg/kg/day based on organ weight effects and vaginal cytology.	LOAEL for endocrine effects: 100 mg/kg/day based on organ weight effects, plasma hormone changes (estradiol), estrus cycle lengthening, and vaginal cytology.
NOAEL for endocrine effects: 100 mg/kg/day.	NOAEL for endocrine effects: cannot be determined.

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

of carcinogenicity, simazine has been reclassified by the CARC as “not likely to be carcinogenic to humans.”

Simazine was negative in a bacterial (Salmonella typhimurium) assay, in a mammalian cytogenetic assay (bone marrow micronucleus), and in an unscheduled DNA synthesis assay in rat hepatocytes.
The following table is the complete toxicity profile for simazine.

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

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

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity (rat)	00143265 (1985) 0, 14.25, 142, or 276 mg/kg/day	NOAEL = not identified. LOAEL = 14.25 mg/kg/day, based on decreased body weight gain, decreased food consumption and hematological changes.
870.3150 13-Week dietary toxicity (dog)	00146655 M: 6.9, 65.2, 133.6 F: 8.2, 64.3, 136.7	NOAEL = 6.9 mg/kg/day (M); 8.2 mg/kg/day (F) LOAEL = 65.2 mg/kg/day (M); 64.3 mg/kg/day (F) based on decreased body weight/body weight gain, decreased food consumption, organ weight changes, decreased serum glutamate oxaloacetate (SGOT) and reduced alkaline phosphatase activities (females).
870.3200 21/28-Day dermal toxicity (rat)	00005767 (1980) 0, 10, 100 or 1000 mg/kg/day	systemic NOAEL = 1000 mg/kg/day systemic LOAEL = not identified.
870.3700a Prenatal developmental in Rat	40614403 (1986) 0, 30, 300 or 600 mg/kg/day	Maternal NOAEL = 30 mg/kg/day LOAEL = 300 mg/kg/day based on decreased body weight/body weight gain, and decreased food utilization. Developmental NOAEL = 30 mg/kg/day LOAEL = 300 mg/kg/day based on skeletal variations.
870.3700b Prenatal developmental in Rabbit	00161407 (1984) 0, 5, 75 or 200 mg/kg/day	Maternal NOAEL = 5 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain, decreased food consumption, increased tremors, and stool alterations. Developmental NOAEL = 75 mg/kg/day LOAEL = 200 mg/kg/day based decreased fetal weight and increased skeletal variations.
870.3800 Reproduction and fertility effects (Rat)	41803601 (1991) 0, 10, 100, or 500 ppm M: 0, 0.56, 5.61, 28.9 mg/kg/day F: 0, 0.7, 7.04, 34.96 mg/kg/day	Parental/Systemic NOAEL = 0.56 mg/kg/day (M); 0.7 (F) LOAEL = 5.61 mg/kg/day (M); 7.04 mg/kg/day (F), based on decreased body weight/body weight gain. Offspring NOAEL = 31.93 mg/kg/day LOAEL = not identified

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity (dog)	40614402 Acceptable-guideline M: 0, 0.68, 3.41, 42.9 mg/kg/day F: 0, 0.76, 3.64, 44.9 mg/kg/day	NOAEL = 3.41 mg/kg/day (M); 0.76 mg/kg/day (F) LOAEL = 42.9 mg/kg/day (M) based on decreased body weight gains, increased platelet counts, and increased adrenal/brain weight ratio; 3.64 mg/kg/day (F), based on decreased body weight gain, hematological effects (decreased levels of red blood cell counts, hemoglobin and hematocrit) and increased adrenal weight, adrenal/brain weight ratio, and adrenal/body weight ratio.
870.4200 Carcinogenicity (rat)	40614405 Acceptable-guideline 0, 10, 100, or 1000 ppm M: 0, 0.4, 4.2, or 45.8 mg/kg/day F: 0, 0.5, 5.3, or 63.1 mg/kg/day	NOAEL = 0.4 mg/kg/day (M); 0.5 mg/kg/day (F) LOAEL = 4.2 mg/kg/day (M) based on decreased leukocyte counts; 5.3 mg/kg/day (F), based on hematological changes and decreased body weight gain. Carcinogenicity -treatment-related increase in mammary carcinomas and fibroadenomas tumor incidence.
870.4300 Carcinogenicity (mouse)	40614404 (1988) Acceptable-guideline 0, 40, 1000 or 4000 ppm M: 0, 5.3, 131.5, 542 mg/kg/day F: 0, 6.2, 160, 652.1 mg/kg/day	NOAEL = 5.3 mg/kg/day (M); 6.2 mg/kg/day (F) LOAEL = 131.5 mg/kg/day (M), 160 mg/kg/day (F) based on decreased body weight/body weight gain. No evidence of carcinogenicity.
Gene Mutation: In vitro Bacterial Gene Mutation (Bacterial system, Salmonella typhimurium) gene mutation assay 870.5100	40614406 (1987) Acceptable-guideline 0, 10, 25, 50, 100, or 250 µg/plate in the in the presence and absence of mammalian metabolic activation (S9-mix)	There was no evidence of induced mutant colonies over background.
Cytogenetics: In vivo Mammalian Cytogenetics - Micronucleus Assay 870.5395	41442901 (1988) Acceptable-guideline 1250, 2500 or 5000 mg/kg	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow.
Unscheduled DNA Synthesis in Rat Hepatocytes/Mammalian Cells 870.5550	41441902 (1989) Acceptable-guideline 1.57, 4.72, 14.17, 42.5, 85 or 170 µg/ml	There was no evidence that UDS was induced by exposure to simazine.
870.6200a Acute neurotoxicity screening battery	Not available.	N/A
870.6200b Subchronic neurotoxicity screening battery	Not available.	N/A

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics (rat)	00143266 (1986) Acceptable-guideline	At the low dose (0.5 mg/kg) of radiolabeled simazine, the principal route of excretion was via the urine, however, at the higher dose (200 mg/kg) the principal route of excretion was via the feces. Significant radioactive residues remained in the tissues of the rat for extended periods of time. Results indicate that 94 to 99% of the elimination of radioactive material occurred within 48 to 72 hours with a half-life of 9 to 15 hours. Elimination of the remaining radioactivity exhibited 21- to 32-hour half-life values. Heart, lung, spleen, kidney, and liver appear to be principal sites of retention of radioactivity. However, erythrocytes concentrated radioactivity to higher levels than did other tissues, perhaps due to high affinity of the triazine ring for cysteine residues of hemoglobin, a phenomenon apparently unique to rodent species.
Dermal Absorption - rat.	40614409 (1988) Acceptable-guideline	Male rats were received doses of 0.1 or 0.5 mg/cm^2 radiolabeled simazine for 2, 4, 10 or 24 hours. Dermal absorption was less than 1% at both doses and all time points. However, 11-20% of the low dose and 31-41% of the high dose remained on skin, and potentially absorbable.
Special Study - in vivo endocrine effects in rats. Acceptable-Non-guideline	43598614	In a special study (MRID 43598614) on in vivo endocrine effects, atrazine and simazine (>96 % a.i.) were administered to11 female rats/dose/strain (both Sprague-Dawley and Fischer 344 rats were used) by oral gavage at dose levels of 0, 100, and 300 mg/kg/day for 14 to 23 days depending on time to achieve proestrus. The LOAEL for systemic toxicity is 100 mg/kg/day for both atrazine and simazine, based on body weight effects and reproductive organ weight effects for atrazine. The NOAEL for toxicity cannot be determined. The LOAEL for endocrine effects of atrazine is 100 mg/kg/day based on organ weight effects, plasma hormone changes (estradiol), estrus cycle lengthening, and vaginal cytology. The NOAEL for endocrine effects of atrazine cannot be determined. The LOAEL for endocrine effects of simazine is 300 mg/kg/day based on organ weight effects and vaginal cytology. The NOAEL for endocrine effects of simazine is 100 mg/kg/day.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Special Study - LH surge in rats Acceptable-Nonguideline	45471002	In a special study (MRID 45471002) on the effects of chlorotriazines on luteinizing hormone (LH) surge, simazine (100%, batch no. SG202028GB10), diaminochlorotriazine (DACT) (96.8%, batch no. GP720301) and atrazine (97.1% , batch no. SG8029BA10) were administered to 20 Sprague-Dawley Crl:CD BR female rats/dose/group by oral gavage at dose levels of 0, 2.5, 5, 40, 200 mg/kg bw/day (equivalent to 12.4, 24.8, 198.3, and 991.6 µmol//kg/day for simazine; for 17.2, 34.4, 274.9, 1374.6 µmol//kg/day for DACT; and 11.6, 23.2, 185.4, 927.2 µmol//kg/day for atrazine) once daily for at least 4 weeks. The LOAEL for systemic toxicity is 40 mg/kg/day for simazine, DACT, and atrazine, based on body weight effects. The NOAEL for all three compounds is 5 mg/kg/day. The LOAEL for endocrine effects for simazine, atrazine, and DACT is 40 mg/kg/day, based on analyses of pre-peak, peak, and post-peak LH concentrations, adjusted peak LH response, and comparison of responses between compounds (at the same dose levels). The NOAEL for endocrine effects for simazine atrazine, and DACT is 5.0 mg/kg/day.

Hydroxy-simazine and Hydroxy-atrazine:

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

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

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

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

4.2.2 Evidence of Neurotoxicity

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

4.2.3 Developmental Toxicity Studies

Developmental Rat Study

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 40614403), simazine (97.5% a.i., batch no. FL-821846) was administered to CR1 female rats by gavage at dose levels of 0, 30, 300, or 600 mg/kg/day from days 6 through 15 of gestation. There were 19 animals/dose in the control and 600 mg/kg groups and 23/dose in the 30 and 300 mg/kg groups.

Maternal body weight in the 300 (MDT) and 600 (HDT) mg/kg groups was statistical significantly decreased compared to control animals on gestation day (GD) 10 (7% and 10, respectively), GD 14 (11% and 14%, respectively) and GD 18 (6% and 9%, respectively). MDT and HDT groups had significantly decreased body weight gains during GD 6-10 (-7 g and -17 g, respectively, vs 10 g in controls) and GD 10-14 (13 g and 7 g, respectively, vs 22 g in controls). Body weight gain for the HDT group was significantly increased, as compared to control, during GD 14-18 (31 g vs 23g) and GD 18-20 (31 g vs 23 g). Food efficiency decreased in the MDT and HDT during GD 7-10 (-0.11, and -0.32 vs 0.11 for controls) and in the HDT during GD 11-14 (0.10 vs 0.22 for controls).

The maternal LOAEL is 300 mg/kg/day, based on decreased body weight, body weight gain, and food efficiency. The maternal NOAEL is 30 mg/kg/day.

No dose related visceral effects were reported in any dose group. There were, however, a significant increase in treatment related skeletal effects seen in the MDT and HDT groups. These effects were mostly higher incidences of unossified bones at various locations on a fetal basis. These effects were: head incompletely ossified (incidence for control, MDT and HDT: 12, 48 and 71, respectively); teeth not ossified (10, 59, 40); sternebrae not ossified (83, 159, 131); unossified centra/vertebrae (8, 44, 39); and rudimentary ribs (8, 27, 19). The parameters affected on a litter basis were presphenoid, at the HDT, and additional lumbar vertebra/centra at the MDT and the HDT

The developmental LOAEL is 300 mg/kg/day, based on unossified: teeth; head; centra/vertebrae; sternebrae; and also on rudimentary ribs. The developmental NOAEL is 30 mg/kg/day.

This study is classified **Acceptable-Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

Developmental Rabbit Study

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00161407), simazine (97% a.i., batch no. 821846) was administered to pregnant female New Zealand White rabbits by gavage at dose levels of 0, 5, 75, or 200 mg/kg/day from days 7 through 19 of gestation. There were 18 animals/dose in all groups except the 200 mg/kg group which had 16 animals.

A compound-related increase in tremors was noted in the two highest dose groups (21% in 75 mg/kg group; 100% in 200 mg/kg/day group), while no tremors occurred in the control and low dose groups. Stool alterations (none, little or soft stool) were observed in 50% of the 5 mg/kg (LDT) animals and 100% of the 75 and 100 mg/kg (MDT and HDT, respectively) animals, whereas no stool alterations were observed in control groups. During days 7-19 (the period of dosing), the MDT and HDT showed statistically significant decreases in weight gain compared to controls (+230g for controls vs -243 and -456g for MDT and HDT, respectively). The corrected body weight (body weight gain minus gravid uterine weight) was also significantly decreased in the MDT and HDT groups. Significant decreases in food consumption were also noted in the MDT and HDT groups as compared to controls and persisted throughout the dosing period. Four animals aborted during the study: one from the MDT and three from the HDT.

The maternal LOAEL is 75 mg/kg/day, based on decreased food consumption and weight gain, and increased female tremors and stool alterations. The maternal NOAEL is 5 mg/kg/day.

There were no teratogenic effects from dosing with the test compound. There were, however, significant decreases in female fetal weights (decreased 13% vs controls) and a significant increase in skeletal variations (50% of fetuses had some type of skeletal variation in the controls vs 88% in the HDT) in the high dose group.

The developmental LOAEL is 200 mg/kg/day, based on reduced mean fetal weight and increased skeletal variations. The developmental NOAEL is 75 mg/kg/day.

The developmental toxicity study in the rabbit is classified **Acceptable-guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b [§83-3b]; OECD 414) in the rabbit.

4.2.4 Reproductive Toxicity Study

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 41803601) simazine (96.9% a.i., batch no. FL 850614) was administered to 240 Sprague-Dawley rats 30/sex/dose in the diet at dose levels of 0, 10 (LDT), 100 (MDT), 500 (HDT) ppm (mean of F_0 and F_1 generation compound intakes for both sexes: 0, 0.56/0.7; 5.61/7.04; 28.89/34.96).

There were no compound related deaths or clinical observations in either sex, at any dose or either generation.

Male body weight and body weight gain were decreased (10% and 27%, respectively) in the 500 ppm group in both the F_0 and F_1 generations throughout the premating and mating phases (days 0-105). Male body weight gain was also significantly decreased (13%) in 100 ppm F_0 males through the premating phase (days 0-70). Conversely, male 10 ppm body weight gains were significantly increased in the F_1 generation throughout the entire duration of the study (days 0-

147). Females in both generations of the HDT had significantly decreased body weight throughout most of the study. F_1 generation MDT females had significantly decreased body weight or body weight gain at only a few time points throughout the study.

Food consumption for HDT males of both generations was significantly decreased through the premating period (10-16% decrease, depending on time point). F_0 and F_1 female food consumption at the HDT was significantly decreased at many time points both during the premating, mating and lactation periods (9-16% decrease, depending on time point). There were no indications of any reproductive toxicity resulting from exposure to the test compound.

The parental LOAEL is 100 ppm (5.61 and 7.04 mg/kg/day for males and females respectively), based on decreased body weight and body weight gain. The NOAEL is 10 ppm (0.56 and 0.7 mg/kg/day) for males and females respectively.

The NOAEL for reproductive toxicity is 500 ppm (31.93 mg/kg/day in both sexes combined). A reproductive LOAEL was not determined.

The NOAEL for offspring toxicity is 500 ppm (31.93 mg/kg/day in both sexes combined). A reproductive LOAEL was not determined.

The reproductive study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800 [§83-4]; OECD 416) in the rat.

4.2.5 Additional Information from Literature Sources

No additional information specific to simazine was identified from literature sources.

4.2.6 Pre-and/or Postnatal Toxicity

Based on the results of the traditional developmental and reproduction studies, in 1998, the HIARC concluded that there is no concern for pre-and/or postnatal toxicity resulting from exposure to Simazine. However, residual concerns remain related to potential neuroendocrine effects on the developing organism were identified. See section 4.5 for discussion on special FQPA factor.

4.2.6.1 Determination of Susceptibility

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

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

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

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Acute and subchronic neurotoxicity studies are not available for simazine. Special studies on atrazine, a triazine similar in structure to simazine, have provided evidence of atrazine-associated neurotoxicity. The neurotoxicity seen in these studies is a central nervous system (CNS) toxicity (specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus). Based on available evidence, Simazine has been grouped with several triazines (e.g., atrazine and DACT) on the basis of a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal (HPG) axis.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

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

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

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

Not applicable.

4.4 Hazard Identification and Toxicity Endpoint Selection

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

In a developmental toxicity study (MRID 40614403) simazine, 97.5% a.i., was administered to CR1 female rats. Dosing was by gavage at dose levels of 0, 30, 300, or 600 mg/kg/day from days 6 through 15 of gestation. There were 19 animals/dose in the control and 600 mg/kg groups and 23/dose in the 30 and 300 mg/kg groups. Maternal body weight in both the 300 (MDT) and 600 (HDT) mg/kg groups was significantly decreased compared to control animals on gestation day (GD) 10 (23% decrease at MDT and 19% at HDT), 14 (21% and 19%)and 18 (23% and 19%). MDT and HDT groups also had significantly decreased body weight gains during the exposure period (-4.25g *vs* 2.5g in controls during GD 6-10; 1.75g *vs* 5.5g in controls during GD 10-14). Food efficiency in the MDT and HDT groups was also significantly decreased in MDT and HDT animals during the treatment period (GD 6-15). GD 7-10 food efficiencies were: 0.11, -0.11, and -0.32 for controls, MDT and HDT respectively. GD 11-14 food efficiencies were: 0.22, 0.16 and 0.1 for controls, MDT and HDT respectively. **The maternal LOAEL is 300 mg/kg/day, based on decreased body weight, body weight gain, and food efficiency. The maternal NOAEL is**

30 mg/kg/day. No dose related visceral effects were reported in any dose group. Statistically significant treatment related skeletal effects were seen in the MDT and HDT groups though. These effects were mostly higher incidences of unossified bones at various locations on a fetal basis. These effects were: incompletely ossified head (incidence for control, MDT and HDT: 12, 48 and 71, respectively); teeth not ossified (10, 59, 40);sternebrae not ossified (83, 159, 131); unossified centra/vertebrae (8, 44, 39); and rudimentary ribs (8, 27, 19). Incidences of several parameters were increased on a litter basis , but none significantly. **The developmental LOAEL is 300 mg/kg/day, based on unossified teeth, head, centra vertebrae, sternebrae, and also on rudimentary ribs. The developmental NOAEL is 30 mg/kg/day.**

This study is classified **Acceptable-Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; § 83-3a) in the rat.

Dose and Endpoint for Risk Assessment: Developmental NOAEL=30 /kg/day. based on unossified teeth, head, centra/vertebrae, and sternebrae; and also on rudimentary ribs at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The team selected this study as most suitable for this endpoint. This study was also selected previously by HIARC. The developmental effects are presumed to occur after a single exposure, and were, thus, considered to be appropriate for the acute risk assessment. The rat study was used over the rabbit study (MRID 252938) because the endpoints on which the developmental LOAEL in the rabbit study are based (decreases in fetal weights and an increase in skeletal variations including, but not limited to unossified bones) were not considered to be the result of a single exposure This dose/endpoint is applicable only to Females 13+.

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

Acute RfD = 30 mg/kg/day/100 = 0.30 mg/kg/day

4.4.2 Acute Reference Dose (aRfD) - General Population

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

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

4.4.3 Chronic Reference Dose (cRfD)

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

MRID No.: 44152102

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

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

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

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

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

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

Comments about Study/Endpoint/Uncertainty Factor: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although an acceptable similar 6-month study is not available on simazine, the atrazine study is used as bridging data and based on common mechanism of toxicity. The available endocrine data (albeit limited) on simazine indicate comparable effects to atrazine on LH surge (28-day study), and less potency in regard to vaginal cytology effects. The atrazine study is considered protective of simazine endocrine-related effects. An acceptable long-term study on the endocrine effects of simazine is not available. The attenuation of the LH surge is considered to be an indicator of atrazine's neuroendocrine mode of action or its potential to alter hypothalamic-pituitary function. This six-month study is considered adequate for use in selecting a chronic endpoint without an additional safety factor being added to account for study duration of less than 12 months. This is based on the fact that examination of estrous cycle data from other studies indicates that beyond 6 months of exposure, the differences in estrous cycle deterioration between treated animals and controls no longer widens as the control animals begin the normal reproductive aging process.

These biomarkers of atrazine's neuroendocrine mode of action (i.e., LH surge attenuation and estrous cycle disruption) are considered to be applicable to the general population including infants and children given that they result from atrazine's CNS mode of action. HIARC noted that this dose is the lowest NOAEL available in the toxicology database on atrazine and

therefore would be protective of other adverse effects, including those occurring in males, infants, and children. Therefore, a separate endpoint is not needed for this population (i.e., males, infants, and children). Although for simazine lower NOAELs were noted in the chronic rat and reproductive toxicity studies, the lower NOAELs are an artifact of dose selection.

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

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Short-Term (1-30 days)

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

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

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

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

Comments about Study/Endpoint: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although a similar pubertal study is not available on simazine, the atrazine study is used as bridging data and based on a common mechanism of toxicity. The available endocrine data (albeit limited) on simazine indicate comparable effects to atrazine on LH surge (28-day study), and less potency in regard to vaginal cytology effects. The atrazine study is considered protective of simazine endocrine-related effects.

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

Intermediate-Term (1 - 6 Months)

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

MRID No.: 44152102

Executive Summary: see under Chronic RfD.

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

Comments about Study/Endpoint: This study was selected as the most appropriate study for endpoint selection for the structurally similar atrazine. Although an acceptable similar 6-month study is not available on simazine, the atrazine study is used as bridging data and based on common mechanism of toxicity. The available endocrine data (albeit limited) on simazine indicate comparable effects to atrazine on LH surge (28-day study), and less potency in regard to vaginal cytology effects. The atrazine study is considered protective of simazine endocrine-related effects. An acceptable long-term study on the endocrine effects of simazine is not available.

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

of other adverse effects, including those occurring in males, infants, and children. Therefore, given the uncertainty of atrazine's potential effect during development *via* the mode of toxicity of atrazine, the use of the NOAEL from the 6-month study is considered protective of the population of concern [infants and children]. Although for simazine lower NOAELs were noted in the chronic rat [NOAELs = 0.4 mg/kg/day (♂), 0.5 mg/kg/day (♀); LOAELs = 4.2 mg/kg/day (♂), 5.3 mg/kg/day (♀)] and reproductive toxicity studies [NOAELs = 0.56 mg/kg/day (♂), 0.71 mg/kg/day (♀); LOAELs =5.61 mg/kg/day (♂), 7.04 mg/kg/day (♀)], the lower NOAELs are an artifact of dose selection.

4.4.5 Dermal Absorption

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

MRID No.: 44152144

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

Supporting Study: Dermal Absorption in the rat (MRID 40614409)

CITATION: Murphy, T., and Orr, G. (1988) Dermal absorption of ^{14}C-simazine in the rat. WIL Research Labs and Agrisense Inc. Laboratory report number: ABR-88042. March 30, 1988. MRID:40614409. Unpublished.

Executive Summary**:** In a dermal absorption study (MRID: 40614409), male Charles River Sprague-Dawley rats received either 0.1, 0.5 mg/cm^2 of ^{14}C-simazine (two vials used: radiochemical purity: 98% for the low dose and 96%, for the high dose, specific activity: 28.0 uCi/mg and 2.4 uCi/mg). Four animals per dose were treated and then the treated area of skin and the surrounding area were covered with a protective device. Animals were then placed in metabolism cages for the duration of the exposure period. Either 2, 4, 10 or 24 hrs following exposure animals were sacrificed. Following sacrifice the exposure sites were washed with liquid Dove and water and both the treated area of skin and skin surrounding the treated area (the skin covered by the protective device) were collected. The soap and water rinses, the skin samples, urine, feces, blood, carcass, cage wash, and other relevant samples were all analyzed for radioactivity. Dermal absorption was less than 1% at both doses and all time points. However, 11-20% of the low dose and 31-41% of the high dose remained on the skin and is thus potentially absorbable.

This dermal absorption study in the rat is classified **Acceptable-Guideline** and satisfies the guideline requirement for a dermal absorption study (85-2) in the rat.

Comments about Study: Studies conducted at identical dose levels, under similar protocols, result in very similar absorption between the two chemicals. Male Charles

River rats exposed to 0.1 mg/cm^3 of simazine for 10 hours have a measured dermal absorption of 0.3% of the dose (MRID 40614409). Male Charles River rats exposed to 0.1 mg/cm^3 of atrazine for 10 hours have a measured dermal absorption of 0.34% of the dose (MRID 43314302). Atrazine and simazine appear to have very similar absorption profiles in the rat. There is no reason to believe absorption profiles would not also be similar in the human. Thus, the dermal absorption factor derived from the human study using atrazine (MRID 44152114) is applied to simazine.

Dermal absorption Factor: 6% (Rounded off)

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

Short- and Intermediate-Term Dermal Endpoints:

Short-Term (1-30 days) Exposure

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

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

Executive Summary: see under Incidental Oral Exposure.

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

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

Intermediate-Term (1 - 6 Months)

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

MRID No.: 44152102

Executive Summary: see under Chronic RfD.

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

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

Long-Term Dermal Endpoints:

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

MRID No.: 44152102

Executive Summary: see under Chronic RfD.

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

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

4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)

Short-Term Inhalation Endpoint:

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

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

Executive Summary: see under Short-Term Dermal.

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

Comments about Study/Endpoint: See under Incidental Oral Exposure for rationale for the selection of atrazine study as bridging data. This study is appropriate for this scenario since it demonstrates an endpoint in the young animal that is consistent with atrazine's mode of toxicity. The endpoint, delayed puberty, is relevant to the population of concern.

Intermediate-Term Inhalation Endpoint:

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

MRID No.: 44152102

Executive Summary: see under Chronic RfD

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

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

Long-Term Inhalation Endpoint:

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

MRID No.: 44152102

Executive Summary: see under Chronic RfD

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

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

4.4.8 Margins of Exposure

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

Route of Exposure	**Duration of Exposure**		
	Short-Term (1-30 Days)	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational Exposure			
Dermal	100	100	100
Inhalation	100	100	100

Residential (non-dietary) Exposure			
Oral	300	300	N/A
Dermal	300	300	300
Inhalation	300	300	300

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

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

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

4.4.10 Classification of Carcinogenic Potential

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

In 1997, the HED Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of atrazine and discussed mode of action data submitted by the Registrant in regards to the ability of atrazine to produce mammary tumors in Sprague-Dawley rats. The CARC evaluated the possibility that any mode of action which may be selected for atrazine would apply for simazine.

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

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

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

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

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

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

On April 14, 2005, the CARC reevaluated the carcinogenic potential of simazine and reclassified simazine as "Not Likely To Be Carcinogenic To Humans." The reclassification was based on the following weight-of-evidence that simazine is not genotoxic and operates via a mode of action for the development of mammary and pituitary tumors in the female SD rat similar to atrazine. See CARC Report (3rd) dated April 14, 2005.

Table 4.4 Summary of Toxicological Doses and Endpoints for Simazine

Exposure Scenario	**Dose used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49)	Developmental NOAEL = 30 mg/kg/day UF = 100 **Acute RfD = 0.3 mg/kg/day**	3X for residual Exposure-based uncertainties for drinking water aPAD = aRfD/FQPA SF **aPAD = 0.1 mg/kg/day**	**Development study in rats w/ simazine** LOAEL = 300 mg/kg/day based on increased incidence of unossified teeth, head, centra vertebrae, sternabrae, and also on rudimentary ribs
Acute Dietary (general population)	NA	NA	No toxic effect attributable to a single dose was identified for the general population
Chronic RfD (all populations)	NOAEL = 1.8 mg/kg/day UF = 100 **Chronic RfD = 0.018 mg/kg/day**	10Xfor residual Hazard-based and Exposure-based uncertainties cPAD = cRfD/FQPA SF **cPAD = 0.0018 mg/kg/day**	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Incidental Oral Short-Term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation

Table 4.4 Summary of Toxicological Doses and Endpoints for Simazine			
Exposure Scenario	**Dose used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral Intermediate-Term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal short-term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (MOE) occupational)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Dermal intermediate-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal long-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Inhalation short-term (1-30 days)	NOAEL = 6.25 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (MOE) occupational)	**28-day Pubertal study in rats w/ Atrazine** LOAEL = 12.5 mg/kg/day based on delayed preputial separation
Inhalation intermediate-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Inhalation long-term (30-180 days)	NOAEL = 1.8 mg/kg/day UF = 100	3X for residual Hazard-based concerns LOC = 300 (MOE) residential LOC = 100 (occupational)	**6-month LH surge study in rat w/ Atrazine** LOAEL = 3.65 mg/kg/day based on estrous cycle alterations and LH surge suppression
Dermal absorption = 6% (human data for atrazine)			
Cancer (oral, dermal, inhalation)	Current Classification: Reclassification by CARC, as noted in April 14, 2005 CARC Report, to “Not Likely to be Carcinogenic to Humans” as per common mode of toxicity with atrazine.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

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

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

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

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

> "Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur compared to reproductive/developmental effects[1]."

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

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

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

HIARC also recommended that the additional Special FQPA Safety Factor of 3X would **not** be required for Acute dietary exposures (aRfD) because the open literature data demonstrate that

---

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

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

The FQPA Committee met on April 8, 2002 to consider the recommendations of the HIARC with respect to any hazard-based residual concerns for atrazine, and to consider any residual "exposure-based" concerns. The FQPA Committee concluded that, as to dietary risk, residual concerns were identified with regard to the drinking water exposure assessment for atrazine based on inadequate monitoring data. Limitations in the extent, frequency, and the lack of monitoring data on the degradates raised uncertainties regarding the level of exposure to atrazine and its metabolites. The monitoring data for simazine is less extensive and has more geographic limitations than the database for atrazine particularly in areas of high use. Both compounds are known to occur in drinking water; both compounds have MCLs. The FQPA Committee concluded that an additional Special FQPA Safety Factor of 3X for "exposure-based" concerns is adequate for assessing drinking water exposures to atrazine based on monitoring data. The team has determined that a Special FQPA Safety Factor of 3X for "exposure-based" concerns should be applied to drinking water exposure assessments based on monitoring data for simazine, as well. However, the team has also determined that the additional Special FQPA Safety Factor of 3X for "exposure-based" concerns should **not** be applied to drinking water exposure assessments based on conservative models, i.e., PRZM/EXAMS. The team considers the model estimates of exposure to be conservative and protective.

The FQPA Committee further concluded that an additional Special FQPA Safety Factor of 3X for "hazard-based" concerns is adequate for assessing residential exposures to atrazine. The Committee believed there were no residual "exposure-based" concerns for residential exposure assessments because the assessments were based on HED Standard Operating Procedures using default values and assumptions that would be protective of infants and children, and drinking water exposures (described above) would have little or no impact on the residential exposure scenarios. The concerns for the effect of the neuroendocrine mode of action on the development of the young remained and the Committee concluded that there are reliable data to address these concerns through use of an additional Special FQPA Safety Factor of 3X. Given that the simazine residential risk assessment uses the same methodology as the atrazine residential assessment and will not underestimate exposure, the simazine team recommends for application of the 3X "hazard-based" FQPA Safety Factor to the residential exposure assessments.

4.6 Endocrine disruption

There is direct evidence that simazine is associated with neuroendocrine disruption. Direct measurements of serum hormones such as certain steroid hormones and luteinizing hormone, as well as, changes in estrus cycling and histomorphic changes in hormone responsive tissues, indicate neuroendocrine disruption.

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid

hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

5.0 Public Health Data

Human incident data for simazine has been requested, but has not yet been made available for this assessment.

5.1 Incident Reports

The incident report was prepared by the HED Chemistry and Exposure Branch (US EPA, 2004). Data bases consulted for the incident report for simazine include the OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation, and National Pesticide Telecommunications Network (NPTN). A total of 21 incidents were reported in the OPP Incident Data System. Many of these incidents involved irritant effects to the eyes, skin and respiratory passages. In addition, several incident reports involved general CNS effects (i.e., nausea, dizziness, headache, restlessness).

Poison Control Incident Data (1993 - 2001) indicated that simazine appears to be much less acutely toxic than other pesticides to cause minor, moderate or life threatening symptoms. The overwhelming majority of symptoms reported due to simazine exposure were eye, dermal, and throat irritation.

74 cases were reported to the California Pesticide Illness Surveillance Program from 1982-1999. Of these, there were 9 cases in which simazine was used alone or was judged to be responsible for the health effects. Simazine ranked 143rd as a cause of systemic poisoning in California based on data for 1982-1994. Direct exposure to simazine (principally from application) can lead to skin or eye effects. Given it's widespread use in California, relatively few cases of simazine illness were reported.

On the list of the top 200 chemicals for which the National Pesticide Telecommunications Network received calls from 1984-1991, simazine ranked 77th with 44 incidents reported for humans and 17 for animals.

The incident report concludes that simazine can be a skin or eye irritant from direct exposures. It is recommended that individuals with substantial exposure to simazine during application and mixing/ loading operations should take appropriate steps to protect eyes, skin, and mouth from accidental exposure. If contact with simazine should occur, skin surfaces should be rinsed off with soap and water and the eyes should be immediately irrigated.

5.2 Other

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Field Trial Data

Adequate simazine residue data are available for: apples, avocados, bananas, blueberries, caneberries, corn (grain, forage, and stover), grapes, olives, peaches, plums, and pecans. An adequate number of field trials have been conducted on these crops depicting residues of simazine and its chloro-metabolites (G-28270 and G-28273) resulting from the application of simazine at the maximum labeled use rate. These residue data showed non-detectable residues (<0.05 ppm, the LOD of the method) for the latter crops. Field trial data on oranges are inadequate but are being required. However, based on metabolism study data, residues of simazine on oranges are expected to be conjugates (proline) rather than the chlorinated triazines, which are the subject of this risk assessment.

Monitoring Data

PDP

There are PDP data from 1994 to 2002 for: apple juice, apple sauce, apples, asparagus, bananas, beef, broccoli, cantaloupe, carrots, celery, cherries, corn syrup, cucumbers, grape juice, grapes, green beans, lettuce, milk, mushrooms, nectarines, orange juice, oranges, peaches, pears, pineapples, potatoes, poultry (fat and muscle), spinach, strawberries, sweet bell peppers, sweet corn, sweet peas, sweet potatoes, tomatoes, wheat, and winter squash. More than 100 samples were analyzed for each crop except for canned sweet corn (19 samples) and fresh sweet peas (9 samples). Samples were analyzed for parent simazine only. No data were reported for the chloro-metabolites. Average LODs ranged from 0.007ppm to 0.03 ppm and none of the samples analyzed showed residues except for one orange sample from the year 1996 (out of a total of 3,375 total orange samples analyzed from 1994 to 2002). PDP also provided some monitoring data for parent simazine in drinking water (from NY and CA only) (see the water section for more details). There is essentially no co-occurrence of simazine and atrazine on foods, although there is about 10% co-occurrence of simazine and atrazine in drinking water monitoring samples.

FDA

FDA did not test for simazine in any food except for a single carp sample in 2001 and a few different fish in 2000. Very limited testing was done in 2002 on the following crops: pears (21 samples), apples (20 samples), oranges (9 samples), peaches (18 samples), tomatoes (13 samples), strawberries (13 samples), broccoli (11 samples), nectarines (10 samples), and head lettuce (10 samples). Samples were analyzed for parent simazine only. No data were reported for the chloro metabolites. All samples had non-detectable residues except for one orange sample from CA.

6.1.2 Acute and Chronic Dietary Exposure and Risk

After consultation with the Risk Assessment Review Committee (RARC), and review and extensive discussion of the available monitoring data for simazine discussed above, the team determined that food-related exposures to simazine residues were insignificant and set food residues to zero in the dietary exposure assessments. The rationale for this decision was presented to the RARC and the RARC concurred with this decision (RARC Report dated October 20, 2004, “Simazine. Report of the Risk Assessment Review committee”). Given the use pattern for

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 field trial databases is not unexpected. Consequently, the dietary exposure to simazine results in a risk estimate of 0% of the aPAD and cPAD, respectively.

6.2 Water Exposure/Risk Pathway

Drinking Water Standards

Simazine is currently regulated under the Safe Drinking Water Act (SDWA). A Maximum Contaminant Level (MCL) of 4 ppb has been established by the Agency's Office of Water (OW). The OW has also established a 1-day and 10-day Health Advisory Level (HAL) at 500 ppb for one-day and short-term exposures to simazine in drinking water.

Environmental Occurrence

Drinking water monitoring data collected by PDP in California and New York indicate that 40% of the samples contain simazine compared to 50% containing atrazine concentrations detected in 2002 and 2003 were in parts per trillion, with a maximum concentration of 17 ppt.

As part of the ecological risk assessment for simazine, EFED examined data from a number of monitoring sources, including the states of California and [South] Florida, as well as the Chesapeake Bay Program and the U.S. Geological Survey's National Water-Quality Assessment (NAWQA) Program. Because the first three data sets were designed as ambient monitoring programs, most of their samples were grab samples which were analyzed for many pesticides. Their intent was to document the existence of pesticide in various aquatic environments for as many pesticides as possible. Therefore, most of the monitoring sites were **not** specifically targeted for heavy simazine use. Also, due to the sampling design for most of the monitoring studies, which were not intended to sample frequently, it is likely that peak pesticide concentrations would have been missed, particularly if the associated runoff events were not captured in the sampling. Most sampling programs sample for simazine only and not its degradates, des-ethyl simazine and diaminochlorotriazine (DACT).

Nevertheless, it is worth noting that in several areas some very high concentrations were found, although they appeared to represent a tiny percentage of the monitoring values. While maximum values in many studies were <1.0 ppb, there were also a number of studies with peak concentrations between 4 ppb and 13 ppb. One study in California reported values up to 39 ppb in 1991 (NAWQA), and one peaked as high as 145 ppb in South Florida (1989). These data demonstrate that ambient concentrations are capable of reaching high levels under the proper conditions. However, such concentrations were not in evidence in the compliance and registrant-supported monitoring data collected on finished drinking water data that EFED examined.

Monitoring Data for Community Water Systems using Groundwater and Surface Water

The following databases were available to assess drinking water exposures: 1) the Population-Linked Exposure Database (PLEX) and 2) the Voluntary Monitoring Program/Atrazine Monitoring Program (VMP/AMP).

Compliance Monitoring: Data in the PLEX database were initially collected by Community Water Systems (CWSs) to comply with the monitoring requirements of the Safe Drinking Water

Act (SDWA). The PLEX database consists of SDWA monitoring data obtained by Syngenta from drinking water regulatory agencies in 32 atrazine and simazine use states from 1993 through 2000 and in all 50 states for 2001 to 2003. Syngenta has reported that the 32 states represent 99.9% of simazine and 99.3% of the atrazine use in the United States. A total of 185,459 samples were collected for simazine analysis over the eleven years. Based on the frequency of monitoring (4 samples/year), these data are most suitable for estimating annual average concentrations of simazine plus its 2 chlorinated degradates.

The CWSs with data in the PLEX database include those with ground water, surface water, combination (blend) of ground and surface water sources, and water purchased from another CWS. The preponderance of samples are from ground water CWSs, with just over 5,300 systems using surface water out of nearly 28,000 who analyzed for simazine from1993 through 2000. From 2001 through 2003, just under 3,000 systems out of 18,000+ reporting for simazine used surface water, while over 15,000 were ground water CWSs. Most of the PLEX samples during this period were collected on a quarterly basis with the focus on parent simazine only. The sampling also collected finished water only. Quarterly sampling alone, however, is not sufficiently frequent to adequately capture the variability in simazine concentrations that result from runoff events. Thus, any assessment based solely on quarterly sampling would be considered, at best, a lower bound on any anticipated exposure due to simazine in the water, and residual exposure-based uncertainty is associated with risk assessments based on these monitoring data.

Targeted Monitoring in CWS with High-End Exposures: The VMP-AMP database, which employs more frequent sampling, was constructed entirely by Syngenta Crop Protection Inc., in order to monitor atrazine at selected Community Water Systems that were located primarily on small reservoirs with a history of atrazine use. In addition, most of these systems had shown past exceedences of the atrazine MCL since 1993, entering the VMP program from 1997-8 onward. Both raw water and finished water were collected in the VMP program. The number of samples collected was 709 for finished water and 728 for raw water, totaling 1437. The VMP/AMP database contains drinking water samples from CWS in the following states: IL, IN, IA, KS, KY, LA, MO, OH, TX. These data are suitable for estimating peak, annual average and 90-average concentrations of simazine plus its 2 chlorinated degradates.

The original VMP focused on atrazine detections only. From 2002 to the first quarter of 2003, under the AMP, a portion (49) of community water systems participating in the VMP was selected to be analyzed for simazine, atrazine, and the 3 chlorinated triazine degradates (G-28273, G-28279 and G-30033) residues. Since the VMP-AMP sites were selected on the basis of atrazine use, these sites are representative of simazine primarily to the extent to which simazine use follows atrazine use patterns. Thus, the sites are more likely to be representative of areas where simazine is used on corn and less likely to be representative of simazine use on other crops that occur outside the major atrazine use area, like CA and FL.

The AMP program with selected CWS using surface water in the United States was initiated as a requirement of the “Memorandum of Agreement (MOA) between the U.S. Environmental Protection Agency and the six technical registrants (Syngenta Crop Protection, Inc., Agan Chemical Manufacturing, Dow AgroScience, Drexel Chemical, Oxon Italia S.P.S., and Platte Chemical) Concerning the Registration of Pesticide Products Containing Atrazine.” The targeted CWSs as well as sampling frequency for the monitoring were agreed upon in the MOA, and represented CWSs with previous concentrations exceeding the agreed upon atrazine level. The samples collected were analyzed for simazine, atrazine, and G-28273, G-28279 and G-30033 residues. Both raw and finished water were collected in AMP program.

Both raw and finished water were collected in the 2003 AMP program. The number of samples collected was 466 for raw water and 380 for finished water, totaling 846 samples. The number of CWS that had some samples assessed for simazine was 83. It should be noted for the 2003 AMP that when the atrazine concentration in either the raw or finished water sample was equal to or greater than 3 ppb, the raw and finished water samples were then generally assessed for the presence of atrazine, simazine, G-28273, G-28279, and G-30033.

PDP: The USDA's Pesticide Data Program (PDP) Monitoring Survey was designed to provide information on pesticide concentrations in drinking water samples from CWSs that supply a variety of population segments across the country, both metropolitan and rural. Currently, 5 states are collecting data from a total of 26 sites in the Pilot phase (2001-2003) of the study. Data have become available from the Pilot to date for three states. EFED examined these data from California, Colorado, and New York in an attempt to supplement information from the PLEX and AMP-VMP sources presented above. All of the available simazine drinking water data from the three participating states were at the parts per trillion level. California, whose sites covered three hydrologic regions of the Central Valley, the San Francisco Bay/Delta area, and the Southern Coastal basins, had the highest levels. Samples from all of these areas in 2001 reached 16.7 ppt.

Analysis for CA and FL

Given the high usage on fruits, nuts and citrus, EFED also looked at the PLEX data specifically for California and Florida. In California the PLEX sites appear to cover areas of higher usage fairly well. Concentration data show that for the state of California there were a total of 3,216 annual means (i.e., each annual mean represents one CWS for 1 year). The top five annual means are shown below:

PWSID Number	Community Water Supply Name	Source Type	Year	Annual Mean * (ppb)
CA5810700	Beale Air Force Base	GW	1994	3.000
CA1510701	EDWARDS AFB - MAIN BASE	OTHER	1995	2.000
CA1510702	EDWARDS AFB - AIR FORCE RESEAR	OTHER	1995	2.000
CA1010019	KINGSBURG, CITY OF	GW	1995	1.000
CA1010019	KINGSBURG, CITY OF	GW	1996	1.000

The top five quarterly samples are shown below:

PWSID Number	Community Water Supply Name	Source Type	Year	Max Sample Conc in Annual Mean *
CA5810700	Beale Air Force Base	GW	1994	3.000
CA1510701	EDWARDS AFB - MAIN BASE	OTHER	1995	2.000
CA1510702	EDWARDS AFB - AIR FORCE RESEAR	OTHER	1995	2.000
CA4210700	VANDENBERG AIR FORCE BASE	OTHER	1995	2.000
CA5010028	CERES, CITY OF	GW	2001	1.300

The higher values are from ground water and other sources. Surface water sources did not appear to have high values. None of the annual means exceeded the simazine MCL of 4 ug/L. However, the PLEX database is based on monitoring under the SDWA, which requires at most 4 samples

per year, which is unlikely to capture peak concentrations in intensive use areas in CA and FL. Peak concentrations may influence 90-day average concentrations.

For the state of Florida there were a total of 5,182 annual means. The top five annual means are depicted below:

PWSID Number	Community Water Supply Name	Source Type	Year	Annual Mean * (ppb)
FL6604861	COLEMAN CITY OF	GW	2003	2.000
FL6094948	CITRUS CO UTL/CHARLES A. BLACK	GW	2002	1.518
FL6581591	SARASOTA CO SPECIAL UTIL DIST	SW	2001	1.500
FL6272180	BROOKSVILLE CITY OF	GW	1993	1.000
FL4060573	HALLANDALE, CITY OF	GW	2000	0.500

The top five quarterly samples are shown below:

PWSID Number	Community Water Supply Name	Source Type	Year	Max Sample Conc in Annual Mean *
FL6094948	CITRUS CO UTL/CHARLES A. BLACK	GW	2002	3.000
FL6604861	COLEMAN CITY OF	GW	2003	2.000
FL6581591	SARASOTA CO SPECIAL UTIL DIST	SW	2001	1.500
FL6272180	BROOKSVILLE CITY OF	GW	1993	1.000
FL4060573	HALLANDALE, CITY OF	GW	2000	0.500

Uncertainty in the Monitoring Databases

Given the uncertainties in the monitoring database, the team decided to model surface water concentrations of simazine in CA and FL to represent upper-bounds for exposure assessment using the PRZM/EXAMS model. Because conservative, health-protective models were used to estimate drinking water exposures in CA and FL, the team determined that an additional FQPA safety factor for exposure-based uncertainties would not be applied to drinking water assessments for CA and FL.

Despite the large volume of data in the PLEX database, there are little or no simazine data available for numerous CWSs due primarily to waivers granted by the states. Furthermore, the amount of data available for individual CWSs having data in the PLEX database varies widely from those having data for one or two quarters only of one year to those having four quarters of data for every year for the period of coverage. Therefore, data in the PLEX database may not represent a census or even a randomly sampled subset for the population of CWSs across the 32 to 50 states.

The PLEX database also has negative bias with respect to the sampling frequency of only one sample/quarter/CWS. The infrequent sampling means that the reported annual maximum

simazine concentration in the PLEX for any given CWS in any given year is likely to be substantially less than the actual annual maximum simazine concentration. That is, the infrequent sampling may have 'missed' periods of higher concentrations which would tend to make peak, annual and 90-day averages higher, also.

The more frequent sampling of the VMP-AMP helps to compensate for this fact in those systems where already high PLEX values did deem more frequent monitoring to be necessary, but this assessment was mostly based on high detections of atrazine. For areas where atrazine and simazine uses overlap, i.e., corn-growing areas in the Midwest, the 49 CWS in the VMP-AMP sampling for simazine plus the 2 chlorinated degradates captures simazine usage as well. However, the VMP-AMP does not include CWS located in counties in CA and FL with high use rates on fruit and nut crops.

Exposure Assessment Methodology

Based on a consideration of the available monitoring data, the team decided to look at the 5 regions where simazine is used: 1) the Midwest, 2) the Mid-Atlantic, 3) Washington State, 4) California, and 5) Florida, and used either monitoring data or models to estimate drinking water exposures, as described below.

The following general approach was used as a screening assessment: EFED used monitoring data and models to estimate drinking water exposures to simazine and its 2 chlorinated degradates. Monitoring databases: 1) the Population-Linked Exposure Database (PLEX), and 2) the Voluntary Monitoring Program/Atrazine Monitoring Program (VMP/AMP) were used to estimate peak, 90-day average, and annual average concentrations of simazine and its 2 chlorinated degradates in finished drinking water of specific community water systems in the Midwest, Washington State, and the Mid-Atlantic coastal states. The team decided to use the monitoring data for these regions because although the PLEX database provides at most 4 samples per year, it does provide broad geographic coverage of simazine use areas, and is supplemented by more frequent/intensive monitoring in the Midwest reflected in the VMP/AMP database. In addition, simazine use in the Midwest, Washington (WA) State, and the Mid-Atlantic is considered to be low to moderate.

EFED used the PRZM-EXAMS model to estimate peak, 90-day average and annual average concentrations of simazine in surface water in Florida (FL) and California (CA). As noted, the team concluded that limitations in the monitoring databases for CA and FL and the high to very high usage in those states, precluded use of the monitoring data to assess drinking water exposures for these use areas i.e., simazine use in CA and FL is not well represented in the monitoring databases. The team believes the intensity of simazine use in these 2 states may result in higher concentrations in drinking water from surface water than is reflected in the PLEX database. The VMP/AMP database which includes more frequent monitoring is more likely to capture peak concentrations contains drinking water samples from CWS in the following states: IL, IN, IA, KS, KY, LA, MO, OH, TX. Unfortunately, CA and FL are not included in the VMP/AMP programs.

In addition, EFED considered the USDA's Pesticide Database Program (PDP) for drinking water monitoring and the USGS National Water Quality Assessment Program (NAWQA), as well as state monitoring data from California and Florida to characterize results of their assessments using both models and monitoring data.

The concentration estimates for peak, 90-day and annual average concentrations based on modeling assessments for CA and FL, or monitoring data from PLEX and the VMP/AMP for specific community water systems (CWS) in the Midwest were compared to Drinking Water levels of Comparison (DWLOCs) for various population subgroups. For CWS in the Midwest, DWLOCs were used to identify individual CWS with concentrations of simazine plus its 2 chlorinated degradates exceeding a level of concern. For those CWS identified with levels of concern under the screen, drinking water monitoring data from the CWS were used in Lifeline to provide a more refined risk assessment. For CA and FL, model estimates of concentrations of simazine plus its 2 chlorinated degradates were compared to DWLOCs without further refinement. (See Section 7.0 Aggregate Assessments for Lifeline™ results.)

Drinking Water levels of Comparison (DWLOCs):

DWLOCs are based on 100% of the aPAD or cPAD, because food exposures have been estimated to be zero.

DWLOCs for acute drinking water exposures assessments using monitoring data incorporate a 300-fold safety factor as described earlier in this document (Section 4.5) to account for inter- and intra-species variations, and a 3X FQPA safety factor for exposure-based residual uncertainties. DWLOCs for chronic drinking water exposure assessments using monitoring data incorporate a 1000-fold safety factor described earlier to account for inter- and intra-species variations, and a 10X FQPA safety factor for exposure-based and hazard-based residual uncertainties.

Acute DWLOC (for females 13-49 only) for comparison against maximum water concentration based on monitoring = 3000 ppb

Chronic DWLOCs for comparison against 90-day and annual average concentrations based on monitoring data:

Infants and children (< 1 year old) = 12.5 ppb

Toddlers (children 1 -= 23 ppb

Children (7 - 12 years old) = 53 ppb

Females (13 - 50 years old) = 60 ppb

General Population = 68 ppb

When models were used to estimate drinking water exposures, acute DWLOCs incorporate a 100-fold safety factor to account for inter- and intra-species variations. Chronic DWLOCs incorporate a 300-fold safety factor to account for inter- and intra-species variations, and a 3X for hazard-based residual uncertainties. The 3X FQPA safety factor for exposure-based residual uncertainties has been reduced to 1X because the models used to estimate drinking water exposures are conservative, protective, and provide an upper bound on concentrations of simazine and its degradates in surface water.

Acute DWLOC (for females 13-49 only) for comparison against maximum water concentration based on models = 9000 ppb

Chronic DWLOCs for comparison against 90-day and annual average concentrations based on models:

Infants and children = 37.5 ppb

Toddlers (1 - 6 years old) = 69 ppb

Children (7 - 12 years old) = 159 ppb
Females (13 to 50 years old) = 180 ppb
General Population = 204 ppb

Estimation of Concentrations of simazine plus 2-chlorinated metabolites: Only parent simazine residues were measured in the PLEX database, while the VMP-AMP provided measured residue values for simazine, atrazine, G-28273, G-28279 and G-30033. DWLOCs, as noted above, are expressed in terms of the sum of simazine and its two chloro- metabolites (G-28273 and G-28279). Since the registrant did not provide any evidence from kinetic studies to estimate the relationship between the residue values of parent simazine and the two chloro- metabolites of interest, EFED followed the practice employed in the atrazine drinking water assessment and used regression analysis to explore a predictive relationship between the two sets of measured values.

For the atrazine risk assessment, EFED developed linear regression equations to estimate the concentration of atrazine's chlorinated metabolites relative to the parent compound (atrazine). Monitoring data on the chlorinated metabolites of atrazine (two of which are common between atrazine and simazine) were sampled in finished drinking water from a subset of 17 CWS included in the VMP/AMP from August 1997 to July 1998. Samples were collected monthly from August through April and biweekly in May, June, and July, and analyzed for atrazine, des-ethyl chlorinated triazine (common to simazine and atrazine) des-isopropyl chlorinated triazine, and diaminochlorotriazine or DACT (common to simazine and atrazine). Ratios of the chlorinated metabolites to atrazine were used to develop a linear relationship. This relationship was then used to estimate concentrations of chlorinated metabolites in other CWS.

With the monitoring data available from approximately 50 systems, primarily in the Midwest, EFED derived a simple linear regression equation to estimate the relationship between the sum of parent plus two chloro- metabolites and levels of parent alone. Based on a total of 2,349 monitoring data points and using the linear regression routine found in the standard EXCEL software program, the equation is given below:

$$\sum(\text{simazine} + \text{G28273} + \text{G28279}) = 0.364 + 1.378 * (\text{simazine})$$

Regression summary statistics are included in the Appendix. This simple equation was used to convert the simazine residue values from the large PLEX database to the sum of simazine and its two chloro metabolites, or to back-calculate from 'total' levels to parent simazine, as needed.

EFED believes that the simple methodology employed above results in estimated concentrations of simazine and its chloro-degradates that are greater than would actually be found in monitoring the parent and both degradates in those sites. Several factors contribute to making the above results more protective than a refinement would provide. First, the residues of G-28273 (2,4-Diamino-6-s-triazine) and G-28279 (2-Amino-4-chloro-6-ethylamino-s-triazine) can be contributed from either simazine or atrazine applications. Since there was no way to distinguish the source of these two metabolites in the database, the sum of simazine and these two chloro-metabolite residue values was regressed against monitored simazine values in the above equation. With atrazine levels being much higher than simazine levels in most of the CWSs in the VMP-AMP, however, it is probably more likely that levels of the degradates were contributed in higher amount by atrazine. This would overestimate levels of TCTs predicted to result from simazine application alone.

Additionally, relationships between parent and degradate chemicals more likely follow one or more functions of a nonlinear nature. It is not entirely clear how a linear expression would differ from the overall outcome of these true relationships; however, such an analysis is beyond the scope of the current assessment.

Finally, unlike the atrazine assessment, the above analysis was carried out using raw and finished water together, and did not sort the data by year or by season. Although performing the analysis separately for each group might provide estimates that are more uniform, especially for finished water or for a particular season, the potential increase in precision is not expected to be significant when compared with the unknown effect of atrazine's contribution to total chloro-triazine levels attributed in this database to simazine alone.

Analyses of Compliance Monitoring (PLEX) Data

The PLEX database contains concentration estimates for simazine and its 2 chlorinated degradates for approximately 23,000 CWS reporting for 1993 to 2000 and 18,000 CWS reporting from 2001 to 2003. The maximum concentration reported for any CWS was 18 ppb for simazine alone and ~25 ppb for simazine plus the 2 chlorinated degradates. The maximum annual average concentration reported for any CWS was ~5 ppb for simazine alone, and 7.2 ppb for simazine plus the 2 chlorinated degradates.

This maximum concentration (25 ppb) was compared against the acute DWLOC simazine of 3000 ppb for females 13+ years old; all maximum concentrations of simazine and the 2 chlorinated degradates are less than the acute DWLOC. Therefore, there is no exceedence of the acute DWLOC for females 13+ years of age of any of the185,459 monitoring data points collected on finished drinking water in the PLEX database. Similarly, the maximum annual mean value was compared against chronic DWLOCs (the lowest which is 12.5 ppb for infants < 1 year old); all annual average concentrations of simazine and the 2 chlorinated degradates are less than the lowest chronic DWLOC.

Because of the monitoring requirements of the SDWA, the sampling reported for the PLEX was on a quarterly basis only. Therefore, a single sample from PLEX is often all that is available to represent its average for the quarter or 90-day period. Based on this data, no average level for the quarter containing the reported PLEX maximum sample could be higher than the reported value itself. Therefore, these quarterly maximum values were compared against the 90-day DWLOC of 12.5 ppb, and two CWS in PLEX were found to exceed.

The 2 CWS with potential exceedences based on estimates of 90-day average concentrations are:

1) The Defiance City CWS of OHIO, serving 17,000 people, had a maximum quarterly concentration of 12.4 ppb simazine/17.5 ppb simazine + 2-chlorinated degradates in 2001, which exceeds the chronic DWLOC for infants and children.

2) The Hillsboro CWS of Illinois, serving 4,400, had a maximum quarterly concentration of 18.0 ppb simazine/25.2 ppb simazine + 2-chlorinated degradates in1994, which also exceeds the chronic DWLOC for infants and children, and toddlers. [The team notes that the Hillsboro CWS may no longer be a source of drinking water.]

Both CWS are served by surface water. Both were identified for refined analysis using Lifeline™. For the State of Washington, where PLEX coverage is moderate and areas can be high in

simazine use, an examination of the 126 entries showed all samples at 0.07 ppb or lower. No CWS exceeded HED's levels of concern. For the Mid-Atlantic states, no CWS exceeded HED's level of concern.

Analyses of VMP-AMP Data

Both the VMP and the AMP are part of monitoring data requirements for atrazine reregistration. Some of the CWSs have participated in both monitoring programs. The simazine monitoring effort was added to the original plan to provide additional residue data for simazine. Both of these two monitoring efforts now include metabolite analyses for both finished water and raw water. The maximum concentration from CWS analyzing for simazine plus the 2 chlorinated degradates in the VMP/AMP was 16.56 ppb for simazine plus the 2 chlorinated degradates. The maximum 90-day average was 5.6 ppb.

Since the purpose of these monitoring programs is to identify any DWLOC exceedence, the lowest chronic DWLOC value of 12.5 ppb has been used for the screening. If the individual residue value is less than this screening level, then the 90-day average associated with that value is also expected to be less than this level. Among all 2,349 samples analyzed for simazine plus the 2 chlorinated degradates in the VMP and AMP, there is only one sample with a residue value greater than 12.5 ppb. The raw water sample taken on May 27, 2003 from Nashville Water Plant in Illinois (pop. 3,200) has a residue value of 16.56 ppb. The other reported residue values for this CWS for the same year are listed below:

Program	Year of Program	PWSID	Type of Water ® or F)	Date Sampled	Measured Simazine	Measured SIM+2Degs
VMP	2003 1Q	IL1890300	R	Jan-13-2003	0.38	1.54
VMP	2003 1Q	IL1890300	R	Feb-10-2003	0.28	1.39
VMP	2003 1Q	IL1890300	R	Mar-10-2003	0.27	1.08
AMP	2003 2Q-4Q	IL1890300	R	May-19-2003	0.61	2.51
AMP	2003 2Q-4Q	IL1890300	R	May-27-2003	14.94	16.56
AMP	2003 2Q-4Q	IL1890300	R	Jun-02-2003	0.49	2.21
AMP	2003 2Q-4Q	IL1890300	R	Jun-23-2003	0.18	5.01
VMP	2003 1Q	IL1890300	F	Jan-13-2003	0.05	0.15
VMP	2003 1Q	IL1890300	F	Feb-10-2003	0.05	0.15
VMP	2003 1Q	IL1890300	F	Mar-10-2003	0.05	0.15
AMP	2003 2Q-4Q	IL1890300	F	May-27-2003	0.05	0.15
AMP	2003 2Q-4Q	IL1890300	F	Jun-02-2003	0.05	0.15
AMP	2003 2Q-4Q	IL1890300	F	Jun-23-2003	0.05	0.15

R = raw water, F = finished water

The highest time-weighted 90-day moving average based on seven raw water samples from this CWS is 5.63 ppb, which is less than the screening value of 12.5 ppb. Therefore, there is no exceedence of any DWLOC based on VMP-AMP monitoring results. Note all finished drinking water samples are < 12.5 ppb.

Rural Wells

The coverage of PLEX sites in Florida may suggest a higher reliance on private wells for drinking water in many areas of the state. EFED examined data for simazine, summarized graphically in

the appendix, from the Rural Well Survey (RWS) that was submitted during atrazine's reregistration process.

In Syngenta's Rural Well Survey that was conducted from September 1992 to March 1995, one sample was collected from each participating well in 7 states and analyzed for simazine and various chloro-triazine and hydroxytriazine degradates. The maximum, 99th percentile, and 95th percentile simazine concentrations are plotted in the appendix, showing that concentrations from this sample of 402 wells ranged up to 11 ppb parent simazine. However, because only one sample was collected per well in this Survey, the reported maximum simazine concentration in the Survey may be substantially less than the actual peak concentration for that well or others during a given year or period.

As was the case for atrazine, degradate concentrations in this groundwater population are likely to be even higher. Also as with atrazine, the question of simazine concentration levels for rural wells remains an uncertainty, and additional data should be furnished.

Modeling

Because of many of the elements mentioned above that contributed to the uncertainty of an assessment in CA, GA, and FL based solely on monitoring data that may be infrequent or sparse in those areas where simazine use is most intensive in those states, EFED attempted to provide an higher-end (upper bound) estimate of potential simazine concentrations in drinking water by performing some limited modeling. Drinking water modeling estimates were derived for citrus, fruit and nut areas in California and for a citrus scenario in Florida.

For these scenarios in which models were used to estimate environmental concentrations, HED used a DWLOC of 9000 ppb for adult females to compare against peak values, and a DWLOC of 37.5 ppb for infants (the lowest chronic DWLOC) to compare against the 90-day and annual average concentration estimates from PRZM/EXAMS. The team believes that where models are used to estimate drinking water exposures, they are conservative and protective, and the additional 3X safety factor to account for exposure-based uncertainties is not warranted.

The modeling estimations representing upper bound estimations of drinking water concentrations are based on EFED's PRZM/EXAMS models with the Index Reservoir (IR) environments. The regional percent crop area (PCA) values of 0.56 and 0.38 are respectively for California and Florida, and 0.87 for Georgia. The modeling effort includes aerial application and ground application. A single application of 4.0 lbs. ai/A was assumed for all aerial application scenarios modeled for California. A single 0.89 lb ai/acre application (based on banded treatment at a 2 lb ai/acre rate) was modeled for all CA ground application scenarios. A single application of 4.0 lbs. ai/A was assumed for all aerial and ground application scenarios modeled for Georgia (GA). A single 9.6 lbs. ai/A was run for aerial and ground applications for Florida citrus. A separate assessment at 4.0 lb ai/acre for other nuts grown in Hawaii (HI), filberts and macadamia, was run using a CA almond scenario.

The results are presented below.

Estimated Environmental Concentrations (EECs) for Simazine/Simazine + 2 Chloros				
Scenario	peak*	90-day average*	annual average*	yearly average
CA- Almond (Aerial) PCA (0.56) @ 4 lb ai/A	66.6/92	**57.1/79**	37.4/51.9	20.2/28
CA - Almond (Ground) PCA (0.56) Banded @ 2 lb ai/A	13/18	**11/15.5**	6.9/9.9	3.0/4.5
CA - Fruit (Aerial) PCA (0.56) @ 4 lb ai/A	27.9/38.8	**24.6/34.2**	16.8/23.5	14/19.6
CA - Fruit (Ground) PCA (0.56) Banded @ 2 lb ai/A	6.7/9.6	**5.0/7.2**	3.6/5.3	2.4/3.7
CA - Citrus (Aerial) PCA (0.56) @ 4 lb ai/A	26.2/36.4	**23.9/33.3**	16.6/23.2	14.4/20.2
CA - Citrus (Ground) PCA (0.38) @ 4 lb ai/A	12/17	**11/15.5**	7.8/11	6/8.6
FL- Citrus (Aerial) PCA (0.38) @ 9.6 lb ai/A	150/207	**98/135**	38.3/53	21.7/30
FL- Citrus (Ground) PCA (0.38) @ 9.6 lb ai/A	146/200	**96/132**	36/50	18.7/26
GA- Pecans/Nuts (Aerial) PCA (0.87) @ 4 lb ai/A	151/207	**96/132**	41/56.8	18/25
GA- Peach (Aerial) PCA (0.87) @ 4 lb ai/A	101/139.5	**83/114.7**	46/63.8	22/30.7
GA- Pecans/Nuts (Ground) PCA (0.87) @ 4 lb ai/A	146/200	**93/128.5**	40/55.5	16/22.4
GA- Peach (Ground) PCA (0.87) @ 4 lb ai/A	87/120.2	**72/99.6**	40/55.5	15/21
CA- Nuts (Aerial) PCA 0.56) @ 4 lb ai/A (Macadamia/Filbert)	67/92	**57/78**	37/51.3	20/28
CA- Nuts (Ground) PCA 0.56) @ 4 lb ai/A (Macadamia/Filbert)	56/77.5	**48/66.6**	31/43.3	13/18
* 1-in-10 year estimates.				

Comparing the 90-day average concentrations for simazine residues to a DWLOC of 37.5 ppb, several scenarios exceed levels of concern: CA almonds (aerial applications only) and FL citrus

(aerial and ground applications), GA fruit and nut (aerial and ground applications), and HI macadamia and filbert nuts. As the table shows, results for simazine only the 1-in-10 yr. 90-day values range as high as about 98 ppb in Florida citrus to about 57 ppb in California almonds, with peak values in almonds ranging to over 66 ppb. Other scenarios are lower. For lower (or higher) application rates, the estimates will be proportionately lower or higher, all other parameters remaining equal. Estimates for simazine plus the 2 chlorinated degradates are provided in the table also.

These results can be compared to the maximum peak concentration of 25 ppb and the maximum annual average concentration of 6 to 7 ppb found in the monitoring databases on finished drinking water. However, the team notes that CA and FL have the most intensive usage of simazine and the existing monitoring databases are not likely to capture seasonal pulses simazine residues in surface water affected by runoff in these areas More intensive surface water monitoring in high use areas of CA and FL would help to alleviate some of the uncertainty and discrepancies between the model estimates and monitoring data.

6.3 Residential (Non-Occupational) Exposure/ Risk Pathway

The information included in this section was extracted from DP Barcode D316475 (SIMAZINE: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document).

Simazine is labeled for residential use to control weeds in lawns and professional application to recreational turf and lawns. It is also labeled for use in fish aquariums, ornamental ponds, and fountains. Homeowners who apply simazine may be exposed for short-term durations via the dermal and inhalation routes. In addition, postapplication dermal exposure for adults and dermal and incidental oral exposures for children contacting treated turf can occur. Residential exposure durations are expected to be short-term (up to 30 days) based upon endpoints extracted from the atrazine HIARC report. Intermediate term exposures (1 to 6 months) are not expected from residential sources of simazine based upon anticipated use patterns.

6.3.1 Home Uses

Simazine exposure by residential handlers and from postapplication activities may occur.

Handlers

The following residential handler scenarios were assessed for simazine:

- Loading/ Applying Granules via Push Type Spreader (based on ORETF data)
- Loading/ Applying Granules via Belly Grinder (based on PHED data)
- Applying Ready to Use Tablet Formulations (no data)
- Applying Ready-to-Use Formulation via Pouring (based on PHED data)

One of the four residential handler scenarios have short-term risks of concern - risks from loading and applying the granular formulation by belly grinder to one-half acre of lawn are a concern (i.e. MOEs are less than 300) with a dermal MOE of 76 and combined dermal + inhalation MOE of 75. The MOEs estimated for the other scenarios ranged from 660 to 33,000. HED has no data to assess applying ready to use tablet formulations to fish aquariums, ornamental ponds, and

fountains. However, the dermal and inhalation exposures are likely to be lower than direct pouring liquid formulations into fish aquariums, ornamental ponds, and fountains. Table 6.3.1.1 presents the estimated residential short-term risks associated with the handling of simazine.

Table 6.3.1.1. Summary of Short-term Residential Handler Non-Cancer Risks						
Exposure Scenario	Crop or Target	Application Rate	Area Treated Daily	Short-term MOEs		
				Dermal	Inhalation	Dermal + Inhalation
Mixer/Loader/Applicator						
Loading/ Applying Granulars via Push Type Spreader (ORETF data)	turf	1.75 lb ai/acre	0.5 acres	12,000	570,000	12,000
Loading/ Applying Granulars via Belly Grinder	turf	1.75 lb ai/acre	0.5 acres	**76**	8,100	**75**
Applying Ready-to-Use Tablet Formulations (no data)	fish aquariums, ornamental ponds, fountains	0.0000068 lb ai/gallon	10,000 gallons	No Data	No Data	No Data
Applying Ready-to-Use Liquid Formulations by Direct Pouring (using PHED liquid mixer/loader data)	fish aquariums, ornamental ponds, fountains	0.0000075 lb ai/gallon	10,000 gallons	34,000	4,900,000	33,000

Postapplication

HED uses the term “postapplication” to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. Simazine can be used in many areas that can be frequented by the general population including residential areas (e.g., home lawns). As a result, individuals can be exposed by entering these areas if they have been previously treated. Postapplication risk scenarios assessed for simazine are as follows:

Adult -

- High Contact Activities on Turfgrass
- Mowing
- Golfing

Youth -

- Golfing

Toddler -

- Residential Turf (High Contact Activities)
- Hand-to-Mouth Activity on Turf
- Object-to-Mouth Activity on Turf
- Incidental Soil Ingestion

Dermal: The residential postapplication exposure and risk assessment indicates, that for postapplication dermal exposures, all scenarios for adults, youths, and toddlers are **not a concern** when atrazine- or simazine-specific TTR data are used. If the default assumption that 5% of the application rate is available for transfer is used instead of the TTR data, then the risks are a concern (i.e. MOEs are less than 300) for high contact lawn activities to adults and toddlers for both granular and spray applications. However, HED believes that the TTR data is more appropriate than default assumptions for this assessment. Adult, youth, and toddler risk estimates for dermal postapplication exposure to simazine are presented in Tables 6.3.1.2, 6.3.1.3, and 6.3.1.4/ 6.3.1.5, respectively.

Oral: The residential postapplication exposure and risk assessment indicates that postapplication incidental oral exposures to toddlers are not a concern for hand-to-mouth transfer of residues, based on atrazine hand press data. If the default assumption that 5% of the application rate is available for transfer is used instead of hand-press data, then the risks are of concern (i.e. MOEs are less than 300). However, HED believes that the hand-press data is more appropriate than default assumptions for this assessment.

Episodic oral ingestion of granular pellets is typically estimated when an acute oral endpoint of concern has been identified. For acute oral exposure, a developmental NOAEL of 30 mg/ kg/ day for females 13 to 49 years old was identified, but would not be applicable to toddler ingestion. No acute endpoint of concern was identified for toddlers, therefore, acute risk for episodic oral ingestion of granular pellets was not estimated.

The risks for incidental ingestion of soil and from object-to-mouth activity on turf were **not of concern.**

6.3.2 Recreational Uses

Risk estimated for golfers on day 0 were **not of concern**. Adult and youth residential risk estimates for golfing are presented in Tables 6.3.1.2 and 6.3.1.3, respectively.

6.3.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for simazine. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

Table 6.3.1.2: Adult Residential Risk Estimates for Postapplication Dermal Exposure to Simazine on Dermal Exposure to Simazine

Exposure Scenario	Formulation	Application Rate (lb ai/acre)	MOE at Day 0								
			Using Atrazine Granular Turf Application Data (MRID 449588-01) Study Application Rate: 2 lb ai/acre				Using Simazine Liquid Turf Application Data (MRID 449587-01) Study Application Rate: 2 lb ai/acre				Using default assumptions
			GA TTR		FL TTR		CA TTR		FL TTR		
			Non-irrigated	Irrigated	Non-irrigated	Irrigated	Non-irrigated	Irrigated	Non-irrigated	Irrigated	
Residential Turf (High Contact Activities)	Granular	1.8	4,800	3,800	1,300	24,000	NA	NA	NA	NA	250
	Liquid	2.0	NA	NA	NA	NA	930	2,800	790	1,400	220
Residential Turf (Mowing)	Granular	1.8	140,000	110,000	38,000	690,000	NA	NA	NA	NA	7,400
	Liquid	2.0	NA	NA	NA	NA	27,000	82,000	23,000	42,000	6,500
Golfer	Liquid	2.0	NA	NA	NA	NA	14,000	41,000	1,100	21,000	3,300

Table 6.3.1.3: Youth Residential Risk Estimates for Postapplication Dermal Exposure to Simazine

Exposure Scenario	Formulation	Application Rate (lb ai/acre)	MOE at Day 0				
			Using Simazine Liquid Turf Application Data (MRID 449587-01) Study Application Rate: 2 lb ai/acre				Using default assumptions
			CA TTR		FL TTR		
			Non-irrigated	Irrigated	Non-irrigated	Irrigated	
Outdoors							
Golfer	Liquid	2.0	7,500	23,000	6,400	12,000	1,800

Table 6.3.1.4: Toddler Residential Risk Estimates for Dermal Postapplication Exposure to Simazine											
Exposure Scenario	Formulation	Application Rate (lb ai/acre)	MOE at Day 0								
			Using Atrazine Granular Turf Application Data (MRID 449588-01) Study Application Rate: 2 lb ai/acre				Using Simazine Liquid Turf Application Data (MRID 449587-01) Study Application Rate: 2 lb ai/acre				Using default assumptions
			GA TTR		FL TTR		CA TTR		FL TTR		
			Non-irrigated	Irrigated	Non-irrigated	Irrigated	Non-irrigated	Irrigated	Non-irrigated	Irrigated	
Outdoors											
Residential Turf (High Contact Activities)	Granular	1.8	2,900	2,200	770	14,000	NA	NA	NA	NA	**150**
	Liquid	2.0	NA	NA	NA	NA	560	1,700	470	860	**130**

Table 6.3.1.5: Toddler Residential Risk Estimates for Incidental Oral Postapplication Exposure to Simazine			
Exposure Scenario	Formulation	Application Rate (lb ai/acre)	MOE at Day 0
Hand to Mouth Activity on Turf	Granular	1.8	230* / 1,100**
	Spray	2.0	210* / 950**
Object to Mouth Activity on Turf	Granular	1.8	930
	Spray	2.0	840
Incidental Soil Ingestion	Granular	1.8	69,000
	Spray	2.0	62,000

* Using 5% default for TTR.

** Using 1.1% TTR from atrazine hand press study.

7.0 Aggregate risk Assessments and Risk Characterization

Simazine has agricultural uses that result in exposures to humans through their diet and drinking water; it also has residential uses on turf that result in dermal and inhalation exposures to adults from handling home use products formulated with simazine, and postapplication dermal exposures to adults and children through recreational activities such as golfing and playing on lawns. All residential exposures are expected to be short-term in duration.

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

The team aggregated residential exposures for those scenarios with risk estimates below HED's levels of concern together with dietary (food and water) exposures. Residential exposure scenarios with risk estimates above HED's levels of concern will not be aggregated with food and water exposures. All food-related exposures have been estimated to be zero. Aggregate risk estimates are driven by either drinking water or residential exposures.

7.1 Acute Aggregate

The acute aggregate risk estimate is based on aggregated food and water exposures. Based on monitoring data from the PDP, field trials and the FDA acute dietary exposures (food-based) at the 99.9th percentile were estimated to be zero for females 13+ years of age.

For populations affected by simazine uses in the Midwest, Mid-Atlantic states and WA State, drinking water monitoring data were used estimate acute aggregate risks. The acute DWLOC of 3000 ppb for females 13+ years of age was compared to the estimated maximum concentrations of simazine and its 2 chlorinated degradates for each CWS sampled for simazine in the PLEX and VMP/AMP databases. No CWS out of 23,000 sampled from 1993 to 2000 across 32 states and 18,000 sampled from 2001 to 2003 across 50 states had a maximum concentration exceeding 25 ppb, and therefore no CWS exceeds HED's level of concern for acute aggregate exposures and risks.

For CA and FL, models were used to estimate acute aggregate risk. The maximum concentration of simazine plus its 2 chlorinated degradates modeled by PRZM/EXAMS was 200 ppb for the FL citrus scenario. This estimate was compared to the acute DWLOC of 9000 ppb for females 13+ years of age. Model estimates for CA and FL do not exceed the acute DWLOC.

Aggregate acute exposures to simazine and its 2 chlorinated degradates do not exceed HED's level of concern.

7.2 Short-term Aggregate Risk

Short-term residential dermal and inhalation exposures were aggregated with chronic dietary exposures for handlers. Dermal postapplication exposures for adults and dermal and incidental oral exposures for children were aggregated with chronic dietary exposures based on common toxic endpoints for neuroendocrine effects. The short-term aggregate risk assessment considers residential turf uses of simazine in FL as the most conservative residential exposure scenario. It also considers estimated water concentrations from models which is also considered conservative and protective. The target Margin of Exposure (MOE) for residential exposures is 300. The target MOE for chronic dietary exposures based on model estimates is also 300. Because the MOEs for short-term residential exposure and chronic dietary exposures is the same, the 1/MOE method was used to aggregate short-term exposures and estimate risks.

Residential handler exposures were estimated through the use of PHED. For postapplication scenarios, simazine-specific turf transferable residue data (TTR) were used to estimate dermal exposures for adults and youths and children from turf studies conducted in FL rather than default assumptions from HED's Residential SOPs. Use of the FL TTR data resulted in the most conservative risk estimates based on chemical-specific data. Atrazine-specific TTR data were used to estimate incidental oral (hand-to-mouth) exposures for children rather than default assumptions from HED's Residential SOPs. Although the atrazine data are surrogate for simazine-specific data they are considered more refined than the default assumptions.

Because exposures from residential turf uses of simazine in the Southeast (FL) were used to estimate residential exposures, the team compared model estimates for drinking water concentrations for FL citrus to short-term DWLOCs.

Table 7.2.1 shows short-term aggregate risk calculations for adult handlers based on females with a 60 kg body weight. The short-term DWLOCs for adult females (600 ppb) exceed the model estimates of annual average concentrations (21 to 53 ppb) and 90-day average concentrations (40 to 135 ppb) of simazine and its 2 chlorinated degradates in water for a FL citrus scenario for all scenarios except that involving belly-grinder application. The short-term DWLOC for handlers using a belly-grinder is zero. Model estimates for the FL water scenario are greater than zero. Risk estimates for residential risks associated with belly-grinders alone exceed HED's level of concern. Risk estimates for handlers using a push-type spreader and ready-to-pour formulations do not exceed levels of concern.

Table 7.2.1 Short-term Aggregate Risk Estimates for Adult Handlers:

Exposure Scenario	Dietary Dose (mg/kg/day)	Dermal MOE	Inhalation MOE	Combined Dermal + inhalation MOE	Average EDWC (ppb)	Short-term DWLOC (ppb)
Applying Granulars w/Push-type spreader	0.00	12,000	570,000	12,000	53/135	600
Applying Granulars w/Belly-Grinder	0.00	76	8100	75	53/135	zero

Table 7.2.1 Short-term Aggregate Risk Estimates for Adult Handlers:						
Exposure Scenario	Dietary Dose (mg/kg/day)	Dermal MOE	Inhalation MOE	Combined Dermal + inhalation MOE	Average EDWC (ppb)	Short-term DWLOC (ppb)
Direct pour, Ready-to-use liquid formulas	0.00	34,000	4,900,000	33,000	53/135	620

Table 7.2.2 shows short-term aggregate risk calculations for post-application exposures for adults (males and females) and youths based on males @ 70 kg and females and youths @ 60 kg body weights. The short-term DWLOCs for adult males, females and youths exceed the model estimates of annual average concentrations (21 to 53 ppb) and 90-day average concentrations (40 to 135 ppb) of simazine and its 2 chlorinated degradates in water for a FL citrus scenario for all exposure scenarios. Risk estimates for aggregate short-term residential postapplication exposures for adults and youths do not exceed HED's level of concern. In addition, HED aggregated short-term dermal and inhalation exposures for adults handling simazine turf products while applying them with post-application dermal exposures for adults for the highest contact activity (playing on turf). The resulting short-term DWLOC for these combined exposures is 335 ppb, which is greater than all estimates for average concentrations of simazine residues in surface and ground water. Combined short-term adult exposures to simazine do not exceed HED's level of concern.

Table 7.2.2 Short-term Aggregate Risk Estimates for Post-application Exposures of Adults and Youths:				
Exposure Scenario	Dietary Dose (mg/kg/day)	Dermal MOE	Average EDWC (ppb)	short-term DWLOC (ppb)
Turf - Granular (High contact Activity)	0.00	1100 - 1300	53/135	455 - 560
Turf - Liquid (High contact Activity)	0.00	680 - 790	53/135	349 - 452
Turf - Granular (Mowing)	0.00	32,000 - 38,000	53/135	619 - 723
Turf - Liquid (Mowing)	0.00	20,000 - 23,000	53/135	615 - 719
Golfer	0.00	6400	53/135	595

Table 7.2.3 shows short-term aggregate risk calculations for post-application exposures for children based on a 15 kg body weight. Risk estimates of combined incidental oral and dermal exposures are marginal. When these exposures are added to dietary exposures from drinking water, the short-term DWLOCs for children are zero for liquid formulations applied to turf and 2 ppb for granular formulations applied to turf. As noted above, model estimates of annual average concentrations (21 to 53 ppb) and 90-day average concentrations (40 to 135 ppb) of simazine and its 2 chlorinated degradates in water for a FL citrus scenario are all greater than zero and 2 ppb. Short-term aggregate residential risk estimates for postapplication exposures of toddlers on turf exceed HED's level of concern for both granular and liquid formulations of simazine applied to residential turf.

Table 7.2.3 Short-term Aggregate Risk Estimates for Post-application Exposures of Children:						
Exposure Scenario	Dietary Dose (mg/kg/day)	Dermal MOE	Combined Incidental Oral MOE	Combined Dermal + Oral MOE	Average EDWC (ppb)	Short-term DWLOC (ppb)
Turf - Granular (High contact Activity)	0.00	770	500	303	53/135	2.0
Turf - Liquid (High contact Activity)	0.00	470	440	227	53/135	zero

7.3 Intermediate-term and Chronic Aggregate Risk

Based on monitoring data from the PDP, field trials and the FDA average chronic dietary exposures (food-based) were estimated to be zero for all subpopulations.

Neither intermediate-term nor chronic residential exposures are anticipated for simazine based on existing use patterns. However, chronic food exposures (0% of cPAD) were aggregated with estimates of intermediate-term (90-day average) and chronic (annual average) drinking water exposures for simazine and its 2 chlorinated degradates for each CWS sampled for simazine using the DWLOC method.

For CA, GA, and FL annual average and 90-day average concentrations from PRZM/EXAMS exceed DWLOCs of 37.5 ppb for almond uses (aerial application only) in CA, fruit and nut uses (aerial and ground applications) in GA, and citrus uses (aerial and ground applications) in FL. Aggregate intermediate-term and chronic risks exceed HED's level of concern for these two uses of simazine.

For populations affected by simazine uses in the Midwest, Mid-Atlantic states and WA State, drinking water monitoring data were used estimate intermediate-term and chronic aggregate risks. The lowest DWLOC calculated for simazine and its 2 chlorinated degradates is for infants < 1 year old and is 12.5 ppb. No CWS in the PLEX and VMP/AMP databases had annual average concentrations of simazine plus its 2 chlorinated degradates greater than 12.5 ppb. The maximum annual average concentration for CWS reporting from PLEX for simazine plus the chlorinated degradates was ~7 ppb. Aggregate chronic exposures to simazine and its 2 chlorinated degradates do not exceed HED's level of concern.

For 90-day exposures in the Midwest, Mid-Atlantic states and WA State based on 49 CWS in the VMP/AMP representative of Midwest corn use, two CWS were identified in the Midwest with estimated 90-day drinking water exposures exceeding 12.5 ppb based on a DWLOC screen. The Lifeline™ model was then used to refine risk estimates for the mos sensitive subpopulation, infants < 1 year old, from exposures to simazine and the chlorinated degradates in drinking water for the 2 CWS identified as having a potential to exceed drinking water levels of concern for 90-day average exposures. At the 99.9th percentile of exposure, both CWS exceed HED's level of concern for aggregate intermediate-term exposures to simazine and its 2 chlorinated degradates. The details of the Lifeline™ assessment for these 2 CWS can be found in Appendix 3.0.

The team concluded that the 49 CWS were representative of CWS in WA State, the Midwest, and the Mid-Atlantic states with low to moderate simazine usage.

Results of the Lifeline™ assessment are provided below.

Table 7.3.1. Intermediate-term (90-day) Exposure and Risk Estimates for infants < 1 year old using Lifeline (mg ai/kg bwt/day).

Percent of Population	Definace City, OH DW Conc=17.5 ppb	Hillsborro, Il DW Conc=25.2 ppb
10%	0.00034	0.00049
20%	0.00041	0.00059
30%	0.00091	0.00138
40%	0.00107	0.00153
50%	0.00113	0.00163
60%	0.00118	0.00169
70%	0.00122	0.00176
80%	0.00127	**0.00183**
90%	0.00135	0.00194
99%	0.00161	0.00224
99.9%	**0.00187 (104% cPAD)**	0.00276 **(153% cPAD)**
100%	0.00190	0.00336
Population Average	**0.00096 (53% of cPAD)**	**0.00140 (78% of cPAD)**

Estimated Chronic Exposure for Infants in the Midwest (Spring)
Lifeline simulations were conducted using a single value for the drinking water concentration during the spring season. The Lifeline model was used since it is capable of providing estimated average daily exposure over a 90 day exposure duration (Spring). Table 1 presents the chronic exposure to Infants during the spring season in the Midwest when drinking water concentrations were set at 17.5 ppb and 25.2 ppb, respectively. These water concentrations were used as point estimates in the assessment, that is, every day during the 90-day (Spring) period, individuals regardless of subpopulation received 17.5 ppb at the CWS in Defiance City, OH and 25.2 ppb at the CWS in Hillsboro, IL. [Note: HED believes the CWS at Hillsboro, IL is no longer a drinking water source.]

The estimates for Infants are provided and discussed in detail here since Infants have the highest drinking water consumption rates (mL/kg bwt/day), and thus, the highest exposure across the various age groups. The mean chronic exposure for all infants is 0.00096 mg ai/kg bwt/day if drinking water concentrations is constant at 17.5 ppb (0.00096= 53% of cPAD), and 0.00140 mg ai/kg bwt/day if the drinking water concentrations is constant at 25.2 ppb (78% of cPAD). The estimated mean chronic exposure for the infant subpopulation is fairly comparable to a single value chronic exposure estimate that could be generated by DEEM. But the information regarding interpersonal variability that is not available in the single value provided by DEEM is relatively important in characterizing the risk assessment when the exposure duration is considerably less than one year (e.g., 90 days, 30 days, 7 days, etc.).[2]

[2] The single value provided by DEEM tends to lose significant information as interpersonal variability

7.4 Cancer Risk

A cancer risk assessment for simazine has not been conducted based on its reclassification as "Not Likely to be Carcinogenic to Humans". The reclassification is based on the common mechanism of toxicity shared by atrazine and simazine and the lack of relevance to humans of the mammary tumors seen in Sprague-Dawley rats treated with atrazine and simazine (CARC Report dated April 14, 2005).

8.0 Cumulative Risk Characterization/Assessment

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

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

9.0 Occupational Exposure/ Risk Pathway

Simazine is a triazine herbicide and algaecide registered to control a variety of annual broadleaf weeds, grassy weeds, and algae. Use sites for simazine include food/ feed crops, non-food crops, ornamental ponds, aquariums, and non-cropped industrial lands, primarily on select turf grasses and fairways, or other residential turf grass. Simazine is formulated for occupational use as a liquid, wettable powder, dry flowable and a granular product.

---

increases with shortened exposure durations (30 days, 7 days, 3 day, etc.). DEEM calculates chronic exposure by calculating 'Average Exposure'(=Average Consumption x Average Residue) for all treated commodities, and summing these averages to obtain total dietary exposure. Average Consumption is based on all diets reported by the subpoopulation. So for Infants, the 1994-98 CSFII data contains 2,972 daily diets and the average drinking water consumption is based on the overall average. For spring, the average drinking water consumption is based on the overall average of 767 infant diets. In contrast, Lifeline and the other aggregate models will calculate average daily exposure during the Spring season based on a subset of food diaries - approximately 91 days of dietary consumption patterns. The average daily drinking water consumption during this period should be very similar since the exposure duration is relatively long (90 days).

The potential for occupational exposure exists with the usage of simazine in a variety of occupational scenarios. Such scenarios include the handling of simazine during the application process (i.e. mixer/ loaders, applicators, flaggers, and mixer/ loader/ applicators) and a potential for postapplication worker exposure from entering into areas previously treated with simazine. Short-term (up to 30 days) and intermediate-term exposures (1 to 6 months) may occur, however, long-term exposures (greater than 6 months) are not expected. Dermal and inhalation absorption rates used for this assessment are 6% and 100%, respectively. Daily dermal and inhalation exposures were added and then compared to the short-/ intermediate-term NOAEL of 6.25 mg/ kg/ day. The oral NOAEL was selected based on a 30-day pubertal screening study in rats (LOAEL of 12.5 mg/ kg/ day based upon a delay in preputial separation). HED's level of concern for simazine dermal and inhalation exposures is an MOE = 100 (10x inter-species extrapolation, 10x intra-species variation).

Risk Assessments have been completed for occupational handler scenarios, as well as, postapplication occupational scenarios for simazine. The occupational handler and postapplication exposure and risk assessment results presented in this section are fully disclosed in "Simazine: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document" (D307024, Steve Weiss, 12/8/04).

9.1 Occupational Handler

The information included in this section was extracted from DP Barcode D316475 (SIMAZINE: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document).

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. It has been determined that exposure to pesticide handlers is likely during the occupational use of simazine in a variety of occupational environments. The anticipated use patterns and current labeling indicate several occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for simazine applications.

In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Database (PHED) Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), were used with other HED standard values of acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. In addition, Outdoor Residential Exposure Task Force (ORETF) Handler Studies (MRID 449722-01) and proprietary data were also used to assess handler exposures.

Risk assessments for the occupational handling of simazine are based on the following scenarios:

Mixer/Loaders:
(1a) Liquids for Aerial Applications
(1b) Liquids for Chemigation Applications
(1c) Liquids for Groundboom Applications
(1d) Liquids for Rights-of-way Applications

(1e) Liquids to Support LCO Handgun Applications
(2a) Wettable Powder for Aerial Applications
(2b) Wettable Powder for Groundboom Applications
(2c) Wettable Powder for Chemigation Applications
(2d) Wettable Powder for Rights-of-way Applications
(2e) Wettable Powder to Support LCO Handgun Applications
(3a) Dry Flowables for Aerial Applications
(3b) Dry Flowables for Chemigation Applications
(3c) Dry Flowables for Groundboom Applications
(4a) Granulars for Aerial Applications;
(4b) Granulars for Tractor Drawn Spreader Applications;

Applicators:
(5) Aerial Spray Applications
(6) Aerial Granular Applications
(7) Groundboom Spray Applications
(8) Tractor-drawn Granular Applications
(9) Handgun Applications
(10) Rights-of-way Spray Applications

Flaggers:
(11) Flagging for Aerial Spray Applications
(12) Flagging for Granular Applications

Mixer/Loader/Applicators:
(13) Liquid: Low Pressure Handwand Sprayer
(14) Liquid: Handgun Sprayer
(15) Wettable Powder: Low Pressure Handwand
(16) Wettable Powder: Handgun Sprayer
(17) Granulars: Pumpfeed Backpack Applicator
(18) Granulars: Gravity-feed Backpack Applicator
(19) Granulars: Push Type Spreader
(20) Granulars: Belly Grinder
(21) Dry Flowable: Handgun Sprayer

Short-term (dermal + inhalation exposure)

In most scenarios, the risks for combined dermal plus inhalation short-term exposures for the occupational handling of simazine are not of concern at some level of risk mitigation. However, some scenarios – particularly those with relatively high acres treated or relatively high maximum application rates – remain a risk concern (i.e. MOEs are less than 100) with maximum risk mitigation, these scenarios are summarized in table 9.1.1.

Intermediate-term (dermal + inhalation exposure)

Several scenarios – particularly those with relatively high acres treated or relatively high maximum application rates – remain a risk concern (i.e. MOEs are less than 100) with maximum risk mitigation, these scenarios are summarized in table 9.1.2.

Table 9.1.1. Occupational Handler Noncancer Scenarios with Short-term MOEs < 100								
Exposure Scenario	Application Rate[a] (lb ai/acre)	Area Treated Daily[b] (acres)	Combined MOEs (Dermal[i] + Inhalation[j])[k]					
			Baseline[c]	Gloves, single layer (no respirator)	Gloves, double layer (no respirator)	Gloves, single layer[d] + PF 5 Respirator[e]	Gloves, double layer[g] + PF 5 Respirator	Engineering Control [h] (no respirator)
Mixing/Loading Dry Flowables to Support Aerial Applications (3a)	16.0	350	16	16	22	19	26	93
Applying Granulars via Aerial Equipment (6)	40.0	350	No Data	No Data	No Data	No Data	No Data	22
Mixing/Loading/Applying Wettable Powders with Low Pressure Handwand (15) (PHED)	16.0	5	No Data	3.4	3.7	7.4	9.2	Not Feasible
	4.0	5	No Data	14	15	30	37	Not Feasible
	3.0	5	No Data	18	20	40	49	Not Feasible
	2.0	5	No Data	27	30	59	74	Not Feasible
Loading/ Applying Granulars via Pumpfeed Backpack Applicator (17)	40.0	10	No Data	17	No Data	18	No Data	Not Feasible
	8.0	10	No Data	86	No Data	90	No Data	Not Feasible
Loading/ Applying Granulars via Gravity-feed Backpack Applicator (18)	40.0	10	No Data	14	No Data	24	No Data	Not Feasible
Loading/ Applying Granulars via Belly Grinder (20)	40.0	1	17	18	27	19	31	Not Feasible

Table 9.1.2. Occupational Handler Noncancer Scenarios with Intermediate-term MOEs < 100								
Exposure Scenario	Application Rate[a] (lb ai/acre)	Area Treated Daily[b] (acres)	Combined MOEs (Dermal[i] + Inhalation[j])[k]					
			Baseline[c]	Gloves, single layer (no respirator)	Gloves, double layer (no respirator)	Gloves, single layer[d] + PF 5 Respirator[e]	Gloves, double layer[g] + PF 5 Respirator	Engineering Control [h] (no respirator)
Mixing/Loading Liquid Concentrates to Support Aerial Applications (1a)	16.0	350	0.11	7.5	8.7	12	15	32
	4.0	1200	0.13	8.7	10	14	18	38
Mixing/Loading Wettable Powders to Support Aerial Applications (2a)	4.0	1200	0.085	0.42	0.44	1.2	1.4	27
	4.0	350	0.29	1.5	1.5	4.1	4.7	92
Mixing/Loading Wettable Powders to Support Chemigation Applications (2c)	4.0	350	0.29	1.5	1.5	4.1	4.7	92
Mixing/Loading Dry Flowables to Support Aerial Applications (3a)	16.0	350	4.1	4.1	5.4	4.7	6.5	23
	4.0	1200	4.8	4.8	6.3	5.5	7.6	28
	4.0	350	16	16	22	19	26	92
Mixing/Loading Dry Flowables to Support Chemigation Applications (3b)	4.0	350	16	16	22	19	26	92

Table 9.1.2. Occupational Handler Noncancer Scenarios with Intermediate-term MOEs < 100								
Exposure Scenario	Application Rate[a] (lb ai/acre)	Area Treated Daily[b] (acres)	Combined MOEs (Dermal[i] + Inhalation[j])[k]					
			Baseline[c]	Gloves, single layer (no respirator)	Gloves, double layer (no respirator)	Gloves, single layer[d] + PF 5 Respirator[e]	Gloves, double layer[g] + PF 5 Respirator	Engineering Control [h] (no respirator)
Applying Sprays via Aerial Equipment (5)	16.0	350	No Data	No Data	No Data	No Data	No Data	52
	4.0	1200	No Data	No Data	No Data	No Data	No Data	61
Applying Granulars via Aerial Equipment (6)	40.0	350	No Data	No Data	No Data	No Data	No Data	6
	4.0	350	No Data	No Data	No Data	No Data	No Data	55
	3.0	350	No Data	No Data	No Data	No Data	No Data	73
Applying Granulars via Tractor Drawn Spreader (8)	40.0	80	19	21	23	50	69	96
Applying Sprays with Rights of Way Equipment (10)	3.0	40	11	33	42	37	50	Not Feasible
Mixing/Loading/ Applying Liquid Concentrates with Low Pressure Handwand (13) (PHED)	16.0	5	0.22	24	26	42	48	Not Feasible
Mixing/Loading/ Applying Liquid Concentrates with a Handgun Sprayer (14) (LCO ORETF data)	16.0	5	No Data	47	80	49	88	Not Feasible
Mixing/Loading/ Applying Wettable Powders with Low Pressure Handwand (15) (PHED)	16.0	5	No Data	0.83	0.92	1.8	2.3	Not Feasible
	4.0	5	No Data	3.3	3.7	7.3	9.1	Not Feasible
	3.0	5	No Data	4.5	4.9	9.8	12	Not Feasible
	2.0	5	No Data	6.7	7.3	15	18	Not Feasible
	1.0	5	No Data	13	15	29	36	Not Feasible
Mixing/Loading/ Applying Wettable Powders with a Handgun Sprayer (16) (LCO ORETF data)	16.0	5	No Data	12	15	22	35	Not Feasible
Loading/Applying Granulars via Pumpfeed Backpack Applicator (17)	40.0	10	No Data	4.2	No Data	4.5	No Data	Not Feasible
	8.0	10	No Data	21	No Data	22	No Data	Not Feasible
	4.0	10	No Data	42	No Data	45	No Data	Not Feasible
	3.0	10	No Data	56	No Data	59	No Data	Not Feasible
Loading/Applying Granulars via Gravity-feed Backpack Applicator (18)	40.0	10	No Data	3.4	No Data	6	No Data	Not Feasible
	8.0	10	No Data	17	No Data	30	No Data	Not Feasible
	4.0	10	No Data	34	No Data	60	No Data	Not Feasible
	3.0	10	No Data	45	No Data	81	No Data	Not Feasible
Loading/Applying Granulars via Push Type Spreader (19) (ORETF)	40.0	5	19	26	39	37	67	Not Feasible
Loading/Applying Granulars via Belly Grinder (20)	40.0	1	4.1	4.4	6.7	4.7	7.6	Not Feasible
	8.0	1	20	22	33	24	38	Not Feasible
	4.0	1	41	44	67	47	76	Not Feasible

Table 9.1.2. Occupational Handler Noncancer Scenarios with Intermediate-term MOEs < 100								
Exposure Scenario	Application Rate[a] (lb ai/acre)	Area Treated Daily[b] (acres)	Combined MOEs (Dermal[i] + Inhalation[j])[k]					
			Baseline[c]	Gloves, single layer (no respirator)	Gloves, double layer (no respirator)	Gloves, single layer[d] + PF 5 Respirator[e]	Gloves, double layer[g] + PF 5 Respirator	Engineering Control [h] (no respirator)
Mixing/Loading/ Applying Dry Flowables Concentrates with a Handgun Sprayer (21) (LCO ORETF data)	16.0	5	No Data	24	32	34	56	Not Feasible

9.2 Short- and Intermediate-term Postapplication Risk

The results indicate that when application rates are 2 or 3 pounds active ingredient per acre, the risks for dermal exposure are not a risk of concern approximately 12 hours after application (for all postapplication tasks). When the application rate is 4 pounds active ingredient per acre, risks are not of concern approximately 12 hours after application for tasks with relatively low transfer coefficients, such as mowing turfgrass and irrigating or scouting during Christmas tree production. However, for tasks with higher transfer coefficients, such a pruning, training, topping, or staking Christmas trees, dermal risks are a concern (i.e. MOEs are less than 100) until 2 days after application. For harvesting, transplanting, or weeding turfgrass on sodfarms at the 4 pound active ingredient per acre rate, risks are of concern until 2 days following application using the TTR values from the unirrigated Florida test site. However, when TTR values from the irrigated test site were used, risks are not of concern approximately 12 hours after application. A summary of the noncancer postapplication risks are provided in Table 9.2.1.

Table 9.2.1: Summary of Postapplication Occupational Risks									
Crops	Transfer Coefficient (cm^2/hr)	Activities	Max Foliar Rate (lb ai/acre)	Day After Application when Target MOE= 100					
				Using Simazine Liquid Turf Application Data (MRID 449587-01) Study Application Rate: 2 lb ai/acre				Using Atrazine Liquid and Dry Flowable Dislodgeable Foliar Residue Data (MRID 448836-01) Study Application Rate: Liquid: 2 lb ai/acre Dry Flowable: 2.5 lb ai/acre	
				Florida Study Data		California Study Data		Liquid Study Data[e]	Dry Flowable Study Data[f]
				Irrigated Test Plot[a]	Non-irrigated Test Plot[b]	Irrigated Test Plot[c]	Non-irrigated Test Plot[d]		
Christmas Trees	1,000	Irrigation, Scouting	4	N/A	N/A	N/A	N/A	0 (12 hours)	0 (12 hours)
	3,000	Staking, Topping, Training, Pruning		N/A	N/A	N/A	N/A	2	2
Nurseries	500	All activities except harvesting cut flowers/foliage	3.0	N/A	N/A	N/A	N/A	0 (12 hours)	0 (12 hours)
Golf courses, Sodfarms (except Florida)	500	Mowing	2.0	0 (12 hours)	0 (12 hours)	0 (12 hours)	0 (12 hours)	N/A	N/A
	16,500	Transplanting, Harvest (hand or mechanical)		0 (12 hours)	0 (12 hours)	0 (12 hours)	0 (12 hours)		

a Florida irrigated test plot: Slope = -0.99084; Day 0 concentration = 0.175 µg/cm^2
b Florida non-irrigated test plot: Slope = -0.085666; Day 0 concentration = 0.319 µg/cm^2
c California irrigated test plot: Slope = -0.032532; Day 0 concentration = 0.0885 µg/cm^2

d California non-irrigated test plot: Slope = -0.067889; Day 0 concentration = 0.27 µg/cm^2
e Atrazine liquid formulation: Slope = -0.044l Day 0 concentration = 2.64 µg/cm^2
f Atrazine dry flowable formulation: Slop = -0.578; Day 0 concentration = 4.21 µg/cm^2

10.0 Data Needs and Label Requirements

10.1 Toxicology

None

10.2 Residue Chemistry

- Limited field trials on representative rotational crops are required
  The registrant is supporting uses on two crops that are normally rotated, corn and strawberry. No rotational crop restrictions are listed under the use directions for strawberries, but extensive restrictions to protect against phytotoxicity are listed under the use directions for corn. These rotation restrictions listed under corn would essentially result in a 2-year rotational crop restriction after corn for all crops except fall-seeded cereal grains, but HED does not consider two year rotational crop restrictions to be enforceable. Because measurable residues (>0.01 ppm) were seen in the confined rotational study for all commodities except wheat grain at the plant-back intervals tested (137 days for wheat, 362 days for all other crops), limited field trials on rotational crops are required to determine if tolerances are needed. If the registrant desired shorter crop rotational restrictions for strawberries than for corn appropriate strawberry-rotational crop studies would also be required

- Field trials are required for almonds, cherries, cranberries, currants, grapefruit, lemons, macadamia nuts, and oranges, pears, strawberries, sweet corn and walnuts.

- In order to use the existing apple data the registrant must propose a PHI or propose some other label restriction that will have the same effect as establishing a PHI. With an appropriate PHI no additional field trials are required for apple; otherwise additional trials are required.

- Storage stability data for up to 3 years are required to support existing field trials on oranges.

- Enforcement methods capable of determining simazine and its chloro-metabolites G-28273 and G-28279 are required for plants commodities and for livestock commodities. There are existing data gathering methods that will suffice if validated as enforcement methods.

- Additional processing studies are required to depict the potential for concentration of simazine residues in processed commodities of apples, corn grain, grapes, olives, and oranges.

Required Label Changes

Directions for the use of tank mixes of Princep[7] with Solicam[7] on grapefruits, lemons, and oranges should be clarified. Label directions on both the 4 lb/gal FlC and the 90% DF labels allow use of a tank mix application of simazine at 4 lb ai/A in conjunction with Solicam[7] DF Herbicide at -3-4 lb ai/A. The 4 lb ai/A

use rate for simazine exceeds the 1.6+1.6 lb ai/A split application rate allowed for simazine alone on lemons and oranges grown in AZ. The tank mix application directions should be amended to read: "apply Princep 4L (or Princep Caliber 90) at the rate given under the appropriate crop directions on this label plus 4-5 lbs. of Solicam DF Herbicide..."

Use directions for macadamia nuts presently include the statement: "Repeat application as necessary." This statement should be replaced to indicate the maximum seasonal rate and a minimum retreatment interval. The available tree nuts data, which will be used to support the use on macadamia nuts, would support a single application at 4 lb ai/A/season.

Labeling for use on corn currently states: "Do not graze treated areas as illegal residues may result". The prohibition against the grazing of treated corn crops should be deleted from both labels. Current Agency policy does not allow a prohibition against the use of significant livestock feed items, such as corn forage. The labels should be amended to include a pregrazing/ preharvest interval (PGI/PHI) for corn; the available residue data would support a 60-day PGI/PHI for corn.

10.3 Occupational and Residential Exposure

None

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

Table 1. Insert yes, no, or "-" as appropriate. Use foot notes to indicate where the guideline is satisfied by studies of a different guideline requirement, or when there is something unusual (e.g. Waiver, a formulation is used to satisfy the technical requirement.)

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

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

2.0 NON-CRITICAL TOXICOLOGY STUDIES

Developmental

In a developmental toxicity study (MRID 00161407), simazine (97% a.i., batch no. 821846) was administered to pregnant female New Zealand White rabbits by gavage at dose levels of 0, 5, 75, or 200 mg/kg/day from days 7 through 19 of gestation. There were 18 animals/dose in all groups except the 200 mg/kg group which had 16 animals.

A compound-related increase in tremors was noted in the two highest dose groups (21% in 75 mg/kg group; 100% in 200 mg/kg/day group), while no tremors occurred in the control and low dose groups. Stool alterations (none, little or soft stool) were observed in 50% of the 5 mg/kg (LDT) animals and 100% of the 75 and 100 mg/kg (MDT and HDT, respectively) animals, whereas no stool alterations were observed in control groups. During days 7-19 (the period of dosing), the MDT and HDT showed statistically significant decreases in weight gain compared to controls (+230g for controls vs -243 and -456g for MDT and HDT, respectively). The corrected body weight (body weight gain minus gravid uterine weight) was also significantly decreased in the MDT and HDT groups. Significant decreases in food consumption were also noted in the MDT and HDT groups as compared to controls and persisted throughout the dosing period. Four animals aborted during the study: one from the MDT and three from the HDT.

The maternal LOEL is 75 mg/kg/day, based on decreased food consumption and weight gain, and increased female tremors and stool alterations. The maternal NOEL is 5 mg/kg/day.

There were no teratogenic effects from dosing with the test compound. There were, however, significant decreases in female fetal weights (decreased 13% vs controls) and a significant increase in skeletal variations (50% of fetuses had some type of skeletal variation in the controls vs 88% in the HDT) in the high dose group.

The developmental LOEL is 200 mg/kg/day, based on reduced mean fetal weight and increased skeletal variations. The developmental NOEL is 75 mg/kg/day.

The developmental toxicity study in the rabbit is classified **Acceptable-guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b [§83-3b]; OECD 414) in the rabbit.

Two-Generation Reproduction - Rat

In a 2-generation reproduction study (MRID 41803601) simazine (96.9% a.i., batch no. FL 850614) was administered to 240 Sprague-Dawley rats 30/sex/dose in the diet at dose levels of 0, 10 (LDT), 100 (MDT), 500 (HDT) ppm (mean of F_0 and F_1 generation compound intakes for both sexes: 0, 0.56/0.7; 5.61/7.04; 28.89/34.96).

There were no compound related deaths or clinical observations in either sex, at any dose or either generation.

Male body weight and body weight gain were decreased (10% and 27%, respectively) in the 500 ppm group in both the F_0 and F_1 generations throughout the premating and mating phases (days 0-105). Male body weight gain was also significantly decreased (13%) in

100 ppm F_0 males through the premating phase (days 0-70). Conversely, male 10 ppm body weight gains were significantly increased in the F_1 generation throughout the entire duration of the study (days 0-147). Females in both generations of the HDT had significantly decreased body weight throughout most of the study. F_1 generation MDT females had significantly decreased body weight or body weight gain at only a few time points throughout the study.

Food consumption for HDT males of both generations was significantly decreased through the premating period (10-16% decrease, depending on time point). F_0 and F_1 female food consumption at the HDT was significantly decreased at many time points both during the premating, mating and lactation periods (9-16% decrease, depending on time point).
There were no indications of any reproductive toxicity resulting from exposure to the test compound.

The parental LOEL is 100 ppm (5.61 and 7.04 mg/kg/day for males and females respectively), based on decreased body weight and body weight gain. The NOEL is 10 ppm (0.56 and 0.7 mg/kg/day) for males and females respectively. The NOEL for reproductive toxicity is 500 ppm (31.93 mg/kg/day in both sexes combined). A reproductive LOEL was not determined.

The reproductive study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800 [§83-4]; OECD 416) in the rat.

Chronic Dog

In a chronic toxicity study (MRID 40614402), simazine (97.5 % a.i, batch no. 840988) was administered to 32 Beagle dogs in the diet at dose levels of 0, 20, 100, 1250 ppm (0, 0.68/0.76, 3.41/3.64, 42.9/44.9 mg/kg/day) for 12 months.

Male body weight gain was significantly decreased at 1250 ppm (HDT) only during the first two weeks of the study. Female body weight gain was significantly decreased throughout most of the study (+27.4% in control vs +13.5% in HDT). Male food consumption was not affected, but female food consumption was significantly decreased during the first 20 weeks of the study.

There were no compound-related gross or microscopic pathology findings nor were there any unscheduled deaths during the study.

By the end of the study, platelet counts in 1250 ppm (HDT) males were increased by 55% compared to controls. Females at the HDT had significantly decreased red blood cell counts (RBC), hemoglobin levels (HGB), and hematocrits (HCT) at 86 and 177 days. Decreases were: 17%/15% for RBCs at days 86/177; 13%/12% for HGB at days 86/177; and 14%/12% for HCT at days 86/177. Females at the 100 ppm (MDT) also showed decreases (2-14%) in these same three parameters, with significant reduction in HGB (11%) and HCT (12%) at day 86.

Adrenal, kidney, and liver weights were increased, though not statistical significantly, in HDT males. The only statistically significant organ weight effect in HDT males was an increase in the adrenal to brain weight ratio. In HDT females, the only three organ

weights and ratios that were consistently statistically significant were adrenal weight (129%, $p<0.01$), adrenal/brain ($p<0.01$), and adrenal/body weight ratio ($p<0.01$).

The LOEL is 1250 ppm (42.9 mg/kg/day) in males based on increased adrenal to brain ratios and increased platelet counts. The LOEL in females is 100 ppm (3.64 mg/kg/day) based on decreased RBC, HGB and HCT levels. The NOEL is 100 ppm in males and 20 ppm in females.

This chronic toxicity study in the dog is **Acceptable-Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in the dog.

Combined Chronic Toxicity/Oncogenicity - Mice

In a carcinogenicity toxicity study (MRID 40614404), simazine (purity not reported, batch no. FL 840988) was administered to CD1 mice, 60/sex/dose, in the diet at dose levels of 0, 40, 1000, 4000 ppm (0, 0.5.3/6.2, 131.5/160, 542/652.1 mg/kg/day, males/females) for 95 weeks. For interim data, additional animals/dose were administered test material in the diet and sacrificed (10 animals per sacrifice) at week 26 or 52. In addition, ten animals in the control and 4000 ppm groups were sacrificed at week 56 after a 4-week recovery period. Sixty animals were also sacrificed at the start of the study to establish baseline parameters and 20 sentinel animals were sacrificed mid-way (52 weeks) into the study to check for viruses.

While there were many clinical observations reported during the study, no observation was determined to be an effect of dosing. Mortality was not significantly increased in treated groups vs controls.

Mean body weight and percent body weight gain were significantly reduced at various time points in both sexes of the 1000 ppm (MDT) and 4000 ppm (HDT) groups. The reductions at the highest dose were significant throughout most of the study and at the mid-dose the reductions were significant in males beginning at week 24 and in females beginning at week 16. After 92 weeks of the study, HDT males and females body weights were significantly reduced by 12% and 20%, respectively, while MDT females body weights were significantly reduced by 8%. Mean food consumption was consistently decreased ($p< 0.05$, 7-16% decrease, depending on time point) in the HDT females from week 2 until the end of the study. Likewise, water consumption was deceased ($p<0.05$) in HDT females from week 2 onward.

Hematology and clinical chemistry parameters did not appear to be affected by exposure to simazine. Organ weights did not appear to be altered either. There were no increased incidences of neoplastic lesions in any dose group compared to controls.

The LOEL is 1000 ppm (131.5/160 mg/kg/day, males/females), based on decreases in body weight and percent body weight gain in both sexes, and decreases in food consumption in males. The NOEL is 40 ppm (5.3/6.2 mg/kg/day, males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls.

This combined chronic/oncogenicity study in mice is **Acceptable-Guideline** and satisfies the guideline requirement for a combined chronic/oncogenicity study [(OPPTS 870.4300); OECD 453] in mice.

Combined Chronic/Oncogenicity - Rat

In a combined chronic / carcinogenicity study (MRID 40614405, 43029701), simazine (96.9% a.i., Batch FL 850614) was administered via the diet to 680 Sprague-Dawley rats (Crl:VAF/Plus CD®): 40 rats/sex in the control and high dose groups of the chronic phase, 30 rat/sex in the low and intermediate dose groups of the chronic phase, and 50 rats/sex/dose in the carcinogenicity phase. Each group was exposed to the test material at dose levels of 0, 10 (LDT), 100(MDT), 1000 (HDT) ppm (0, 0.41/0.52, 4.2/5.3 and 45.8/63.1 mg/kg/day, males/females) for 52 weeks (chronic) or 104 weeks (carcinogenicity).

Over the duration of the study, significant decreases in body weight and body weight gain were noted in the HDT group for both sexes compared to control. At the end of the study body weight gain was decreased 27% for males and 28% for females. Food consumption in the HDT group was significantly decreased in both males and females throughout most of the study. Food consumption was decreased by 10-16% in males and 6-11% in females depending on the time point.

Many hematology parameters in HDT females were statistically different from controls after 104 weeks and were as follows: decreased red blood cell counts (RBC); decreased hemoglobin (HGB) and hematocrit (HCT) values; increased mean corpuscular hemoglobin; increased mean corpuscular hemoglobin concentration (at day 174); increased white blood cell counts; increased platelet counts; increased percent neutrophils and decreased lymphocyte count. The MDT female group displayed statistically significant decreases in HCT and HGB at 104 weeks and significant increases in platelet counts at 104 weeks. In males, MCHC was significantly increased in the HDT group at 52 weeks. Leukocyte counts were significantly lower in both MDT and HDT males at 77 weeks.

Many clinical chemistry parameters were altered following exposure to simazine. The only alteration which is likely attributable to compound exposure, though, is the decrease in serum glucose levels seen in HDT female rats at 52, 77, and 104 weeks. In HDT females, heart wts. were increased 23%, kidney wts. were increased 31% and liver wts. were increased 430%. In HDT males liver and testes wts., relative to body weight, were significantly increased (20% for liver, 28% testes). Heart weight was decreased absolutely by 15% and was decreased relative to brain wt. by 13%.

In the original study (MRID 40614405), no nonneoplastic findings in the male rat were significantly increased in any dose group vs controls. In females, liver hematopoiesis, splenic hematopoiesis and cystic mammary glandular hyperplasia were all significantly increased in incidence in the HDT vs the controls. A reevaluation of selected ovarian tissue and Sertoli cell changes (MRID 43029701) subsequent to the original study determined that there was a significantly increase after 24 months exposure to 1000 ppm in-ovarian atrophy and Sertoll Cell hyperplasia. Animals treated for 52 weeks and then allowed 52 weeks recovery did not display these changes.

Mortality in the entire study (both chronic and oncogenicity portions up to completion of study) was increased HDT females. Mortality was 80% in these animals compared to 66% in the control females. Male HDT mortality dropped from 61% for controls to 40% for HDT.

Increases in mammary, pituitary and kidney neoplasms were seen in HDT females. Only the increases in mammary tumors were found to be statistically significant. Mammary carcinomas ($p<0.001$, 35/70 HDT vs 14/70 control) and fibroadenomas ($p<0.01$, 40/70 vs 22/70) were significantly increased in HDT females, while only mammary carcinomas were increased ($p<0.05$) in mid-dose females. Males displayed non-significant increases in liver tumors (combined adenoma and carcinoma 1/70 control vs 6/70 HDT).

The LOEL is 100 ppm (4.2/5.3 mg/kg/day, males/females) based on decreases in HCT, HGB and platelet counts in females and decreased leukocyte counts in males. The NOEL is 10 ppm (0.41/0.52 mg/kg/day, males/females).

At the doses tested, there was a treatment related increase in mammary carcinomas and fibroadenomas tumor incidence when compared to controls. Dosing was considered adequate based on hematology alterations,

This chronic/carcinogenicity study in the rat is **Acceptable-Guideline** and satisfies the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rat.

21-day Dermal

In a 21 day dermal study (MRID 000057567), New Zealand White rabbits, 10/sex/dose, were administered simazine (97.6%, batch no. not reported) to shaved skin for 6 hrs per day, 5 days/week (15 applications total) for 21 days at concentrations of 0, 10, 100 or 1000 mg/kg/day. Five animals/sex/dose had their skin abraded before the first application and then once weekly thereafter. All animals had their dosed area wrapped in an impervious material for six hours after dosing with the wraps then removed and the area wiped clean.

There was no dose-related systemic toxicity in either the abraded or the intact skin animals. Hematology and clinical chemistry parameters did not indicate any differences between control and treatment groups. Organs examined at histology were not different between groups. Slight erythema was present in two animals in the intact skin groups: a 1000 mg/kg/day male and a 10 mg/kg/day female. Ulcerative dermatitis was found in two 100 mg/kg/day males and one 1000 mg/kg/day female. The small number of dermal observations and their none-dose related distribution indicate that these findings are not related to compound exposure.

The NOEL is greater than 1000 mg/kg/day. A LOEL was not established.

This 21-day dermal toxicity study in the rabbit is **Acceptable-Guideline** and satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200 [§82-2]; OECD 410) in rabbits.

Subchronic Oral - Dog

In a subchronic toxicity study (MRID 00146655), simazine (97.50 % a.i., batch no. FL 840988) was administered to 32 Beagle dogs 4/sex/dose in diet at dose levels of 0, 200 (LDT), 2000 (MDT) and 4000 (HDT) ppm (0, 6.9/8.2 male/female, 65.2/64.3 male/female, 133.6/136.7 male/female mg/kg/day).

There were no deaths during the study. Clinical signs of toxicity were only observed in the high dose groups. Tremors were observed in all the high dose males and 3/4 high dose females. Alopecia was seen in 2 HDT males and one HDT female. Three HDT males (but no HDT females) were found to have dermatitis and one was cachexic. Emesis was increased in 3/4 high dose females. No control animals of either sex displayed tremors, alopecia, cachexia, or dermatitis.

Food consumption was statistically significantly decreased in both sexes of the MDT and HDT groups. Compared to controls, food consumption was decreased 22% and 25% in the MDT and HDT males, respectively, and 32% and 36% in the MDT and HDT females, respectively. Body weight and percent body weight gain were also decreased in MDT and HDT animals. Controls males showed a 19.7% increase in body weight and control females a 6.6% increase during the 13 week study. MDT males showed only a 1.5% increase, while MDT females showed a 7.8% decrease in body weight. The effects in HDT animals were more severe, with males showing a 9.5% decrease in body weight and females an 18.4% decrease. LDT food consumption, body weight and body weight gains were also decreased compared to controls, though not statistically significantly. The following hematology parameters were altered in the HDT after 13 weeks of exposure: red blood cell counts (-26%/-23%, M/F), hemoglobin (-22%, both sexes), and hematocrit (-24%/-23%, M/F), percent neutrophils (+21%, M), percent lymphocytes (+50%, M), percent eosinophil (-80%), platelet counts (+52%), and prothrombin times (-7%, M). At 13 weeks, both male and female had decreased serum glutamate oxalacetate (SGOT) (26%/24%, M/F) and Ca^{2+} serum levels (3%/5%, M/F). HDT male albumin, globulin and albumin/globulin ratios were decreased by 8%, 18% and 20% at 13 weeks. HDT male creatinine was decreased 17% at 13 weeks. Both MDT and HDT females showed 45% and 55% decreases in alkaline phosphate levels, respectively, at 7 weeks. The 13 week measurements for alkaline phosphatase were 43% decreased at the MDT and 36% decreased at the HDT which, in neither case, was statistically significant.

Compared to control, relative brain and liver weights were increased 28% and 35%, respectively, in HDT males, while HDT female relative brain and liver weights were increased 31% and 23%, respectively. Relative liver and brain weights were also decreased in the male at the MDT by 24% for the liver and 19% for the brain. In HDT, both relative and absolute heart weights were decreased in both sexes - absolute weight by 35% and 37% in the males and females respectively and relative weight by 13 and 17% in the males and females respectively. Male absolute heart weight was decreased by 28% at the MDT and by 10% at the LDT. Male HDT absolute testes weight was decreased 46% and relative testes weight was decreased 27% compared to controls. Males at the MDT had absolute testes weight reduced 33% compared to controls.

The LOEL is 2000 ppm (65.2/64.3 mg/kg/day, males/females), based on increased relative brain and liver weights, decreased absolute heart weight and testes weight, in the males and reduced alkaline phosphate levels and SGOT levels in the female. The NOEL is 200 ppm (6.9/8.2 mg/kg/day males/females).

This subchronic toxicity study is classified **Acceptable-Guideline** and satisfies the guideline requirement for a subchronic oral study (OPPTS 870.3150 [§82-1b]; OECD 409) in the dog.

In a subchronic toxicity study (MRID 00143265), simazine (97.5% a.i., batch no. FL 840988) was administered to 100 Sprague-Dawley rats, 10/sex/dose, in the diet at dose levels of 0, 200, 2,000, 4,000 ppm group(0, 12.6/15.9, 126/158.3, 247/304.8 mg/kg/day, M/F) and a baseline non-dosed group.

Subchronic Oral - Rat

There were no compound-related effects on mortality, clinical signs or gross pathology. Food consumption was reduced in a dose-related manner in all groups (low to high dose in males/females: 6.5%/7.9%, 37.2%/32.1%, 52.5%/46.4%). Similarly, body weight gain was decreased in a dose-related manner during the duration of the study (low to high dose males/females: 94%/52%, 49%/27%, 29%/23%). Selected hematology and clinical chemistry parameters were affected. Red blood cell counts (RBC) and hematocrits (HCT) were significantly reduced in both sexes of the 2,000 (MDT) and 4,000 (HDT) ppm groups. Male white blood cell counts (WBC) were significantly decreased at all dose groups while female % neutrophils and platelet counts were significantly increased at the MDT and HDT groups only. Percent monocytes were decreased in the MDT and HDT males and HDT females. Serum glucose and calcium levels were significantly decreased in MDT and HDT males while sodium levels were significantly decreased only in HDT males. Males also showed increased cholesterol, chloride and phosphorus levels; chloride and phosphorus only in the HDT and cholesterol in both MDT and HDT. Female blood urea nitrogen (BUN), creatinine and serum glutamate oxalacetate transaminase levels were significantly decreased in MDT and HDT females. BUN levels were also significantly decreased in 200 ppm females. Serum cholesterol and phosphorus levels were significantly increased in MDT and HDT females.

The only microscopic findings were in the kidney. Histopathology revealed an increase in renal calculi at all doses and an increase in renal epithelial hyperplasia in HDT males. Absolute kidney, liver, spleen, brain heart and gonad weights were reduced at MDT and HDT. Relative to body weight, adrenal, kidney, liver, testes, heart and brain weights were significantly increased at mid and high doses.

The LOEL is 200 ppm (14.25 mg/kg/day), based on decreased food consumption, body weight gain, decreased male WBC and female BUN. The NOEL was not determined.

This subchronic toxicity study is classified **Acceptable/Guideline** and satisfy the guideline requirement for a subchronic oral study (OPPTS 870.3100 [§82-1a]; OECD 408) in the rat.

3.0 DRINKING WATER RISK ASSESSMENT

Results of the Lifeline™ assessment are provided below.

Table 1 Lifeline Intermediate-term (90-day) Exposure for Infants (Single Value DW Concentrations)

	Chronic Exposure to Infants (mg ai/kg bwt/day)	
Pct of Subpopulation	DW Conc=17.5 ppb	DW Conc=25.2 ppb
10%	0.00034	0.00049
20%	0.00041	0.00059
30%	0.00091	0.00138
40%	0.00107	0.00153
50%	0.00113	0.00163
60%	0.00118	0.00169
70%	0.00122	0.00176
80%	0.00127	**0.00183**
90%	0.00135	0.00194
99%	0.00161	0.00224
99.9%	**0.00187**	0.00276
100%	0.00190	0.00336
Population Average	**0.00096 (53% of cPAD)**	**0.00140 (78% of cPAD)**

Estimated Chronic Exposure for Infants in the Midwest (Spring)
Lifeline simulations were conducted using a single value for drinking water concentration during the spring season. The Lifeline model was used since it is capable of providing estimated average daily exposure over a 90 day exposure duration (Spring). Table 1 presents the chronic exposure to Infants during the spring season in the Midwest when drinking water concentrations were set at 17.5 ppb and 25.2 ppb, respectively. The estimates for Infants are provided and discussed in detail here since Infants have the highest drinking water consumption rates (mL/kg bwt/day), and thus, the highest exposure across the various age groups. The mean chronic exposure for all infants is 0.00096 mg ai/kg bwt/day if drinking water concentrations is constant at 17.5 ppb (0.00096= 53% of cPAD), and 0.00140 mg ai/kg bwt/day if the drinking water concentrations is constant at 25.2 ppb (78% of cPAD). The estimated mean chronic exposure for the infant subpopulation is fairly comparable to a single value chronic exposure estimates that could be generated by DEEM. But the information regarding interpersonal variability that is not available in the single value provided by DEEM is relatively important in characterizing the risk assessment when the exposure duration is considerably less than one year (e.g., 90 days, 30 days, 7 days, etc.).[3]

[3] The single value provided by DEEM tends to lose significant information as interpersonal variability increases with shortened exposure durations (30 days, 7 days, 3 day, etc.). DEEM calculates chronic exposure by calculating 'Average Exposure'(=Average Consumption x Average Residue) for all treated commodities, and summing these averages to obtain total dietary exposure. Average Consumption is based on all diets reported by the subpoopulation. So for Infants, the 1994-98 CSFII data contains 2,972 daily diets and the average drinking water consumption is based on the overall average. For spring, the average drinking water consumption is based on the overall average of 767 infant diets. In contrast, Lifeline and the other aggregate models will calculate average daily

Distribution of Chronic Exposure for Affected Population
In addition to the overall mean, Lifeline also provides chronic exposure estimates for the subpopulation of infants. Based on Table 1, approximately 99% of all infants are expected to have average daily exposure less than the cPAD (0.0018 mg/kg bwt/day) if drinking water concentrations were 17.5 ppb during this Spring season. Similarly, almost 80 percent of the subpopulation would have average daily exposure less than the cPAD if drinking water concentrations were 25.2 ppb; approximately 20 percent of the subpopulation are anticipated to have average daily exposure exceeding the cPAD.

Table 2. Mean DW Consumption Rates, By Age & Age Groups \1

Age	Mean DW Consumption (mL/day)					Mean DW Consumption (mL/kg bwt/day)				
	Spring	Summer	Fall	Winter	Annual	Spring	Summer	Fall	Winter	Annual
0	458	537	446	515	490	62.3	75.4	63.8	71.8	68.5
1	368	404	374	295	358	31.2	35.1	31.9	25.1	30.7
2	413	513	411	421	438	29.1	36.3	29.8	30.3	31.3
3	488	546	415	472	480	31.0	34.6	26.0	30.3	30.5
4	534	571	473	454	510	30.0	32.2	26.7	26.0	28.8
5	527	614	533	554	557	26.1	30.2	25.9	28.9	27.7
6	522	733	554	509	573	23.8	32.0	24.1	23.0	25.5
7	508	598	528	464	524	20.8	23.5	19.9	16.7	20.3
8	625	655	522	600	599	22.1	21.5	17.9	21.5	20.6
9	630	674	511	591	606	19.9	19.1	15.8	18.8	18.5
10	609	845	691	707	702	17.5	24.2	19.4	18.7	19.6

exposure during the Spring season based on a subset of food diaries - approximately 91 days of dietary consumption patterns. The average daily drinking water consumption during this period should be very similar since the exposure duration is relatively long (90 days).

11	808	668	680	696	713		19.6	16.5	15.9	17.2	17.2
12	642	1,034	914	625	838		13.7	22.0	18.4	12.8	17.5
Age Group	Spring	Summer	Fall	Winter	Annual		Spring	Summer	Fall	Winter	Annual
Infants	458	537	446	515	490		62.3	75.4	63.8	71.8	68.5
Toddlers, 1to3 yr old	424	489	400	391	425		30.4	35.3	29.3	28.3	30.8
Children, 4to12 yr old	596	714	601	580	622		22.0	24.6	20.5	20.4	21.9
Youths, 13to19 yr old	908	1,109	899	869	949		14.8	17.2	14.3	14.5	15.2
Adults, 20to49	1,426	1,548	1,380	1,395	1,437		19.4	21.0	18.9	19.1	19.6
Adults, 50plus	1,539	1,512	1,480	1,489	1,505		21.0	20.7	20.5	20.3	20.6
Females 13to49 yrs old	1,236	1,295	1,269	1,219	1,255		19.0	20.0	19.4	19.4	19.4
General Population	1,232	1,319	1,194	1,193	1,235		20.8	22.5	20.1	20.3	20.9

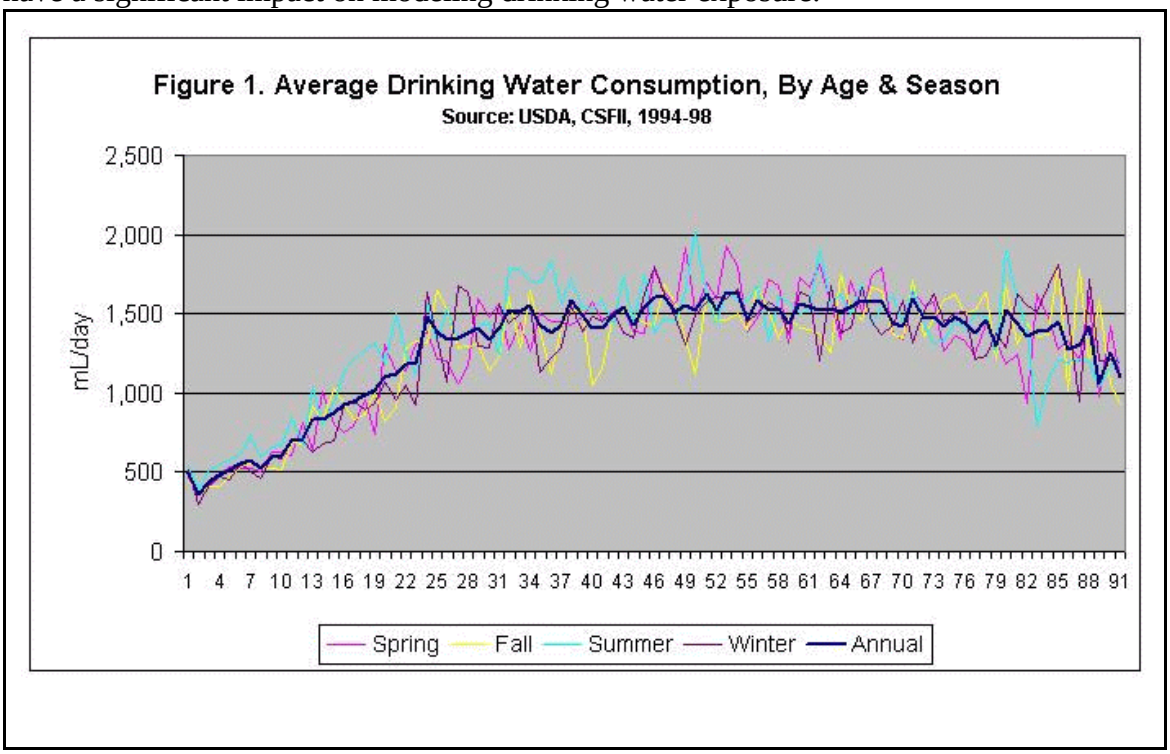
/1 Statistics calculated from the 1994-1998 USDA CSFII (SAIC, Watfin98d1d2)

The other aggregate probabilistic models (Calendex, CARES and SHEDs) also have the ability to produce distributions of chronic exposures across specific subpopulations (infants, 1to2 yr olds, 3to5 yr olds, etc). While these models may produce slightly different estimates,[4] all of these models rely upon the same data source for drinking water consumption, the 1994-1998 USDA Continuing Survey of Food Intake by Individuals (CSFII). The 1994-1998 CSFII data was used to produce the statistics in this section. As Table 2 indicates, there is considerable variability in drinking water consumption patterns across subpopulations, and some, but not considerable variability over seasons.

Temporal Consistency: Matching DW Concentrations with DW Consumption
Lifeline and the other aggregate models maintain temporal consistency in calculating drinking water exposure. In particular, the drinking water consumption reported during

[4] The Lifeline model may have additional variability over the other 3 models due to it use of its anthropomorphic models for individual body weights in generating drinking water consumption rates. Further technical description on Lifeline can be found in the SAP document, http://www.epa.gov/scipoly/sap/index.htm#April 2004, SAP_ModCompFinal.pdf.

the Spring season are matched with drinking water concentrations during Spring months. This temporal consistency may be important to the extent that consumption patterns vary over the year. For example, if drinking water consumption is higher during the summer months due to increased activity, and drinking water concentrations were also higher during the summer months due to use patterns, then such correlation would produce a higher likelihood of high exposure than if drinking water residues were randomly drawn for any particular consumption pattern (i.e., how DEEM uses dw residues). Table 2 indicates that average drinking water consumption is slightly higher during the Summer (1.319 Liters/day) than during the Spring (1.232 Liters/day), Fall (1.194 Liters/day), Winter (1.193 Liters/day) and overall average (1.235 Liters/day).[5] Average drinking water consumption during the spring season is not much different than the overall annual average. Children seem to have slightly higher summer dw consumption patterns than adults. Figure 1 charts drinking water consumption (Liters/day) by age and season. As indicated in both Table 2, Spring drinking water consumption patterns are not markedly different than the overall consumption patterns; suggesting that this issue is not going to have a significant impact on modeling drinking water exposure.



Discrepencies with DW LOC Calculations

Based on standard assumptions regarding drinking water consumption, the preliminary DW LOC (no food exposure) for an Infant weighing 7 kg and consuming 1 Liter of water per day is 12.6 ppb. Therefore, one might have anticipated Lifeline to predict the mean exposure among infants exceeding the cPAD when drinking water concentrations were set at 17.5 ppb and 25.2 ppb. However, the estimated mean exposure values for Infants (and

[5] This amount reflects the total estimated drinking water consumption reported by CSFII respondents; i.e., includes both direct and indirect water consumption, from all sources (tap water, bottled, other); watfin98d1d2.sas7bdat data file.

other subpopulations) was considerably less than the cPAD for those two scenarios (53% and 78% of the cPAD respectively), as reported in Table 1. This discrepency is primarily due to the fact that the 1994-1998 CSFII data used by Lifeline (as well as DEEM, Calendex, CARES and SHEDs), indicate that mean drinking water consumption rates are much lower than the assumed values used to calculate DW LOCs. Table 2 presented mean drinking water consumption rates for various age groups. The average daily intake by infants (490 mL/day), toddlers between 1to3 yrs old (425 mL/day) and children between 4and14 yrs old (622 mL/day) is less than the 1000 mL/day (1 Liter) used to calculate DW LOCs. Similarly, the mean consumption among Females 13to49 yrs old (1255 mL/day) and all Adults ages 20to49 (949 mL/day), and ages 50+ (1.437 mL/day) is less than the 2000 mL/day (2 Liters) assumed for those subpopulations. The actual mean intake rates remain lower when drinking water consumption is measured in mL/kg bwt/day: e.g., 1000 mL/7 kg bwt/day = 142.9 mL/kg bwt/day is greater than the actual intake of 68.5 mL/kg bwt/day for infants (or 0.1429 kg water/kg bwt/day > 0.0685 kg water/kg bwt/day).

Table 3 presents the assumed intake rates with the estimated mean drinking consumption amounts for each of the DW LOC subpopulations, and compares the corresponding preliminary DW LOCs for the different drinking water consumption rates. Again, if a 7 kg infant consumed 1 Liter of water (0.1429 kg water/kg bwt/day), then a drinking water concentration of 12.6 ppb would provide exposure equal to the cPAD. The mean drinking water consumption for Infants is less than half that assumed amount, at 0.0685 kg water/kg bwt/day, and therefore, a much higher drinking water concentration of 26.3 ppb is required for the average chronic exposure would reach the cPAD.[6] This explains why Lifeline estimated the average infant chronic exposure at a fraction (53%) of the cPAD when drinking water concentrations were assumed to be 17.5 ppb during the spring even though the preliminary DW LOC for infants was calculated to be 12.6 ppb.

Table 3 Effect of DW Consumption assumptions used in DW LOC Calculations

Age Group	DW Consumption (kg H_20/kg bwt)	DW Residues (ppm=mg/kg H_20)	DW Exposure (mg ai/kg bwt)	%cPAD (0.0018)	Prelim DW LOC (ppm)
Infants					
(7 kg bwt,1 Liter)	0.1429	0.0175	0.00250	139%	0.0126
(Mean DW Consumption)	0.0685	0.0175	0.00120	67%	0.0263
Toddlers, 1to3 yr olds					
(13 kg bwt, 1 Liter/day)	0.0769	0.0175	0.00135	75%	0.0234
(Mean DW Consumption)	0.0308	0.0175	0.00054	30%	0.0584
Children, 4to12 yr olds					
(30 kg bwt, 1 Liter/day)	0.0333	0.0175	0.00058	32%	0.0540
(Mean DW Consumption)	0.0219	0.0175	0.00038	21%	0.0822

[6] The expected mean chronic exposure estimates in Lifeline will differ from these estimated values since Lifeline uses its own anthropomorphic body weight models rather than the CSFII respondents' body weights to generate drinking water consumption values for each modeled individual. See Reference cited in Footnote 2 for further details.

Females, 13to49 yr olds					
(67 kg bwt, 2 Liters/day)	0.0299	0.0175	0.00052	29%	0.0603
(Mean DW Consumption)	0.0194	0.0175	0.00034	19%	0.0928
Adults					
(76 kg bwt, 2 Liters/day)	0.0286	0.0175	0.00050	26%	0.0684
(Mean DW Consumption)	0.0209	0.0175	0.00037	20%	0.0861

4.0 TOLERANCE REASSESSMENT

With the exceptions of fish and bananas, tolerances for simazine residues are currently expressed in terms of simazine *per se*. Tolerances for simazine residues in/on fish and bananas [40 CFR 180.213(a)(2)] are currently expressed as the combined residues of simazine and its two chlorometabolites, G-28270 and G-28273.

The tolerance expression in 40 CFR 180.213(a)(1) should be changed to reflect the combined residues of simazine and its chlorometabolites, 2-amino-4-chloro-6-ethylamino-*s*-triazine (G-28279) and 2-chloro-4,6-diamino-*s*-triazine (G-28273), and the two paragraphs should be combined.

A summary of the simazine tolerance reassessment and recommended modifications in commodity definitions are presented in Table C; reassessments are based on tolerances redefined as simazine and its chlorometabolites.

Tolerances Listed Under 40 CFR 180.213(a)(1):

Sufficient data are available to reassess tolerances for residues of simazine and its chlorometabolites in/on, avocados, blueberries, raspberries and other caneberries (blackberries, boysenberries, and loganberries),corn (forage, fodder, and grain), filberts, grapes, olives, peaches, pecans, and plums. Currently no PHI exists for apples. If an acceptable PHI is proposed for apples no additional field trials are required. If no PHI is proposed then additional field trials are needed. Additional residue data are required on almonds (nutmeats and hulls), cherries, corn (K+CWHR), cranberries, citrus fruit (grapefruit, lemons, and oranges), currants, macadamia nuts, pears, strawberries and walnuts.

As Syngenta is not supporting uses of simazine on alfalfa, artichokes, asparagus, grasses, and sugarcane, tolerances for all commodities derived from these crops should be revoked.

The available corn fodder data support maintaining the tolerance for corn stover at 0.25 ppm.. The available residue data on avocados, corn forage and grain, grapes, and olives support lowering the tolerances on these commodities from 0.25 ppm to 0.20 ppm. The available residue data on blueberries and caneberries support establishing a crop group tolerance for the berries crop group at 0.20 ppm, and deleting the separate tolerances for blackberries, blueberries, boysenberries, currants, dewberries, loganberries, raspberries.

The available data from pecans and filberts would support setting a tolerance at 0.20 ppm; additional data are required to support tolerances in on almonds, macadamia nuts and walnuts.

The currently available residue data on apple support lowering the tolerance to 0.20 ppm, however, 6 additional trials are required for apples. Until these data are reviewed the tolerance cannot be reassessed. No adequate data are currently available to support a tolerance on pears. No field trials are required if a PHI based on existing residue data is proposed.

The available residue data on peaches and plums support lowering the tolerances to 0.20 ppm; additional data are required to support a tolerance in/on cherries.

Sufficient data are available to reassess tolerances for residues of simazine and its chlorometabolites in animal commodities. Based upon the MTDB of 0.42-0.45 ppm for beef and dairy cattle and residue data from the ruminant feeding study, residues of simazine and its chlorometabolites are unlikely to occur at quantifiable levels in fat of cattle, goats, horses, and sheep; therefore tolerances for these commodities should be revoked. These data also indicate that tolerances for residues of simazine and its chlorometabolites should be increased to 0.03 ppm (combined LOQ) in milk and in meat-byproducts (mbyp) and meat of cattle, goats, horses, and sheep.

Data from the ruminant feeding study also indicate that a Category 3 [40 CFR 180.6(a)(3)] situation also exists for simazine residues in fat, meat, and mbyp of hogs; therefore, tolerances for residues in these commodities should be revoked.

Based on the maximum dietary burden for poultry (0.16 ppm) and data from the poultry feeding study, a Category 3 [40 CFR 180.6(a)(3)] situation also exists for simazine residues in poultry fat, meat, and mbyp. Therefore, tolerances for residues in these commodities should be revoked. However, the tolerance for residues in eggs should be increased to 0.03 ppm to reflect the combined LOQ for simazine and its chlorometabolites in eggs.

Tolerances Listed Under 40 CFR 180.213(a)(2):

All aquatic uses of simazine have been cancelled, except for ornamental ponds. HED has therefore concluded that the tolerance for residues in fish should be revoked.

Syngenta is not supporting the use of simazine on bananas; however, residue data are available supporting the 0.20 ppm tolerance for residues in/on bananas. If another registrant supports the use of simazine on bananas in Central America, then the tolerance for bananas should be reassigned to 40 CFR 180.213(a)(1).

Tolerances Needed Under 40 CFR 180.213(a)(1):

Additional data are also required on processing studies of apples, corn, grapes, oranges, and olives treated at exaggerated rates. Therefore, tolerances for residues in processed commodities of these crops may be required at a later date. The existing processing study on oranges indicates that a tolerance of at least 0.30 ppm will be required for simazine residues in citrus oil.

Limited field trials are required for a root and tuber crop, a leafy green vegetable and a small grain. Rotational crop tolerances will be established as required after these data have been submitted.

Table C. Tolerance Reassessment for Simazine

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances Currently listed under 40 CFR 180.213(a)(1):			
Alfalfa	15.0	Revoke	Uses on alfalfa are not being supported.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Alfalfa, forage	15.0	Revoke	Uses on alfalfa are not being supported.
Alfalfa, hay	15.0	Revoke	Uses on alfalfa are not being supported.
Almond	0.25	TBD	Additional residue data are required to support a tolerance for almonds
Almond, hulls	0.25	TBD	Additional residue data are required to support a tolerance for almond, hulls.
Apple	0.25	0.20	The available residue data support lowering the tolerance to 0.20 ppm.
Artichoke	0.5 [a]	Revoke	Uses on these crops have been cancelled.
Asparagus	10.0 [a]	Revoke	Uses on these crops have been cancelled.
Avocado	0.25	0.20	The available residue data support lowering the tolerance.
Blackberry	0.25	0.20	The available residue data support lowering the tolerance.
Boysenberry	0.25	Reassign	The boysenberry tolerance is covered by the blackberry tolerance.
Blueberry	0.25	0.20	The available residue data support lowering the tolerance.
Cattle, fat	0.02 (N) [b]	Revoke	There is no reasonable expectation of finding quantifiable residues fat.
Cattle, meat byproducts	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, and its G-28279, and G-28273 metabolites.
Cattle, meat	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, and its G-28279, and G-28273 metabolites.
Cherry, Sweet	0.25	TBD	Additional residue data are required to reassess the tolerance
Cherry, Tart	0.25	TBD	Additional residue data are required to reassess the tolerance
Corn, field, fodder	0.25	0.25	Change to Corn, field, stover
Corn, field, forage	0.25	0.20	The available data indicate that the tolerance can be lowered to 0.20 ppm
Corn, sweet, grain	0.25	TBD	Change to Corn, sweet, kernal + cob with husks removed Additional residue data are required to reassess this tolerance

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Corn, field, grain	0.25	0.20	The available data indicate that the tolerance can be lowered to 0.20 ppm
Cranberry	0.25	TBD	Additional residue data are required to reassess this tolerance
Currant	0.25	TBD	Additional residue data are required to reassess this tolerance
Dewberry	0.25	Reassign	Dewberry is covered by the blackberry tolerance.
Egg	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, G-28279, and G-28273 in eggs.
Filbert	0.25	0.20	The available data indicate that the tolerance can be lowered to 0.20 ppm
Goat, fat	0.02 (N)	Revoke	There is no reasonable expectation of finding quantifiable residues in fat.
Goat, meat byproducts	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, G-28279, and G-28273.
Goat, meat	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, and its G-28279, and G-28273 metabolites.
Grapefruit	0.25	TBD	Residue data are required to reassess this tolerance.
Grape	0.25	0.20	Tolerance should be set at the combined LOQ (0.2 ppm) for simazine, G-28279, and G-28273.
Grasses	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, forage	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, hay	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, Bermuda	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, Bermuda, forage	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, Bermuda, hay	15.0	Revoke	Food/feed uses on grasses are not being supported.
Grasses, forage	15.0	Revoke	Food/feed uses on grasses are not being supported.
Hog, fat	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of hogs.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Hog, meat byproducts	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of hogs.
Hog, meat	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of hogs.
Horse, fat	0.02 (N)	Revoke	There is no reasonable expectation of finding quantifiable residues in fat.
Horse, meat byproducts	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, G-28279, and G-28273.
Horse, meat	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, and its G-28279, and G-28273 metabolites.
Lemon	0.25	TBD	Residue data are required to set tolerances on lemons.
Loganberry	0.25	0.20	The available residue data support lowering the tolerance.
Nut, Macadamia	0.25	TBD	Residue data are required to set tolerances on macadamia nuts.
Milk	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, G-28279, and G-28273.
Olive	0.25	0.20	The available data indicate that the tolerance can be lowered to 0.20 ppm
Orange	0.25	TBD	Additional data are required to set tolerances on oranges.
Peach	0.25	0.20	The available residue data support lowering the tolerance to 0.20 ppm.
Pear	0.25	TBD	Residue data are required for pears.
Pecan	0.1 (N)	0.20 (N)	The available residue data support increasing the tolerance to 0.20 ppm.
Plum	0.25	0.20	The available residue data support lowering the tolerance to 0.20 ppm.
Poultry, fat	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of poultry.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Poultry, meat byproducts	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of poultry.
Poultry, meat	0.02 (N)	Revoke	A category 6(a)(3) situation exists for the potential of simazine residues in meat, mbyp, and fat of poultry.
Raspberry	0.25	0.20	The available residue data support lowering the tolerance.
Sheep, fat	0.02 (N)	Revoke	There is no reasonable expectation of finding quantifiable residues in fat.
Sheep, meat byproducts	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, G-28279, and G-28273.
Sheep, meat	0.02 (N)	0.03	Tolerance should be set at the combined LOQ (0.03 ppm) for simazine, and its G-28279, and G-28273 metabolites.
Strawberry	0.25	TBD	Residue data for strawberries are required.
Sugarcane, cane	0.25 [a]	Revoke	Uses on sugarcane have been canceled.
Sugarcane, molasses	1.0	Revoke	Uses on sugarcane have been canceled.
Walnut	0.2	TBD	Additional data for walnuts are required.
Tolerances Listed under 40 CFR 180.213(a)(2):			
Banana	0.2	Reassign	Tolerance should be moved to 40 CFR 180.213(a)(1)
Fish	12.0	Revoke	Aquatic uses, except for decorative ponds, have been canceled
Tolerances needed under 40 CFR 180.213(a):			
Rotational Crops	None	TBD	The need for tolerances on rotational crops will be re-evaluated after limited field trials have been completed.
Citrus, oil	None	TBD	Additional data are required; however, the existing orange processing study indicates that a tolerance of at least 0.30 ppm is necessary for citrus oil.

[a] Uses on artichokes, asparagus, and sugarcane have been canceled.

[b] (N) indicates tolerance set at the limit of detection.

CODEX HARMONIZATION

No maximum residue limits (MRLs) for simazine have been established or proposed by Codex for any agricultural commodity. Canada and Mexico do not currently have MRLs for simazine. Therefore, no compatibility questions exist with respect to U.S. tolerances.

References:

1. SIMAZINE: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document. Steven Weiss, Environmental Health Scientist, Wade Britton, Industrial Hygienist, Health Effects Division, DP Barcode: D307024, PC Code: 080807, December 8, 2004.

2. SIMAZINE: Residue Chemistry Considerations for the Reregistration Eligibility Decision Document. David Soderberg, Chemist, Health Effects Division, May 26, 2005.

3. Review of Simazine Incident Reports, Jerome Blondell, Ph.D., Health Statistician, Chemistry and Exposure Branch 1, Health Effects Division, DP Barcode D276337, PC Code: 080807, July 19, 2001.

4. SIMAZINE: Product Chemistry Considerations for the Reregistration Eligibility Decision Document. David Soderberg, Chemist, Health Effects Division, December 8, 2004.

5. "Drinking Water Assessment for Simazine", M. Frankenberry, EFED/C. Eiden HED, October 28, 2004.

6. SIMAZINE: Third Report of the Cancer Assessment Review Committee. April 14., 2005.