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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**Date:** 20-DEC-2017

**SUBJECT:** **Ametryn** – Preliminary Human Health Risk Assessment for Registration Review.

**PC Code:** 080801
**Decision No.:** 530423
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical/Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** D440785
**Registration Nos.:** 100-786, SLN# HI-120004
**Regulatory Action:** Registration Review Risk Assessment
**Case No.:** 2010
**CAS No.:** 834-12-8
**40 CFR:** §180.258

**From:** Sarah J. Levy, Chemist
Cassi Walls, Ph.D., Biologist
Connor Williams, Toxicologist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

**Through:** Christine L. Olinger, Branch Chief
George F. Kramer, Ph.D., Branch Senior Scientist
RAB1/HED (7509P)

**To:** Christian Bongard, Chemical Review Manager
Kelly Sherman, Branch Chief
Risk Management and Implementation Branch 3
Pesticide Re-Evaluation Division (PRD) (7508P)

As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of OPP has requested that HED evaluate the hazard and exposure data and conduct occupational and residential exposure (ORE) assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's Preliminary Registration Review risk assessment of the dietary, occupational and residential handler, post-application exposure, and aggregate risk from the registered/proposed uses of ametryn (*N*-ethyl-*N'*-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine).

A summary of the findings and an assessment of human risk resulting from the registered and proposed uses are provided in this document. The risk assessment, dietary risk assessment, and residue chemistry review were provided by Sarah Levy (RAB1), the occupational/residential exposure and risk assessment was provided by Cassi Walls (RAB1), the hazard characterization

was provided by Connor Williams (RAB1), and the drinking water assessment was provided by Joshua Antoline of the Environmental Fate and Effects Division (EFED).

**Table of Contents**

**1.0 Executive Summary** ..... 4
**2.0 HED Conclusions** ..... 6
2.1 Data Deficiencies ..... 6
2.2 Tolerance Considerations ..... 6
2.2.1 Enforcement Analytical Method ..... 6
2.2.2 Revisions to Established Tolerances ..... 7
2.2.3 International Harmonization ..... 8
2.3 Label Recommendations ..... 8
**3.0 Ingredient Profile** ..... 8
3.1 Chemical Identity ..... 8
3.2 Pesticide Use Pattern ..... 9
3.3 Anticipated Exposure Pathways ..... 11
3.4 Consideration of Environmental Justice ..... 11
**4.0 Hazard Characterization and Dose-Response Assessment** ..... 11
4.1 Toxicology Studies Available for Analysis ..... 11
4.2 Absorption, Distribution, Metabolism, & Elimination (ADME) ..... 12
4.2.1 Dermal Absorption ..... 12
4.3 Summary of Toxicological Effects ..... 13
4.4 Safety Factor for Infants and Children (FQPA Safety Factor) ..... 13
4.4.1 Completeness of the Toxicology Database ..... 14
4.4.2 Evidence of Neurotoxicity ..... 14
4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal ..... 14
4.4.4 Residual Uncertainty in the Exposure Database ..... 14
4.5 Toxicity Endpoint and Point of Departure Selections ..... 14
4.5.1 Dose-Response Assessment ..... 14
4.5.2 Recommendations for Combining Routes of Exposures for Risk Assessment ..... 15
4.5.3 Cancer Classification and Risk Assessment Recommendation ..... 15
4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Health Risk Assessment ..... 16
4.6 Endocrine Disruptor Screening Program ..... 17
**5.0 Dietary Exposure and Risk Assessment** ..... 18
5.1 Metabolite/Degradate Residue Profile ..... 18
5.1.1 Summary of Plant and Livestock Metabolism Studies ..... 18
5.1.2 Summary of Environmental Degradation ..... 18
5.1.3 Comparison of Metabolic Pathways ..... 19
5.1.4 Residues of Concern Summary and Rationale ..... 19
5.2 Food Residue Profile ..... 20
5.3 Drinking Water Residue Profile ..... 20
5.4 Dietary (Food + Drinking Water) Risk Assessment ..... 21
5.5 Percent Crop Treated Estimates ..... 22
**6.0 Residential (Non-Occupational) Exposure/Risk Characterization** ..... 22
6.1 Residential Bystander Post-Application Inhalation Exposure ..... 22
6.2 Non-Occupational Spray Drift Exposure and Risk Estimates ..... 23
**7.0 Aggregate Exposure/Risk Characterization** ..... 24
**8.0 Cumulative Exposure/Risk Characterization** ..... 24
**9.0 Occupational Exposure/Risk Estimates** ..... 25
9.1 Occupational Handler Exposure/Risk Estimates ..... 25
9.2 Occupational Post-Application Exposure/Risk Estimates ..... 28
9.2.1 Occupational Inhalation Post-Application Exposure/Risk Estimates ..... 28
9.2.2 Occupational Dermal Post-Application Exposure/Risk Estimates ..... 28
**10.0 Public Health and Pesticide Epidemiology Data** ..... 29
**11.0 References** ..... 29

**Appendix A. Toxicology Profile and Executive Summaries** ..... 31
A.1 Toxicology Data Requirements ..... 31
A.2 Toxicity Profiles ..... 31
**Appendix B. Physical/Chemical Properties.** ..... 34
**Appendix C. IRLS.** ..... 34

## 1.0 Executive Summary

This assessment has been conducted to support the Registration Review of the herbicide ametryn (*N*-ethyl-*N′*-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine). As part of Registration Review, the PRD of Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary and occupational/residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of ametryn.

***Background*:** Ametryn is a selective methylthiotriazine herbicide currently undergoing registration review. It is registered for use on field corn, popcorn, pineapple, and sugarcane. There are no residential or non-agricultural uses registered for ametryn. There is currently one end-use product (EUP) containing ametryn as the active ingredient (ai) sold under the name Evik® DF (100-786). The last risk assessment for ametryn was part of the Reregistration Eligibility Decision (RED) document issued in 2005 (Memo, W. Donovan *et al.*, 15-JUN-2005; D316695).

Humans may be exposed to ametryn in food and drinking water since ametryn may be applied directly to growing crops and application may result in residues reaching surface and ground water sources of drinking water. Residential handler and post-application exposures to ametryn are not expected. Non-occupational exposures may occur as a result of spray drift. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application exposures may occur when workers enter previously treated agricultural areas. This risk assessment considers all of the aforementioned exposure pathways based on the existing ametryn uses.

***Hazard Assessment*:** Following subchronic and chronic oral exposures to rabbits, mice, dogs, and rats, the most consistent effect observed in the database was decreased absolute body weight. The effects in the chronic dietary study in dogs included degenerative and inflammatory liver effects. In rats following chronic exposure, histopathological lesions in the kidney, testes, and pituitary gland were observed in male rats and histopathological lesions in the liver and pancreas were observed in female rats. No adverse effects were seen in rabbits following dermal exposures up to the limit dose. There was no indication of either quantitative or qualitative susceptibility in prenatal or developing animals.

The Cancer Assessment Review Committee (CARC), based of a weight of the available data, re-classified ametryn as “Suggestive Evidence of Carcinogenic Potential”. EPA has concluded that quantification of cancer risk using a non-linear approach (i.e., reference dose or RfD) will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to ametryn.

Ametryn is classified as having low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). It is mildly irritating to the eyes but is not irritating to the skin and is not a dermal sensitizer.

***Dose-Response Assessment*:** All of the points of departure (PODs) for ametryn, with the exception of the chronic dietary endpoint, are based upon decreased absolute body weight and food consumption and increased absolute and relative liver weights as observed in the maternal animals in the developmental toxicity study in rabbits. The lowest-observed-adverse-effect level (LOAEL) is 60 mg/kg/day and the no-observed-adverse-effect-level (NOAEL) is 10 mg/kg/day. The POD for chronic dietary exposure is based on degenerative and inflammatory liver effects observed in the chronic toxicity study in dogs at a LOAEL of 70 mg/kg/day and a NOAEL of 7.2 mg/kg/day. An acute dietary endpoint was not selected. A dermal endpoint was not selected as there were no adverse effects observed in the dermal toxicity study up to the limit dose of 1000 mg/kg/day.

The risk assessment team determined that the Food Quality Protection Act Safety Factory (FQPA SF) should be reduced to 1X. Therefore, for all exposure scenarios, a 100-fold uncertainty factor (10X interspecies extrapolation, 10X intraspecies variation, and 1X FQPA, when applicable) was applied.

***Residue Chemistry*:** There are adequate residue chemistry data are available to support the registered and proposed uses. HED is requesting modification to one of the tolerance values and the tolerance expression (see Section 2.2.2).

***Dietary (Food and Water) Exposure and Risk*:** A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16 which incorporates consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). The chronic analysis assumed tolerance-level residues, 100% crop treated (CT), default processing factors, and modeled drinking water estimates. The highest chronic exposure estimate was for the population subgroup all infants (<1 year old), which utilized 38% of the chronic population-adjusted dose (cPAD) for ametryn. An acute endpoint was not selected as there are no adverse single dose effects in the database; therefore, an acute dietary exposure assessment was not conducted. Ametryn was classified as "suggestive evidence of carcinogenic potential"; however, the existing chronic endpoint is protective of potential effects. Therefore, a cancer dietary exposure and risk assessment was not conducted for ametryn.

***Residential (Non-Occupational) Exposure and Risk*:** Since there are no existing residential uses for ametryn, a quantitative residential handler and post-application exposure assessment was not conducted.

***Non-Occupational Spray Drift Exposure and Risk*:** A quantitative non-occupational spray drift assessment was conducted for Registration Review. Children's (1 to <2 years old) incidental oral risk estimates from exposure to ametryn associated to spray drift residues results in no risks of concern at the field edge for either groundboom or aerial applications. Dermal exposures were not quantitatively assessed since no dermal hazard was identified

***Aggregate Exposure and Risk*:** The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-

occupational exposures). Since there are no residential uses of ametryn that require a quantitative risk assessment, the acute and chronic aggregate risk assessments are equal to the acute dietary and chronic dietary estimates (food and water only), respectively. The acute and chronic aggregate exposures to the general U.S. population and all other population subgroups from the uses of ametryn do not exceed HED's LOC.

***Occupational Exposure and Risk*:** There is the potential for occupational exposure from the existing uses of ametryn. Since no dermal hazard was identified, a quantitative dermal assessment was not conducted for the occupational uses. The occupational handler exposure and risk estimates indicate that the short- and intermediate-term inhalation margins of exposure (MOEs) are not of concern to HED (i.e., inhalation MOEs ≥ 100) at labeled personal-protective equipment (PPE) attire (i.e., PF5 respirator).

Occupational post-application dermal exposure and risk estimates were not assessed since a dermal hazard was not identified. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for ametryn at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for ametryn.

***Environmental Justice*:** Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf.

## 2.0 HED Conclusions

Provided revisions to the current tolerances are made as recommended in Section 2.2.2, the toxicological, residue chemistry, and ORE databases are adequate to support all currently registered uses. There are no risks of concern identified for the currently registered uses.

## 2.1 Data Deficiencies

There were no data deficiencies identified in the residue chemistry, toxicological, or exposure databases.

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

Adequate methods are available for enforcing tolerances and/or collecting data on ametryn residues in/on plant and livestock commodities. Two gas chromatography (GC) methods are available for enforcing tolerances of ametryn in plant commodities and are listed as Methods I and A in the Pesticide Analytical Method Volume II (PAM II; Section 180.258). Method I is a GC/microcoulometric (MC) detection method for determining ametryn *per se*, with a limit of

quantitation (LOQ) of 0.05 ppm. Method A is a GC/flame-photometric detection (sulfur mode, FPD-S) method for determining residues of ametryn and its three thiomethyl metabolites (GS-11354, GS-11355, and GS-26831), with a LOQ of 0.05 ppm for parent and 0.1 ppm for each metabolite.

### 2.2.2 Revisions to Established Tolerances

Permanent tolerances are established in 40 CFR §180.258 for residues of ametryn in various plant commodities. A revision is recommended at this time as listed in Table 2.2.2 to include the number of significant figures to be consistent with HED policy.

Furthermore, based on the HED Interim Guidance on Tolerance Expressions (S. Knizner, 27-MAY-2009), the tolerance expression should be changed to conform to current HED policy. Specifically, the tolerance expression for 40 CFR §180.258(a) should be as follows:

> Tolerances are established for residues of the herbicide ametryn, including its metabolites and degradates, in or on the commodities listed in the following table. Compliance with the tolerance levels specified below is to be determined by measuring only ametryn (*N*-ethyl-*N*′-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine), in or on the following commodities:

**Table 2.2.2. Summary of Recommended Tolerances for Ametryn.**

| Commodity | Currently Established Tolerance (ppm) | HED-Recommended Tolerance (ppm) | Comments (*correct commodity definition*) |
|---|---|---|---|
| **§180.258 (a) General** | | | |
| Corn, field, forage | 0.1 | 0.10 | Correct number of significant figures to be consistent with HED policy. |
| Corn, field, grain | 0.05 | 0.05 | |
| Corn, field, stover | 0.05 | 0.05 | |
| Corn, pop, grain | 0.05 | 0.05 | |
| Corn, pop, stover | 0.05 | 0.05 | |
| Pineapple | 0.05 | 0.05 | |
| Sugarcane, cane | 0.05 | 0.05 | |

### 2.2.3 International Harmonization

An International Residue Limit Status (IRLS) form is appended to this document as Appendix C. U.S. permanent tolerances (listed in 40 CFR §180.258). There are no Canadian, Mexican, and Codex Maximum Residue Limits (MRLs) established for ametryn; therefore, harmonization is not an issue.

## 2.3 Label Recommendations

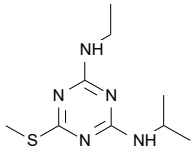
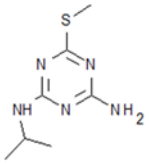
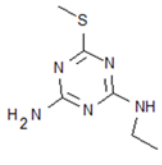
None.

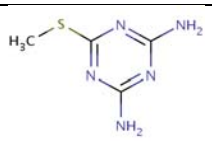
# 3.0 Ingredient Profile

## 3.1 Chemical Identity

The chemical structure and nomenclature of ametryn and its metabolites are presented in Table 3.1. The physicochemical properties of ametryn are summarized in Appendix B.

**Table 3.1. Ametryn Nomenclature.**

| | |
|---|---|
| Compound |  |
| Common name | Ametryn |
| Molecular Formula | $C_9H_{17}N_5S$ |
| IUPAC name | *N*$^2$-ethyl-*N*$^4$-isopropyl-6-methylthio-1,3,5-triazine-2,4-diamine |
| CAS name | *N*-ethyl-*N*′-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine |
| CAS registry number | 834-12-8 |
| Chemical structure |  |
| Common name | NA |
| Company experimental name | GS-11354; CG-3 |
| IUPAC name | NA |
| CAS name | *N*-isopropyl-6-(methylthio)-1,3,5-triazine-2,4-diamine |
| CAS registry number | 4147-57-3 |
| Chemical structure |  |
| Common name | NA |
| Company experimental name | GS-11355; CG-4 |
| IUPAC name | NA |

| Table 3.1. Ametryn Nomenclature. | |
|---|---|
| CAS name | *N*-ethyl-6-(methylthio)-1,3,5-triazine-2,4-diamine |
| CAS registry number | 4147-58-4 |
| Chemical structure |  |
| Common name | NA |
| Company experimental name | GS-26831; CG-2 |
| IUPAC name | NA |
| CAS name | 6-(methylthio)-1,3,5-triazine-2,4-diamine |
| CAS registry number | 5397-01-3 |

## 3.2 Pesticide Use Pattern

Ametryn is a selective herbicide currently registered for use on corn, pineapple, and sugarcane. There is currently one EUP and one SLN registration containing ametryn as the active ingredient. The EUP, Evik® DF (100-786), is a dry-flowable (DF) formulation containing 78.9% ai used on corn, pineapple, and sugarcane. The SLN (HI-120004) is the same formulation as the EUP but can be used in HI on sugarcane at elevated wind speeds. Ametryn can be applied by groundboom or aerial (FL sugarcane only) applications. The current label requires handlers to wear baseline attire (defined in this assessment as a long-sleeved shirt, long pants, shoes and socks), chemical-resistant gloves, and a minimum of a National Institute for Occupational Safety and Health (NIOSH) approved filtering face piece respirator (PF5). There are currently no registered residential or homeowner uses. The use pattern and formulation for this ametryn is summarized in Table 3.2.

| Table 3.2. Summary of Use Patterns for Ametryn. | | | |
|---|---|---|---|
| **Formulation** | **Method of Application** | **Maximum Application Rate** | **Use Restrictions** |
| **Corn (field corn, popcorn)** | | | |
| Evik® DF<br>EPA Reg #100-786<br><br>DF<br>(78.9% ai) | Ground | 1.6 lb ai/A | Apply by ground using a minimum of 20 gal water/A<br>Do not apply by air<br>1 application per year<br>12-hour REI.<br>PHI: 30 days<br>PPE: long-sleeved shirt and pants, shoes plus socks, chemical resistant gloves, and NIOSH filtering face piece respirator |
| **Pineapple** | | | |
| Evik® DF<br>EPA Reg #100-786<br><br>DF<br>(78.9% ai) | Ground | 1.6 lb ai/A | Apply by ground using a minimum of 20 gal water/A<br>Do not apply by air<br>2 applications per year<br>12-hour REI.<br>PHI: 160 days<br>PPE: long-sleeved shirt and pants, shoes plus socks, chemical resistant gloves, and NIOSH filtering face piece respirator |
| **Sugarcane** | | | |
| Evik® DF<br>EPA Reg #100-786<br><br>DF<br>(78.9% ai) | Ground | 2.4 lb ai/A | HI<br>3 applications per year<br>12-hour REI.<br>PPE: long-sleeved shirt and pants, shoes plus socks, chemical resistant gloves, and NIOSH filtering face piece respirator |
| | Aerial | 1.2 lb ai/A | Florida Only<br>Apply by air using a minimum of 5 gal water/A<br>3 applications per year<br>12-hour REI.<br>Human Flagging is prohibited<br>PPE: long-sleeved shirt and pants, shoes plus socks, chemical resistant gloves, and NIOSH filtering face piece respirator |
| | Ground | 1.2 lb ai/A | FL, TX, LA<br>Apply by ground using a minimum of 20 gal water/A<br>3 applications per year<br>12-hour REI<br>PPE: long-sleeved shirt and pants, shoes plus socks, chemical resistant gloves, and NIOSH filtering face piece respirator |
| Evik® DF<br>EPA Reg #100-786<br>EPA SLN# HI-120004<br><br>DF<br>(78.9% ai) | Ground | 2.4 lb ai/A | 3 applications per year<br>12-hour REI.<br><br>Can be applied at wind speeds up to 10-20 mph |

### 3.3 Anticipated Exposure Pathways

Humans may be exposed to ametryn in food and drinking water, since its registered uses allow application directly to growing crops, which may also result in residues reaching surface and ground water sources of drinking water. There are no registered residential uses of ametryn; therefore, human exposure in residential or non-occupational settings are not expected to occur. However, there is a potential for short-term incidental post-application exposure to occur from residues on turf resulting from spray drift. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

This risk assessment considers all of the aforementioned exposure pathways based on the existing registered uses.

### 3.4 Consideration of Environmental Justice

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

## 4.0 Hazard Characterization and Dose-Response Assessment

### 4.1 Toxicology Studies Available for Analysis

The toxicological database for ametryn is adequate for hazard characterization, toxicity endpoint selection, and FQPA SF consideration. The Hazard and Science Policy Council (HASPOC) evaluated all existing hazard and exposure data for ametryn and concluded using a weight-of-evidence approach that the neurotoxicity (acute and subchronic) and immunotoxicity studies are not required at this time (Memo, J. Van Alstine, 20-FEB-2013; TXR# 0056557 and Memo, U.

Habiba, 18-NOV-2014; TXR# 0057074). Additionally, the HASPOC evaluated the need for a subchronic inhalation study. Initially, the HASPOC concluded a subchronic inhalation study was required (Memo, J. Van Alstine, 20-FEB-2013; TXR# 0056557); however, in a response to comments document, it was noted that if sugarcane is assessed as a "typical" acreage crop (for aerial applications in Florida and groundboom applications in Hawaii) and if a PF5 respirator is added to the registered labels, MOEs for all scenarios would be sufficiently high (i.e., ≥1,000) to warrant a waiver for the inhalation study (Memo; K. Lowe, 12-NOV-2015; D427954). Subsequently, the registrant agreed to revise the registered labels to require a PF5 respirator; therefore, HASPOC concluded that an inhalation study is not required at this time (Memo, A. Wray, 20-DEC-2017; TXR# 0057693). Appendix A includes a summary of the ametryn toxicological database. Ametryn was evaluated for the following:

1) Subchronic oral toxicity in rats;
2) Chronic oral toxicity in rats and dogs;
3) Subchronic dermal toxicity in rabbits;
4) Developmental toxicity in rats and rabbits;
5) Reproductive and postnatal toxicity in rats;
6) Carcinogenicity in mice and rats;
7) Genotoxicity and mutagenicity studies; and
8) Absorption, distribution, metabolism, and excretion (ADME) in rats.

## 4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Ametryn is readily absorbed by rats after a single or multiple oral doses of 0.5 or 200 mg/kg, or an intravenous dose of 0.5 mg/kg. It is widely distributed, being found in all tissues and organs sampled at study termination, although at low levels. It is metabolized to several polar products, 13 of which were identified as major metabolites. It is excreted mainly through the urine (47-55% in females, 52-59% in males) within 48 hours with the feces being the other major route (30-39% in females, 29-36% in males). No significant differences in metabolic and bioavailability parameters were seen among dosing groups (singular oral high and low, multiple low) or between sexes.

N-Dealkylation of the molecule and glutathione conjugation, leading to mercapturic acid analogs, were the major routes of biotransformation in the rats. Oxidation of the n-isopropyl side chain to n-isopropionate and sulfate conjugation were also observed.

### 4.2.1 Dermal Absorption

There are no dermal penetration studies available for ametryn. In the previous risk assessment (Memo, W. Donovan, 03-NOV-2004; D309463), a dermal-absorption factor (DAF) of 6% was derived from the LOAEL of 1000 mg/kg/day in the dermal toxicity study in rabbits based on decreased body weight gain and food consumption and the LOAEL from the oral developmental toxicity study in rabbits (60 mg/kg/day) based on decreased food consumption, increased liver weight and body weight loss (i.e., 60/1000 x 100% = 6%). The effects in the dermal toxicity study are no longer considered adverse according to current practices in hazard evaluation. Although decreases in body weight gain and food consumption were observed, there was no corresponding adverse effect on absolute body weights. As a result, there were no adverse

effects seen in the dermal toxicity study up to the limit dose (1000 mg/kg/day). Therefore, as there is also no indication of susceptibility in offspring, a dermal endpoint is not considered necessary.

## 4.3 Summary of Toxicological Effects

Following subchronic and chronic oral exposures to rabbits, mice, dogs, and rats, the most consistent effects observed in the database were effects on body weight and food consumption and changes in the liver. Dogs were the most sensitive species, and, following chronic exposure, degenerative and inflammatory effects were observed in the liver (granulomatous, purulent, and lymphocytic inflammation; isolated cellular necrosis; endogenous pigment deposition; vacuolar degeneration; bile duct hyperplasia; and necrosis). In rats, chronic exposure elicited various effects including decreased body weight and body weight gain (both sexes), histopathological lesions in the kidney, testes, and pituitary gland (males only), and in the liver and pancreas (females only). No adverse effects were seen in rabbits following dermal exposures up to the limit dose.

There was no evidence of increased pre- or post-natal quantitative susceptibility for ametryn in the developmental or the reproductive studies. There were no adverse developmental effects observed in rats or rabbits in either study at the doses tested. Maternal effects included an increased incidence of ptosis and salivation in rats and body weight loss, decreased food consumption and increased liver weight in rabbits. In the two-generation reproduction study in rats, offspring effects (decreased pup body weights in the $F_2$ generation) occurred at same dose producing parental toxicity (decreased body weight, weight gain and food efficiency).

Tumor formation was observed at the highest dose tested in the combined chronic/ carcinogenicity study in rats. However, the high dose used in the study initially also produced excessive systemic toxicity until the dose was stepped down for the final year of the study. CARC evaluated the data and concluded that based on the evidence of carcinogenic activity, combined with the inability to draw more precise conclusions due to study limitations, ametryn displayed “suggestive’ evidence of carcinogenicity. The mutagenicity and genotoxicity batteries for ametryn all returned negative results. The carcinogenicity study in mice also showed no indications of carcinogenicity or tumorigenesis up to the highest dose tested.

Ametryn is classified as having low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). It is minimally irritating to the eyes (Toxicity Category III) and essentially non-irritating to the skin (Toxicity Category IV). Ametryn is not a dermal sensitizer.

## 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[1]

The RAB1 risk assessment team determined that the FQPA SF should be reduced to 1X for all exposure scenarios. The toxicological database for ametryn is complete. The dietary and residential exposure analyses are unlikely to underestimate exposure. Furthermore, there was no

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

evidence of neurotoxicity or increased offspring susceptibility in the ametryn toxicological database.

### 4.4.1 Completeness of the Toxicology Database

The existing toxicological database for ametryn is complete. Developmental toxicity studies in rats and rabbits as well as a two-generation reproduction toxicity study are available for FQPA consideration.

### 4.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity in the ametryn toxicological database. The HASPOC concluded using a weight-of-evidence approach that the acute and subchronic neurotoxicity screening batteries were not required at this time (Memo, J. Van Alstine, 20-FEB-2013; TXR# 0056557).

### 4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There was no evidence of increased quantitative or qualitative susceptibility in the developmental toxicity studies in rabbits or rats or the two-generation reproduction toxicity study in rats.

### 4.4.4 Residual Uncertainty in the Exposure Database

The exposure databases for ametryn are complete or are estimated based on data that reasonably account for all potential exposures. There are no registered residential uses and/or commercial uses at residential sites at this time. Therefore, a full residential exposure assessment is not required.

The dietary exposure analyses are conservative and are not expected to underestimate exposure and risk. The dietary analysis assumed tolerance-level residues, default processing factors, 100% CT, and modeled drinking water estimates.

## 4.5 Toxicity Endpoint and Point of Departure Selections

Table 4.5.4.1 and 4.5.4.2 summarize the toxicological doses and endpoints selected for dietary, non-occupational, and occupational risk assessments. The rationale for the dose/endpoint selection is also described below. Since the last risk assessment (Memo, W. Donovan, 15-JUN-2005; D316695), several of the endpoints and PODs have changed. All endpoints have been reevaluated and several have been updated to reflect current practices in hazard evaluation.

### 4.5.1 Dose-Response Assessment

***Acute dietary (all populations):*** An acute dietary endpoint was not selected since there were no adverse effects seen in the database that could be attributed to a single dose exposure.

***Chronic dietary (all populations):*** The chronic toxicity study in dogs was selected for the chronic dietary exposure. The LOAEL of 70 mg/kg/day (NOAEL = 7.2 mg/kg/day) was based on degenerative and inflammatory liver effects. This study is appropriate for the route and duration of exposure and is protective of all other chronic effects seen in the database. The cPAD of 0.072 mg/kg/day is based on the NOAEL of 7.2 mg/kg/day and a 100-fold UF (10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 1X for FQPA SF).

***Short-term incidental oral:*** The rabbit developmental study was selected for the short-term incidental oral exposure. The LOAEL of 60 mg/kg/day (NOAEL = 10 mg/kg/day) was based on body weight loss, decreased feed consumption, and increased liver weight. This study is appropriate for the route and duration of exposure. The NOAEL of 10 mg/kg/day is protective of all other effects seen in the database and supported by a similar NOAEL (13 mg/kg/day) observed in the two generation reproduction toxicity study. The developmental study in rats had a slightly lower NOAEL of 5 mg/kg/day and a LOAEL of 50 mg/kg/day based on a slight increase in the incidence of clinical signs (ptosis and salivation) in maternal animals. However, the rabbit developmental study is considered protective considering the minimal effects seen in the rat developmental study at a similar LOAEL and given the fact that the relatively small difference in NOAEL values is likely due to dose spacing. The LOC for incidental oral exposures is 100 (10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 1X FQPA SF).

***Short-term dermal:*** There were no adverse effects observed in the route-specific dermal toxicity study up to the limit dose. Since there is no concern for increased quantitative offspring or fetal susceptibility from ametryn exposure, the effects of concern are adequately assessed in the dermal toxicity study. As a result, a dermal endpoint was not selected.

***Short-term inhalation:*** A route-specific subchronic inhalation study was not available for ametryn and, as a result, an oral study was selected. The developmental toxicity study in rabbits is considered to be protective of all other short- and intermediate-term effects, including developmental and offspring effects, as described above for the incidental oral endpoint. Therefore, this study is protective of all populations including children and pregnant females. The LOC for inhalation exposures is 100 (10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 1X for FQPA SF, when applicable).

### 4.5.2 Recommendations for Combining Routes of Exposures for Risk Assessment

Since the same study/effects were selected for assessment of incidental oral and inhalation exposures; these routes may be combined.

### 4.5.3 Cancer Classification and Risk Assessment Recommendation

Ametryn was previously classified as “Data are Inadequate for an Assessment of Human Carcinogenic Potential”. The CARC reconsidered the acceptability of the rat chronic toxicity/carcinogenicity study and based of a weight of the available data re-classified ametryn as “Suggestive Evidence of Carcinogenic Potential”. This classification is based on tumors observed only at a high dose that was considered excessive during the first 8 months of the study, the absence of treatment-related tumors in mice, structure activity relationship (SAR) support

from ametryn analogs, and lack of concern for mutagenicity (Memo, M. Wilson, 20-DEC-2017; TXR# 0057664).

EPA has concluded that quantification of cancer risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to ametryn.

### 4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Health Risk Assessment

**Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Ametryn for Use in Dietary, Non-Occupational and Human Health Risk Assessments.**

| Exposure/ Scenario | POD | Uncertainty/ FQPA Safety Factors | RfD, PAD, LOC for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Acute Dietary (All populations) | Endpoint not selected as there are no adverse effects in the database from dermal exposure at levels relevant to human health risk assessment (<1000 mg/kg/day). | | | |
| Chronic Dietary (All Populations) | NOAEL = 7.2 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF = 1X | cRfD = cPAD = 0.072 mg/kg/day | **Chronic Toxicity – Dog:** LOAEL = 70 mg/kg/day based on degenerative and inflammatory liver effects. |
| Incidental Oral Short-Term (1-30 days) | NOAEL = 10 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF = 1X | Residential LOC for MOE <100 | **Developmental Toxicity - Rabbit:** Maternal LOAEL = 60 mg/kg/day based on body weight loss, decreased feed consumption, and increased liver weight. |
| Dermal Short-Term (1-30 days) | Endpoint not selected as there are no adverse effects in the dermal toxicity study up to 1000 mg/kg/day and there is no concern for quantitative offspring or fetal susceptibility. | | | |
| Inhalation Short- Term (1-30 days) | NOAEL = 10 mg/kg/day<br><br>Inhalation assumed equivalent to oral – 100% | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF = 1X | Residential LOC for MOE <100 | **Developmental Toxicity - Rabbit:** Maternal LOAEL = 60 mg/kg/day based on body weight loss, decreased feed consumption, and increased liver weight. |
| Cancer (oral, dermal, inhalation) | Ametryn is classified as "Suggestive Evidence of Carcinogenic Potential" Quantification of cancer risk is not required. Using a non-linear approach (i.e., RfD) will adequately account for chronic toxicity, including potential carcinogenicity, that could result from exposure ametryn. | | | |

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). $UF_{DB}$ = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose (a = acute, c = chronic). MOE = margin of exposure. LOC = level of concern.

| Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Ametryn or Use in Occupational Human Health Risk Assessments.[1] | | | | |
|---|---|---|---|---|
| **Exposure/ Scenario** | **POD** | **Uncertainty/ FQPA Safety Factors** | **RfD, PAD, LOC for Risk Assessment** | **Study and Toxicological Effects** |
| Dermal Short-Term (1-30 days) | Endpoint not selected as there are no adverse effects in the database from dermal exposure at levels relevant to human health risk assessment (<1000 mg/kg/day). | | | |
| Inhalation Short- Term (1-30 days) | NOAEL = 10 mg/kg/day<br><br>Inhalation assumed equivalent to oral – 100% | $UF_A$ = 10X<br>$UF_H$ = 10X | Occupational LOC for MOE <100 | **Developmental Toxicity - Rabbit:** Maternal LOAEL = 60 mg/kg/day based on body weight loss, decreased feed consumption, and increased liver weight. |
| Cancer (oral, dermal, inhalation) | Ametryn is classified as "Suggestive Evidence of Carcinogenic Potential". Quantification of cancer risk is not required. Using a non-linear approach (i.e., RfD) will adequately account for chronic toxicity, including potential carcinogenicity, that could result from exposure ametryn | | | |

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). $UF_{DB}$ = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern.

## 4.6 Endocrine Disruptor Screening Program

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

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[2] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Livestock Metabolism Studies

The nature of the residue in primary crops and livestock is adequately understood based on the available corn, sugarcane, banana, goat, and hen metabolism studies. In plants, ametryn is extensively metabolized by *N*-dealkylation and desulfation (oxidation/hydroxylation) to a variety of triazine ring containing metabolites. The metabolism of ametryn in livestock also involves *N*-dealkylation of the isopropyl and ethyl side chains, as well as modification at the 6-position, followed by conjugation, with the triazine ring structure remaining intact.

#### 5.1.2 Summary of Environmental Degradation

The following summary is from the EFED memorandum D440789 (J. Antoline, 06-SEP-2017). Ametryn is classified as moderately mobile on soil and highly soluble in water by FAO guidelines (FAO, 2000). In soil column leaching studies, ametryn leached through sandy loam, loam, and clay soils and was detected in the leachate. There are no batch equilibrium data on the transformation products, but two of the four residues of concern (GA-11354 and GS-11355)

[2] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[3] http://www.epa.gov/endo/

were more mobile than the parent in aged soil column studies. There is no mobility data submitted for transformation products NOA 423271 or NOA 428383. EPI (Estimation Programs Interface) Suite™ estimates the $K_{OC}$ for NOA 423271 and NOA 428383 to be 43.83-682.1 and 1.47-10 L/kg, respectively, indicating that they are comparably or more mobile than the parent.

The primary routes of degradation are aerobic soil metabolism ($t_{1/2}$ = 9.6-319 days at 20 ℃) and aerobic aquatic metabolism ($t_{1/2}$ = 96.3-210 days at 20 ℃). The aqueous photolysis half-life is 72.9 days at 30-50 °N latitude, but that is not expected to be a major contributing factor to the dissipation of ametryn in the environment due to a lack of aquatic uses. The bioconcentration factor (BCF) in bluegill (*Lepomis macrochirus*) was 83 L/kg-wet weight in whole fish, with 60-80% eliminated after a 28-day depuration period. Consistently with the log $K_{ow}$ of 2.6, this indicates that substantial bioconcentration in fish tissue is not expected.

Ametryn is stable to hydrolysis and to anaerobic metabolism. Although no acceptable soil photolysis or terrestrial field dissipation data were provided, water monitoring data demonstrate that ametryn can and does leach to groundwater.

### 5.1.3 Comparison of Metabolic Pathways

Qualitatively, the metabolism of ametryn is similar across the various matrices studied. The major metabolites and degradates found in the plant, livestock and water studies were also found in the rat metabolism study.

### 5.1.4 Residues of Concern Summary and Rationale

The residues of concern in primary crops, rotational crops, livestock, and drinking water are shown in Table 5.1.4, below.

**Table 5.1.4. Residues of Concern in Crops, Livestock, and Drinking Water[1].**

| Matrix | | Tolerance Expression | Residues for Risk Assessment |
|---|---|---|---|
| Plants | Registered Crops | ametryn | ametryn |
| | Rotational Crops | ametryn | ametryn |
| Livestock[2] | Ruminants | ametryn + GS-11354, GS-11355, and GS-26831 | ametryn + GS-11354, GS-11355, and GS-26831 |
| | Poultry | ametryn + GS-11354, GS-11355, and GS-26831 | ametryn + GS-11354, GS-11355, and GS-26831 |
| Drinking Water | | NA | ametryn + GS-11354, GS-11355, NOA 423271, and NOA 428383 |

[1] Memo, W. Donovan, *et al*., 03-NOV-2004; D307104.

[2] If new ametryn uses are added so that tolerances are needed for livestock commodities, the regulated residues in livestock commodities should include parent and its three thiomethyl metabolites (GS-11354, GS-11355, and GS-26831) for the purpose of tolerance reassessment and risk assessment.

The nature of the residue in plants and animals is adequately understood based on the available corn, sugarcane, banana, goat and hen metabolism studies. HED previously determined that the residue of concern for purposes of tolerance enforcement and risk assessment (food only), is the parent ametryn (Memo, W. Donovan, *et al*., 03-NOV-2004; D307104). Furthermore, HED concluded that there is no reasonable expectation of quantifiable residues of ametryn occurring

in livestock commodities [40 CFR §180.6(a)(3)]. If new ametryn uses are added so that tolerances are needed for livestock commodities, the regulated residues in livestock commodities should include parent and its three thiomethyl metabolites (GS-11354, GS-11355, and GS-26831) for the purpose of tolerance reassessment and risk assessment. For drinking water, four degradates (GS-11354, GS-11355, NOA 423271, and NOA 428383) were identified as residues of concern, and are combined in a TTR approach. Due to the lack of fate and toxicity data on these residues, and their structural similarity to the parent, they are assumed to be of comparable toxicity and mobility as the parent (EFED Memo, D307097).

## 5.2 Food Residue Profile

Adequate field trial data are available to support the use of ametryn on corn (field and pop), pineapples, and sugarcane. An adequate number of trials were conducted in the appropriate geographical regions using the appropriate formulation applied at the maximum use rate. These studies are also supported by adequate storage stability data. The available processing studies for corn, pineapple, and sugarcane are adequate and indicate that residues of ametryn and its three thiomethyl metabolites are not likely to be quantifiable (≥0.02 ppm) in corn, pineapple, or sugarcane processed fractions derived from crops treated at the maximum labeled rates.

Adequate methods are available for enforcing tolerances and/or collecting data on ametryn residues in/on plant and livestock commodities. Two GC methods are available for enforcing tolerances of ametryn in plant commodities and are listed as Methods I and A in the Pesticide Analytical Method Volume II (PAM II; Section 180.258). Method I is a GC/MC detection method for determining ametryn *per se*, with a LOQ of 0.05 ppm. Method A is a GC/flame-photometric detection (sulfur mode, FPD-S) method for determining residues of ametryn and its three thiomethyl metabolites (GS-11354, GS-11355, and GS-26831), with a LOQ of 0.05 ppm for parent and 0.1 ppm for each metabolite.

Considering the data from the available livestock metabolism and feeding studies and the calculated maximum theoretical dietary burdens (MTDBs) of 0.15-0.18 ppm for cattle and 0.04 ppm for poultry and swine, HED concludes that there is no reasonable expectation of quantifiable residues of ametryn occurring in livestock commodities [40 CFR §180.6(a)(3)]. Therefore, tolerances for livestock commodities are not required at the present time.

An adequate confined rotational crop study is available and indicates that the metabolism in rotational crops is similar to the primary crops. Adequate field rotational crop studies are also available and indicate that the labeled plant back intervals are appropriate and rotational crop tolerances are not required.

## 5.3 Drinking Water Residue Profile

Estimated drinking water concentrations (EDWCs) were generated using EFED's current models and under current guidance (Memo, J. Antoline, 06-SEP-2017; D440789). EDWCs in surface water were determined using the Pesticides in Water Calculator (PWC v1.52), which generated multi-decadal daily concentration time series and corresponding 1-in-10-year EDWCs of ametryn total toxic residues (TTR) in a representative surface water body assumed to be adjacent

to application sites receiving runoff and spray drift. The Pesticide Root Zone Model for Groundwater (PRZM-GW), also implemented in PWC, was used to generate groundwater EDWCs to estimate potential concentrations of ametryn TTR in vulnerable drinking water aquifers. Four degradates (GS-11354, GS-11355, NOA 423271, and NOA 428383) were identified in the previous DWA (EFED Memo, D307097) as residues of concern, and are being combined in the TTR approach. They are assumed to be of comparable toxicity and mobility as the parent. For this assessment, EDWCs were determined for the use with the current highest maximum label rate (sugarcane). The models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

EFED notes that ametryn has been detected in national water monitoring data collected by the United States Geological Survey (USGS). Concentrations ranged from <0.003 µg/l (<LOQ) to 12 µg/l for surface water, and 0.021-54 µg/l for groundwater. The monitoring was not targeted to correspond with times or locations of ametryn application, and the sampling intervals at specific locations were not sufficiently short to ensure the recording of maximum concentrations.

Tier II maximum EDWCs for ametryn residues in surface water and groundwater are presented in Table 5.3; those listed in bold are recommended for use in the human health dietary assessment. Since the chronic EDWC was highest in groundwater, the chronic dietary analysis was conducted assuming water residues of 0.507 ppm for all water sources (direct and indirect).

**Table 5.3. EDWCs of Ametryn TTR.[1,3]**

| Scenario | Use Rate/Applications/ Retreatment Interval (kg a.i./ha/year, number of apps, days) | Concentrations (µg/L) | | |
|---|---|---|---|---|
| **Surface Water** | | | | |
| | | **1-Day mean (Acute)** | **Annual Mean (Chronic)** | **Overall Mean (Cancer)** |
| Florida Sugarcane, Ground spray | 1.35, 2, 30 | **196** | **33.9** | 19.3 |
| Florida Sugarcane, Aerial Spray | 1.35, 2, 30 | 194 | 19.2 | **19.4** |
| Louisiana Sugarcane[2] (2005 DWA) | 1.35, 2, 30 | 75.9[4] | 13.9 | 10.1 |
| **Groundwater** | | | | |
| | | **Peak (Acute)** | **Post-Breakthrough Mean (Chronic and Cancer)** | |
| Hawaiian Sugarcane | 2.69, 3, 30 | **554** | **507** | |
| Hawaiian Sugarcane [2] (2005 DWA) | 2.69, 3, 30 | 3.1[2] | | |

[1] Bolded values are highest across all scenarios for their respective water source.
[2] Highest EDWC estimated by SCI-GROW.
[3] Total residues simulated include NOA423271, NOA428383, GS-11354, GS11355.
[4] 2005 DWA surface water EDWC value is the 1-in-10 year annual peak value.

## 5.4 Dietary (Food + Drinking Water) Risk Assessment

A chronic aggregate dietary (food and drinking water) exposure and risk assessments was conducted using DEEM-FCID, ver. 3.16 which incorporates consumption data from the USDA

NHANES/WWEIA; 2003-2008. The chronic analysis assumed tolerance-level residues, 100% CT, DEEM (ver. 7.81) default processing factors, and modeled drinking water estimates. The highest chronic exposure estimate was for the population subgroup all infants (<1 year old), which utilized 38% of the cPAD for ametryn. An acute dietary exposure assessment was not performed for ametryn as an endpoint was not selected (there are no adverse single dose effects in the database). Ametryn was classified as "suggestive evidence of carcinogenic potential"; however, the existing chronic endpoint is protective of potential effects. Therefore, a cancer dietary exposure and risk assessment was not conducted for ametryn.

**Table 5.4. Summary of Dietary (Food + Drinking Water) Exposure and Risk for Ametryn.**

| Population Subgroup[1] | Acute Dietary | | Chronic Dietary | | Cancer | |
|---|---|---|---|---|---|---|
| | Dietary Exposure (mg/kg/day) | % aPAD | Dietary Exposure (mg/kg/day) | % cPAD | Dietary Exposure (mg/kg/day) | Risk |
| General U.S. Population | N/A[2] | N/A | 0.010709 | 15 | N/A | N/A |
| All Infants (<1 year old) | | | 0.027537 | **38** | | |
| Children 1-2 years old | | | 0.015538 | 22 | | |
| Children 3-5 years old | | | 0.013131 | 18 | | |
| Children 6-12 years old | | | 0.009471 | 13 | | |
| Youth 13-19 years old | | | 0.007849 | 11 | | |
| Adults 20-49 years old | | | 0.010671 | 15 | | |
| Adults 50-99 years old | | | 0.010521 | 15 | | |
| Females 13-49 years old | | | 0.010630 | 15 | | |

[1] The subpopulation with the highest risk estimate value for the highest exposed population is bolded.
[2] N/A = not applicable.

## 5.5 Percent Crop Treated Estimates

The ametryn assessment assumed 100% crop treated.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no registered residential uses or use sites at this time; therefore, residential handler and post-application exposure assessments were not assessed.

## 6.1 Residential Bystander Post-Application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2014-0219-0003&disposition=attachment&contentType=pdf). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for ametryn.

## 6.2 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50-feet-wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications that, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[4] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of ametryn. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDRIFT® (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Ametryn is used on corn, pineapple, and sugarcane and can be applied via groundboom and aerial equipment. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDRIFT® option for high boom height and using very fine to fine spray type using the 90$^{th}$ percentile results.
- **Aerial applications** are based on the use of AgDRIFT® Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).

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

Exposures were considered for 50-feet-wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. Results are presented in Table 6.2 and indicate that there are no risks of concern at the field edge.

**Table 6.2. Children (1<2 years old) Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Ametryn for the Incidental Oral Route of Exposure.**

| Application Equipment | Spray Type/ Nozzle Configuration | Appl. Rate[1] (lb ai/A) | TTR[2] (µg/cm$^2$) | HtM MOEs At Edge |
|---|---|---|---|---|
| **Corn (field and pop)** | | | | |
| Groundboom | High Boom Very fine to Fine | 1.6 | 0.18 | 2,200 |
| **Pineapple** | | | | |
| Groundboom | High Boom Very fine to Fine | 1.6 | 0.18 | 2,200 |
| **Sugarcane** | | | | |
| Aerial (FL only) | Fine to Medium | 1.2 | 0.13 | 2,100 |
| Groundboom | High Boom Very fine to Fine | 1.2 | 0.13 | 2,900 |
| Groundboom (HI only) | High Boom Very fine to Fine | 2.4 | 0.27 | 1,500 |

[1] See Table 3.2.
[2] Chemical-specific TTR data were not available for ametryn; therefore, default assumptions were used to estimate transferable residue.

## 7.0 Aggregate Exposure/Risk Characterization

The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Since there are no residential uses of ametryn that require a quantitative risk assessment, the acute and chronic aggregate risk assessments are equal to the acute dietary and chronic dietary estimates (food and water only), respectively. The acute and chronic aggregate exposures to the general U.S. population and all other population subgroups from the uses of ametryn do not exceed HED's LOC.

## 8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding ametryn and any other substances and ametryn does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that ametryn has a common mechanism of toxicity with other substances. In 2016,

EPA's OPP released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common-mechanism groups (CMGs)[5] and conducting cumulative-risk assessments (CRA)[6]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for ametryn suggests a candidate CMG may be established with other pesticides. If a CMG is established, then a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

## 9.0 Occupational Exposure/Risk Estimates

Based on the current application scenario and toxicological considerations, non-cancer occupational handler inhalation assessment was conducted. The uses were evaluated in the cited memorandum and the resulting occupational exposure/risks were reviewed by the HED Science Advisory Council for Exposure (ExpoSAC; Memo, C. Walls, 20-DEC-2017, D444269).

## 9.1 Occupational Handler Exposure/Risk Estimates

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios listed in Table 9.1.

For ametryn, handler exposure is expected to be short- and intermediate-term durations based on information on the labels. However, the short- and intermediate-term PODs are the same; therefore, estimates for short-term durations are protective of intermediate-term exposure durations.

No chemical-specific handler exposure data were submitted in support of the current uses. It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include Pesticide Handlers Exposure Database (PHED) 1.1, the Agricultural Handler Exposure Task Force (AHETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures," are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/exposure-surrogate-reference-table-pesticide-risk), which, along with additional

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

information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Since a dermal hazard was not identified, only estimates of inhalation exposure were assessed. Inhalation exposures were calculated for baseline level of PPE (i.e., no respirator) as well as labelled PPE which includes baseline attire (long-sleeved shirt, long pants, shoes and socks), chemical-resistant gloves, and a NIOSH filtering face piece respirator (PF5).

The short- and intermediate-term risks (MOEs) for occupational handlers are included in Table 9.1. The results indicate that inhalation risk estimates do not exceed HED's LOCs, with MOEs greater than 100 at the labelled PPE scenarios (PF5 respirators). It should be noted that HED was requested by the Registrant to review justification for assessing sugarcane at a lower acreage treated. HED, along with the Biological and Economic Analysis Division (BEAD), reviewed the provided information and agreed with the Registrant (Memo, K. Lowe, 12-NOV-2015; D427954). Based on the review typical acreage usage for aerial applications in FL and groundboom applications in HI were used in the assessment.

**Table 9.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ametryn.**

| Exposure Scenario | Crop | Application Rate (lb ai/A)[2] | Area Treated (acres/day)[3] | Inhalation Unit Exposures (ug/lb ai)[1] | | | Inhalation Dose (mg/kg-day)[4] | | | Inhalation MOE[5] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No-R | PF5 R | EC | No-R | PF5 R | EC | No-R | PF5 R | EC |
| **Mixer/loader for dry flowable formulations** | | | | | | | | | | | | |
| Aerial | Sugarcane (FL) | 1.2 | 350 | 8.96 | 1.792 | NA | 0.047 | 0.0094 | NA | 210 | 1,100 | NA |
| Groundboom | Corn | 1.6 | 200 | 8.96 | 1.792 | NA | 0.036 | 0.0072 | NA | 280 | 1,400 | NA |
| Groundboom | Pineapple | 1.6 | 80 | 8.96 | 1.792 | NA | 0.014 | 0.0029 | NA | 690 | 3,500 | NA |
| Groundboom | Sugarcane (HI) | 2.4 | 80 | 8.96 | 1.792 | NA | 0.022 | 0.0043 | NA | 470 | 2,300 | NA |
| Groundboom | Sugarcane (FL, TX, LA) | 1.2 | 200 | 8.96 | 1.792 | NA | 0.027 | 0.0054 | NA | 370 | 1,900 | NA |
| **Applicators** | | | | | | | | | | | | |
| Aerial | Sugarcane (FL) | 1.2 | 350 | No Data | No Data | 0.0049 | No Data | No Data | 2.6E-05 | No Data | No Data | 390,000 |
| Groundboom | Corn | 1.6 | 200 | 0.34 | 0.068 | NA | 0.0014 | 0.00027 | NA | 7,400 | 37,000 | NA |
| Groundboom | Pineapple | 1.6 | 80 | 0.34 | 0.068 | NA | 0.00054 | 0.00011 | NA | 18,000 | 92,000 | NA |
| Groundboom | Sugarcane (HI) | 2.4 | 200 | 0.34 | 0.068 | NA | 0.00082 | 0.00016 | NA | 12,000 | 61,000 | NA |
| Groundboom | Sugarcane (FL, TX, LA) | 1.2 | 200 | 0.34 | 0.068 | NA | 0.0010 | 0.00020 | NA | 9,800 | 49,000 | NA |

NA: not assessed.

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data);

2 Based on registered label (Reg. No. 100-786).

3 Based on Exposure Science Advisory Council Policy #9.1, Registrant submitted information (D427954.mem).

4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A) ÷ BW (80 kg).

5 Inhalation MOE = Inhalation NOAEL (10 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Bolded values are less than the target MOE of 100.

## 9.2 Occupational Post-Application Exposure/Risk Estimates

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

### 9.2.1 Occupational Inhalation Post-Application Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010 (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2014-0219-0003&disposition=attachment&contentType=pdf). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for ametryn.

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

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

### 9.2.2 Occupational Dermal Post-Application Exposure/Risk Estimates

Although post-application dermal exposure is expected for workers entering treated fields performing various field activities, it was not quantitatively assessed since a dermal hazard was not identified.

Restricted Entry Interval
Ametryn is classified as Toxicity Category III via the dermal route and Acute Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not conducted since there was no dermal hazard identified. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to ametryn. HED would recommend a REI of 12 hours which is the REI listed on the current label, and is considered protective of post-application exposure.

## 10.0 Public Health and Pesticide Epidemiology Data

Ametryn incidents were previously reviewed in 2013 (Memo, Recore and Evans, 31-JAN-2013; D407648). At that time, no incidents were identified in either the Incident Data System (IDS) or National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR)-Pesticides and further analysis was not warranted.

In the current IDS analysis from January 1, 2012 to September 12, 2017, no cases involving ametryn were reported to either Main or Aggregate IDS. A query of SENSOR-Pesticides 1998-2013 identified no cases involving ametryn.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's NIOSH, and the US EPA. Ametryn is included in the AHS; however, it is not currently included in any AHS publications and therefore does not provide information for this report.

Based on the continued lack of ametryn incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

## 11.0 References

*Previous Risk Assessments*
Memo, W. Donovan, *et al.*, 03-NOV-2004; D309436.
Memo, W. Donovan, *et al.*, 15-JUN-2005; D316695.

*Scoping Document*
Memo, K. Lowe, *et al.*, 09-MAY-2013; D407652.

*Hazard Documents*
Memo, M. Wilson, 20-DEC-2017; TXR# 0057664.
Memo, J. Van Alstine, 20-FEB-2013; TXR# 0056557.
Memo, U. Habiba, 18-NOV-2014; TXR# 0057074.

Memo, K. Lowe, 14-JAN-2015; D424516.
Memo; K. Lowe, 12-NOV-2015; D427954.
Memo, A. Wray, 20-DEC-2017; TXR# 0057693.

*ORE Document*
Memo, C. Walls, 20-DEC-2017, D444269.
Memo, K. Lowe, 12-NOV-2015; D42795.

*Residue Chemistry/Dietary Documents*
Memo, W. Donovan, *et al*., 03-NOV-2004; D307104.
Memo, S. Levy, 06-DEC-2017; D443316.

*EFED's Drinking Water Document*
Memo, J. Antoline, 06-SEP-2017; D440789.
Memo, D307097.

RDI: RAB1 (15-NOV-2017)
S. J. Levy:S10953:PY-S:(703)305-0783:7509P:RAB1

# Appendix A. Toxicology Profile and Executive Summaries

## A.1 Toxicology Data Requirements

The requirements (40 CFR §158.500) for food use for ametryn are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

| Study | Technical | |
|---|---|---|
| | Required | Satisfied |
| 870.1100 Acute Oral Toxicity | yes | yes |
| 870.1200 Acute Dermal Toxicity | yes | yes |
| 870.1300 Acute Inhalation Toxicity | yes | yes |
| 870.2400 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[1] |
| 870.3200 21-Day Dermal | yes | yes |
| 870.3250 90-Day Dermal | no | - |
| 870.3465 90-Day Inhalation | yes | no[2] |
| 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 |
| 870.5375 Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5395 Mutagenicity—Other Genotoxic Effects | yes | yes |
| 870.6100a Acute Delayed Neurotoxicity (hen) | no | - |
| 870.6100b 90-Day Neurotoxicity (hen) | no | - |
| 870.6200a Acute Neurotoxicity Screening Battery (rat) | yes | waived[3] |
| 870.6200b 90-Day Neurotoxicity Screening Battery (rat) | yes | waived[3] |
| 870.6300 Developmental Neurotoxicity (rat) | no | - |
| 870.7485 General Metabolism | yes | yes |
| 870.7600 Dermal Penetration | no | - |
| 870.7800 Immunotoxicity | yes | waived[4] |

1. A subchronic dog study is not needed given a chronic dog study was submitted.
2. The HASPOC concluded that a repeated exposure inhalation toxicity study is required for ametryn at this time (K. Lowe, 14-JAN-2015; D424516).
3. The HASPOC waived the neurotoxicity (acute and subchronic) studies (J. Van Alstine, 20-FEB-2013; TXR# 0056557).
4. The HASPOC waived the immunotoxicity study (U. Habiba, 18-NOV-2014; TXR# 0057074).

## A.2 Toxicity Profiles

**Table A.2.1. Acute Toxicity Profile – Ametryn.**

| Guideline No. | Study Type | MRID(s) | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 | Acute oral-rat | 40995814 | $LD_{50}$ = 1356 (1164-1581) mg/kg (M) $LD_{50}$ = 1009 (829-1229) mg/kg (F) | III |
| 870.1200 | Acute dermal-rabbit | 40995815 | LD50 >2020 mg/kg | III |
| 870.1300 | Acute inhalation-rat | 42470902 | LC50 >5.03 mg/L | IV |
| 870.2400 | Acute eye irritation-rabbit | 40995817 | No corneal involvement, mild | III |

| | | | | |
|---|---|---|---|---|
| | | | conjunctiva irritation (redness, chemosis, and discharge) reversed by 72 hours in washed eyes. | |
| 870.2500 | Acute dermal irritation-rabbit | 40995818 | Essentially non-irritating. | IV |
| 870.2600 | Dermal sensitization-guinea pig | 40995819 | Not a sensitizer | N/A |

**Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Ametryn.**

| Guideline No. | Study Type | MRID No. (Year)/ Classification /Doses | Results |
|---|---|---|---|
| 870.3100 | 4-Week range-finding oral study (rat) | 40382001 (1987) Acceptable/Non-Guideline 0, 144/172, 275/295, 365/425, or 465/558 mg/kg/day [M/F] | NOAEL <144/172 mg/kg/day [M/F]. LOAEL = 144/172 mg/kg/day [M/F] based on decreased absolute bodyweight, weight gain and food consumption. |
| 870.3100 | 90-Day oral toxicity (rat) | 46467501 (1998) Acceptable/Guideline 0, 1.9/2.0, 7.4/7.6, 36.1/36.2, or 146.3/139.5 mg/kg/day [M/F] | NOAEL = 36.1/36.2 mg/kg/day [M/F]. LOAEL = 146.3/139.5 mg/kg/day [M/F] based on decreases in absolute bodyweight and changes to hematological and clinical chemistry. |
| 870.3200 | 21-Day dermal toxicity (rabbit) | 41067902 (1989), Acceptable/Non-Guideline 0, 10, 100, or 1000 mg/kg/day | NOAEL = 1000 mg/kg/day. LOAEL not established. Note: Study is non-guideline because only 5 animals/sex/dose-group were used. |
| 870.3700a | Prenatal developmental (rat) | 00153215 (1985) Acceptable/Guideline 0, 5, 50, or 250 mg/kg/day | Maternal NOAEL = 5 mg/kg/day. LOAEL = 50 mg/kg/day based on ptosis and salivation. Developmental NOAEL = 250 mg/kg/day. LOAEL was not established. |
| 870.3700b | Prenatal developmental (rabbit) | 00153214 (1985) Acceptable/Guideline 0, 1, 10, or 60 mg/kg/day | Maternal NOAEL = 10 mg/kg/day. LOAEL = 60 mg/kg/day based on body weight loss, decreased feed consumption and increased liver weight. Developmental NOAEL = 60 mg/kg/day. LOAEL was not established. |
| 870.3800 | Two-generation reproduction and fertility effects (rat) | 40349905 (1987) Acceptable/Guideline 0, 20, 200 or 2000 ppm; 0, 1.3, 13, or 131 mg/kg/day in males and 0, 1.2, 12, or 117 mg/kg/day in females. | Parental NOAEL = 13 mg/kg/day. LOAEL = 131 mg/kg/day based on decreased body weight and weight-gain and decreased feed efficiency. Reproductive NOAEL = 131 mg/kg/day. LOAEL not established. Offspring NOAEL = 13 mg/kg/day. LOAEL = 131 mg/kg/day based on decreased pup weights and weight gain in the $F_2$ generation. |
| 870.4100 | Chronic toxicity (2-year; dog) | 40349902 (1987) Acceptable/Guideline 0, 0.71, 7.2, 70, 103, or 83 mg/kg/day in males and 0, 0.84, 8.1, 74, 112, or 92 mg/kg/day in females. | NOAEL = 7.2 mg/kg/day. LOAEL = 70 mg/kg/day based on degenerative and inflammatory liver effects. |
| 870.4300 | Combined Chronic Toxicity/ Carcinogenicity (rat) | 40349906 (1987), 41184201 (1987) and 40382001 (1987) Acceptable/Non-Guideline – 0, 2, 21, or 145 mg/kg/day for males and 0, 2.5, 26, or 176 mg/kg/day for females. | NOAEL = 21 mg/kg/day. LOAEL = 145 mg/kg/day based on based on decreased body weight and weight gain in both sexes and histopathological lesions in the kidney, testes, and pituitary in male rats and in the liver and pancreas in male and female rats. |

| Table A.2.2. Subchronic and Chronic Toxicity and Genotoxicity Profile – Ametryn. | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (Year)/ Classification /Doses | Results |
| 870.4200 | Carcinogenicity (mouse) | 40349904 (1981)<br>"CORE MINIMUM"<br>0, 1.5, 150, or 300 mg/kg/day. | NOAEL = 300 mg/kg/day.<br>LOAEL was not established.<br>No evidence of carcinogenicity.<br>Note: Marked decreases in body weight at 3000 ppm justify selection of 2000 ppm (i.e. about 300 mg/kg/day) as an acceptable dose. |
| 870.5100 | Bacterial Gene Mutation | 40995820 and 41189701 (1984)<br>Acceptable/Guideline<br>0, 20, 80, 320, 1280, or 5120 µg/mL, without S9 activation;<br>0, 20, 80, 320, 1280, or 5120 µg/mL, with S9 activation | No evidence of mutagenicity in *Salmonella* strains TA98, TA 100, TA 1535 and TA 1537 up to levels causing cytotoxicity with or without S9 activation. |
| 870.5300 | *In Vitro* mammalian cell assay | 47399003 (2008)<br>Acceptable/Guideline<br>0, 9.4, 18.8, 37.5, 75.0, 112.5, or 150 µg/mL (+S9, Experiment 1); 0, 18.8, 37.5, 75.0, 150, 225.0, or 300 µg/mL (-S9, Experiment 1); 0, 6.3, 12.5, 25, 50, 75, or 90 µg/mL (+S9, Experiment 2); and 0, 28.1, 56.3, 112.5, 225, 281, 338, 394, or 450 µg/mL (-S9, Experiment 2) | No evidence of induced mutant colonies over background in the presence or absence of S9-activation. |
| 870.5375 | Structural chromosomal aberrations | 41067903 (1989)<br>Acceptable/Guideline<br>1. 800 mg/kg, harvest at 16, 24, and 48 hours.<br>2. 200, 400, or 800 mg/kg: harvest at 24 hours. | Negative for increased MPCEs up to clinical toxicity (death). |
| 870.5395 | Unscheduled DNA synthesis in rat hepatocytes | 41067904 (1989)<br>Acceptable/Guideline.<br>1. 0.1 to 100 µg/mL<br>2. 0.137 to 33.3 µg/mL | No evidence in either assay that unscheduled DNA synthesis, as determined by radioactive tracer procedures, was induced. The positive control induced the expected response in UDS. |
| 870.6200a | Acute neurotoxicity screening battery (rat) | Waived by HASPOC (J. Van Alstine; 20-FEB-2013; TXR# 0056557) | |
| 870.6200b | Subchronic neurotoxicity screening battery (rat) | Waived by HASPOC (J. Van Alstine; 20-FEB-2013; TXR# 0056557) | |
| 870.7485 | Metabolism and pharmacokinetics (rat) | 41463301, 41463302, 41463303 (all 1990)<br>Acceptable. | Ametryn is readily absorbed by rats after a single or multiple oral doses of 0.5 or 200 mg/kg. It is widely distributed, being found in all tissues and organs tested although in low levels. It is metabolized to several polar products, 13 of which were identified. It is excreted mainly through the urine (47-55% in females, 52-59% in males) within 48 hours with the feces being the other major route (30-39% in females, 29-36% in males). No significant differences in pharmacokinetic parameters were seen among dosing groups (singular oral high and low, multiple low) or between sexes. |
| 870.7485 | Immunotoxicity (mice) | Waived by HASPOC (U. Habiba; 18-NOV-2014; TXR# 0057074) | |

## Appendix B. Physical/Chemical Properties.

| **Physicochemical Properties of Ametryn.** | | |
|---|---|---|
| Parameter | Value | Reference |
| Melting point | 84.5-86 °C | MRID 40877301; Ametryn PC RED Chapter |
| pH | 8-9 at 20 °C (1% solution in water) | |
| Density, bulk density, or specific gravity | 0.373 g/mL at 20 °C | |
| Water solubility | 0.020 g/100 mL at 20 °C | |
| Solvent solubility | 56.9 g/100 mL in acetone<br>61.4 g/100/mL in methylene chloride<br>51.6 g/100 mL in methanol<br>46.0 g/100 mL in toluene<br>24.2 g/100 mL in n-octanol<br>1.4 g/100 mL in *n*-hexane | |
| Vapor pressure | 2.74 x $10^{-6}$ mm Hg at 25 °C | |
| Dissociation constant, $pK_a$ | 4.02 at 20 °C | |
| Octanol/water partition coefficient | $K_{OW}$ = 423 (log P = 2.63) | |
| UV/visible absorption spectrum | $\lambda_{max}$ = 223 nm | |

## Appendix C. IRLS.

Ametryn (080801; 11/08/2017)

| **Summary of US and International Tolerances and Maximum Residue Limits** | | | | |
|---|---|---|---|---|
| ***Residue Definition*:** | | | | |
| **US** | | **Canada** | **Mexico[2]** | **Codex[3]** |
| 40 CFR §180.258:<br>Plant: ametryn [*N*-ethyl-*N'*-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine] | | | | |
| ***Commodity[1]*** | ***Tolerance (ppm) /Maximum Residue Limit (mg/kg)*** | | | |
| | **US** | **Canada** | **Mexico[2]** | **Codex** |
| **Plants** | | | | |
| Corn, field, forage | 0.1 | | | |
| Corn, field, grain | 0.05 | | | |
| Corn, field, stover | 0.05 | | | |
| Corn, pop, grain | 0.05 | | | |
| Corn, pop, stover | 0.05 | | | |
| Pineapple | 0.05 | | | |
| Sugarcane, cane | 0.05 | | | |
| | | | | |
| Completed: S. Levy; 11/08/17 | | | | |

[1] Tolerance values are those established in 40 CFR.

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

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.