OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION
WASHINGTON, D.C. 20460

MEMORANDUM

DATE: **July 16, 2024**

SUBJECT: **Ethaboxam.** Human Health Risk Assessment for the Proposed New Uses on Leaf Petiole Vegetable (Crop Subgroup 22B) in Greenhouses.

PC Code: 090205
CAS No.: 162650-77-3
Decision No.: 591231
Petition No.: 3E9052
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D467651
Task Group No.: 00484701
Parent Case No.: 00475265
Registration No.: 59639-185, 59639-211
Regulatory Action: Section 3
Case No.: NA
40 CFR: §180.622

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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

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1.0 Executive Summary

Background
Ethaboxam (N-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide) is a thiazole carboxamide fungicide that controls various diseases caused by oomycetes. Ethaboxam's pesticidal mode of action is interference with beta-tubulin assembly, mitosis, and cell division. It inhibits penetration on the plant surface and is reported to inhibit mycelia growth and sporulation of *Phytophthora infestans*. It also weakly inhibits germination of zoospores or cysts.

Ethaboxam is currently registered for use on Brassica head and stem vegetables (crop group 5-16), Brassica leafy greens (crop subgroup 4-16B), cucurbit vegetables (crop group 9), ginseng, peppers/eggplants (crop subgroup 8-10B), and tuberous and corm vegetables (crop subgroup 1C), as well as for seed treatment uses on a variety of seeds (i.e., legume vegetables [crop group 6], cereal grains [crop group 15] except rice and wild rice, rapeseed [crop subgroup 20A], sunflower subgroup 20B, sugar beets, and alfalfa). A tolerance without US registration has been established for ethaboxam residues in grapes.

Interregional Research Project No. 4 (IR-4) on behalf of the registrant, Valent U.S.A. LLC, is requesting a Section 3 registration for the proposed new use of ethaboxam on leaf petiole vegetable subgroup 22B grown in greenhouses.

Use Profile
The proposed end-use product, V-10208 4 SC Fungicide (EPA Reg. No. 59639-211) is formulated as a suspension concentrate containing 42.5% ethaboxam (4 pounds (lb) active ingredient (ai) per gallon of product). The proposed greenhouse use is for handheld broadcast and soil-directed applications at a single maximum application rate of 0.0125 lb ai/gallon of solution and broadcast applications via ground and chemigation equipment at a single maximum application of 0.25 lb ai/acre. The proposed label allows a maximum of 2 applications per season with a re-treatment interval (RTI) of 14 days. Applicators and handlers are required to wear baseline attire (i.e., long-sleeve shirt, long pants and shoes plus socks) along with personal protective equipment (PPE) consisting of chemical-resistant gloves. Workers may not re-enter a treated area until 12 hours after application (restricted entry interval (REI) of 12 hours).

Exposure Profile
Humans may be exposed to ethaboxam in food and drinking water due to its registered and proposed agricultural uses. The proposed uses are expected to result in short- (1 to 30 days) and intermediate-term (1 to 6 months) occupational handler dermal and inhalation exposures and short-term occupational dermal post-application exposure. Long-term occupational exposure is not expected for the proposed uses. Since there are no registered residential uses associated with ethaboxam, and no commercial uses in residential settings, residential exposure is not anticipated. Non-occupational (resulting from spray drift) exposures are not expected from the proposed use as it is limited to greenhouses.

Hazard Characterization and Dose Response Assessment
The ethaboxam toxicology database is complete. The Hazard and Science Policy Council (HASPOC) recommended to waive the subchronic inhalation toxicity study (TXR 0056543, K. Rury, 20-MAR-2013). The toxicological doses and endpoints used for risk assessment have not changed since the most recent ethaboxam human health risk assessment (D464820, K. Chan, 08-SEP-2022).

Toxicological studies are available in rats, mice, rabbits, and dogs. In rats, alterations to the male reproductive organs, as well as functional effects on reproduction were seen in oral studies; however, no treatment-related effects on male reproductive organs were observed in studies with mice, rabbits, or dogs. Effects were seen in mouse liver and in dog thymus and spleen. No evidence of immunotoxicity was observed, and there is no concern for neurotoxicity. No evidence of increased quantitative or qualitative susceptibility was seen in the developmental toxicity studies in rats and rabbits; however, increased qualitative susceptibility was seen in the rat reproduction study where decreased body weight, decreased viability, and delayed sexual maturation was seen in offspring in the presence of limited parental effects. HED based the risk assessment for ethaboxam on the most sensitive species and effects observed in the toxicological database; thus, points of departure (PODs) selected for risk assessment are protective of all treatment-related effects observed after exposure to ethaboxam. The dermal short- and intermediate-term endpoint and dose were selected from the 28-day dermal study in the rat. The short and intermediate-term inhalation endpoint and dose were selected from the 13-week oral toxicity study in the rat.

Ethaboxam is classified as having "Suggestive Evidence of Carcinogenicity," based on an increased incidence of benign Leydig cell tumors in male rats. The Agency has determined that quantification of cancer risk using a non-linear approach will adequately account for all chronic toxicity, including carcinogenicity, resulting from ethaboxam exposures (TXR 0054172, J. Kidwell, 23-MAR-2006).

Based on both hazard and exposure considerations, HED reduced the required 10X Food Quality Protection Act (FQPA) Safety Factor (SF) to 1X. The total uncertainty factor (UF) is 100, based on the combined interspecies (10X) and intraspecies (10X) uncertainty factors (UFs) and the 1X FQPA SF, where applicable.

Dietary Exposure Assessment
An acute endpoint attributable to a single dose was not identified. Therefore, acute dietary risk from ethaboxam is not of concern.

HED performed a screening-level chronic dietary exposure assessment that was based on tolerance level residues, 100 percent crop treated (PCT) assumptions, and conservative default processing factors. The ethaboxam chronic risk estimates are not of concern for the US population or any population subgroup. Chronic risk estimates are 8.6% of the chronic population adjusted dose (cPAD) for the general US population, and 39% of the cPAD for children 1-2 years old, the population subgroup with the highest exposure. As the cPAD is protective of potential carcinogenicity, dietary cancer risk is not of concern and HED did not perform a separate cancer dietary risk assessment.

Residential Exposure and Risk Assessment
There are no proposed or registered residential uses associated with ethaboxam. Therefore, a residential exposure assessment is not required.

Aggregate Risk Assessment
In the absence of residential uses, aggregate risk estimates are equivalent to the chronic dietary (food and drinking water) risk estimates, which are not of concern.

Spray Drift Assessment
The proposed use for greenhouse applications is not likely to result in spray drift.

Occupational Exposure and Risk Assessment
Short- and intermediate-term occupational handler dermal and inhalation risk estimates are not of concern (i.e., MOEs ≥ LOC of 100) for all scenarios when assessed with baseline attire, defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator. The risk estimates are margins of exposure (MOEs)ranging from 1,800 to 21,000 and 1,300 to 630,000 for dermal and inhalation exposure, respectively.

Short-term dermal occupational post-application exposures were not of concern with dermal MOEs ranging from 3,600 to 19,000 (LOC = 100) on the day of application (0-days after treatment (0-DAT)) for all post-application occupational activities using default dislodgeable foliar residue (DFR) assumptions.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for ethaboxam 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 ethaboxam.

Environmental Justice
Potential areas of environmental justice concern, 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.[1]"

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database, and the Agricultural Re-entry Task Force (ARTF) database are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[2].

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice
[2] Available online: Occupational Pesticide Handler Exposure Data | US EPA and Occupational Pesticide Post-application Exposure Data | US EPA

2.0 HED Recommendations

There are no risk estimates of concern associated with the proposed new uses of ethaboxam and associated tolerances. Therefore, HED has no objection to the registration of the proposed greenhouse use of ethaboxam.

2.1 Tolerance Considerations

2.1.1 Enforcement Analytical Method

Method RM-49C-1
D429263; J. Cowins; 10-NOV-2016

Method RM-49C-1, titled *Determination of Ethaboxam in Crops*, is a validated tolerance enforcement method. Briefly, for the determination of ethaboxam in all raw agricultural commodities (RACs) except potato, samples are extracted twice using a mixture of acetonitrile (ACN)/water (7:3, v:v), centrifuged, and filtered. An aliquot of the extract is diluted with ACN and partitioned twice with hexane. The ACN is removed by rotary evaporation and the residue is re-dissolved and partitioned twice with dichloromethane (DCM). The DCM phase is evaporated to dryness and re-dissolved in methanol/water (1:1, v:v), then analyzed without further clean-up using high-performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS).

Method RM-49R
D429263; J. Cowins; 10-NOV-2016

Method RM-49R, titled *Ethaboxam: Determination of Ethaboxam, EEO and EEHO in Crops*, is also a validated tolerance enforcement method.

Briefly, samples are extracted twice with acetone/water (3:1, v:v) and centrifuged. The combined extracts are diluted with methanol or an internal standard solution and water, then filtered through a syringe filter for analysis via LC/MS/MS.

Both analytical methods have passed both independent laboratory validation (ILV) and Agency validation, and are adequate for enforcement purposes. They are also adequate for data collection. Based on the method of instrumental analysis (LC/MS/MS monitoring two ion transitions), the methods are considered to have acceptable specificity for residues of ethaboxam. For both methods, the limit of quantitation (LOQ) is 0.010 ppm and the limit of detection (LOD) is 0.005 ppm.

Currently, there is no expectation for finite residues of ethaboxam in livestock commodities (40CFR §180.6(a)(3)). Therefore, a tolerance enforcement method is not needed for livestock commodities at this time.

The Food and Drug Administration's (FDA's) Multi-Residue Methods (MRMs) are not suitable for the analysis of ethaboxam. The QuEChERS multi-residue method appears to be suitable for the analysis of ethaboxam (D313733, M. Doherty, 27-APR-2006).

2.1.2 Recommended Tolerances

Table 2.1.2. Tolerance Summary for Ethaboxam.			
Commodity	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments (*Correct commodity definition*)**
Leaf petiole vegetable subgroup 22B	0.15	0.15	Tolerance based on calculation using the OECD Calculator on IR-4 greenhouse celery data

2.1.3 Revisions to Petitioned-For Tolerances

None.

2.1.4 International Harmonization

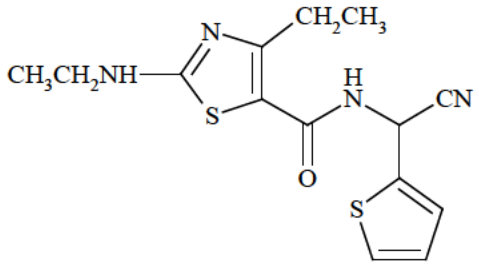
Neither Codex Alimentarius nor Canada's Pest Management Regulatory Agency (PMRA) have established Maximum Residue Limits (MRLs) for ethaboxam in commodities that are members of Leaf petiole vegetable subgroup 22B. Therefore, there are no harmonization issues with Codex or PMRA regarding the proposed new use.

2.2 Label Recommendations

None.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Ethaboxam Nomenclature.	
Compound	
Common name	Ethaboxam
Company experimental name	LGC-30473
IUPAC name	(*RS*)-*N*-(α-cyano-2-thienyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5-carboxamide
CAS name	*N*-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide
CAS registry number	162650-77-3
End-use product	V-10208 4 SC (also referred to as Elumin Fungicide). EPA Reg. No. 59639-211

3.2 Physical/Chemical Characteristics

Technical-grade ethaboxam is a liquid at room temperature. The compound is non-volatile; therefore, the possibility for exposure to ethaboxam in a vaporous phase is unlikely. It has a relatively low solubility in water and low to moderate solubility in various organic solvents. Its octanol/water partition coefficient suggests that some bioaccumulation of ethaboxam in fatty tissues is possible. A table of physical and chemical properties for ethaboxam is included in Appendix B.

3.3 Pesticide Use Pattern

The proposed end-use product, V-10208 4 SC Fungicide (EPA Reg. No. 59639-211) is formulated as a suspension concentrate containing 42.5% ethaboxam (4 pounds (lb) active ingredient (ai) per gallon of product). The proposed use is for handheld broadcast and soil-directed applications at a single maximum application rate of 0.0125 lb ai/gallon of solution and broadcast applications via ground and chemigation equipment at a single maximum application of 0.25 lb ai/acre. The proposed label allows a maximum of 2 applications per season with a re-treatment interval (RTI) of 14 days.

Table 3.3. Summary of Directions for Proposed Use of Ethaboxam on Leaf Petiole Vegetable (crop subgroup 22b) in Greenhouses.

Applic. Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Year	Max. Annual Applic. Rate	Use Directions and Limitations
Broadcast, Chemigation	Soluble Concentrate [59639-211]	0.25 lb ai/A	2	0.5 lb ai/A	RTI = 14 days. REI = 12 hours. PHI = N/A. PPE = chemical- resistant gloves made of any waterproof material, socks and shoes. Following the second application, after V-10208 4 SC Fungicide has dried on the plant, transplant celery into the field.
Broadcast, Groundboom					
Broadcast, Backpack		0.0125 lb ai/ gal solution*		0.025 lb ai/gal	
Broadcast, Manually-pressurized Handwand					
Broadcast, Mechanically-pressurized Handgun					
Drench/Soil-/Ground-directed, Mechanically-pressurized Handgun					

* Based on 20 gal/A application volume (i.e., [(0.25 lb ai/A ÷ 20 gal/A = 0.0125 lb ai/gal solution]).

3.4 Anticipated Exposure Pathways

Humans could be exposed to ethaboxam in food and drinking water since ethaboxam may be applied directly to growing crops. There are no residential uses of ethaboxam; therefore, residential handler and post-application exposures are not anticipated. Occupational exposures by the dermal and inhalation routes are expected from the application of ethaboxam and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways for ethaboxam.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this

human health risk assessment, in accordance with US 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 US 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 is also being considered whenever appropriate. 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

The toxicology database is complete for ethaboxam. The HASPOC recommended to waive the subchronic inhalation toxicity study (TXR 0056543, K. Rury, 20-MAR-2013). The toxicological doses and endpoints used for risk assessment have not changed since the most recent human health risk assessment, (D464820, K. Chan, 08-SEP-2022). These doses and endpoints were based on a prior comprehensive risk assessment that included a detailed description of the toxicological effects of ethaboxam (D396490, D. McNeilly, 21-MAY-2013). Refer to the 2013 risk assessment for additional details on hazard characterization.

4.1 Toxicological Effects

The male reproductive system is a target for ethaboxam, with alterations to the male reproductive organs as well as functional effects on reproduction observed in several oral subchronic and chronic rat studies. In the subchronic oral toxicity study in rats, histopathological alteration and decreased epididymal weights were observed, along with abnormal spermatids. Similar effects were also seen in the two-generation reproduction and chronic toxicity studies, including decreased epididymal and seminal vesicle weights, seminiferous tubule atrophy, small/flaccid testes and epididymides, abnormal spermatogenic cells in the epididymal duct, absent sperm, epididymal vacuolation, reduced colloid in the prostate, and reduced fertility in males. There were no treatment-related male reproductive effects observed in mice, rabbits, or dogs. In mice, liver toxicity was observed in the chronic toxicity study. In dogs, decreased thymus weights and thymus atrophy/involution, and hematopoiesis of the spleen were noted after subchronic exposure, but there were no treatment-related effects in dogs

after chronic exposure. There were no effects related to neurotoxicity or immunotoxicity in any of the studies.

No evidence of increased quantitative susceptibility was seen in the developmental toxicity studies in rats and rabbits. In the developmental rat study, thin diaphragm with liver protrusion, decreased fetal body weight, misshapen pituitary, diaphragmatic hernia, and skeletal anomalies were seen in the presence of comparable maternal toxicity (salivation, significant decreased body weight/body weight gain). In the developmental rabbit study, there were no developmental effects observed. Qualitative susceptibility was seen in the rat reproduction study. Decreased body weight, decreased viability, and delayed sexual maturation were seen in offspring, while parental effects were limited to decreased body weight and body weight gain in both sexes.

Ethaboxam is classified as having "suggestive evidence of carcinogenic potential," based on an increased incidence of benign Leydig cell tumors in male rats (TXR 0054172, J. Kidwell, 23-MAR-2006). Although there is evidence of benign Leydig cell tumors, the POD used to establish the cRfD (5.5 mg/kg/day) is approximately 6-fold lower than the lowest dose that induced tumors (35.8 mg/kg/day, highest dose tested). HED determined that assessment of cancer risk using a nonlinear approach adequately accounts for all chronic toxicity, including carcinogenicity, that could result from exposure to ethaboxam.

4.2 Safety Factor for Infants and Children (FQPA Safety Factor)[3]

Based on both hazard and exposure considerations, HED previously reduced the required 10X FQPA SF to 1X. This determination was based on the completeness of the toxicity database, the lack of neurotoxicity, the use of endpoints and doses protective of observed qualitative susceptibility, and the conservative nature of the dietary exposure assessment (tolerance-level residues, high end drinking water estimates, and 100% crop treated assumptions) that ensures exposure will not be underestimated. This analysis has not changed.

4.3 Toxicity Endpoint and Point of Departure Selections

4.3.1 Dose Response Assessment

Based on the use pattern and the toxicological profile of ethaboxam, HED selected endpoints and doses for chronic dietary risk assessment and short- and intermediate-term occupational handler and post-application assessment. There are no residential uses associated with ethaboxam.

Certain no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) within the toxicity profile table (Appendix A) contain results that are no longer considered adverse based upon current practices (e.g., decreased body weight gain in the absence of decreased absolute body weight); however, these studies do not quantitively impact endpoint selection.

[3] 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)

Acute Dietary (General Population): An acute dietary risk assessment was not conducted since there were no adverse toxicological effects in the database that could be attributed to a single exposure.

Chronic Dietary: For chronic dietary exposure and risk assessment, a NOAEL of 5.5 mg/kg/day was selected from the combined chronic/carcinogenicity study in rats based on effects seen in male reproductive organs (testes, epididymis, prostate, and seminal vesicles) at the LOAEL of 16.4 mg/kg/day. The NOAEL is protective of all effects observed in the ethaboxam database. The total UF is 100X (10X to account for interspecies extrapolation, 10X to account for intra-species variation, and 1X FQPA SF). The chronic reference dose (cRfD, 0.055 mg/kg/day) is equal to the cPAD (0.055 mg/kg/day).

Occupational Dermal (Short- and Intermediate-term): The 28-day dermal study in the rat was selected for short- and intermediate-term dermal exposure and risk assessment. The LOAEL of 1,000 mg/kg/day is based on decreased body weight and body weight gains (NOAEL of 300 mg/kg/day). Since the short- and intermediate-term dermal POD was selected from a route-specific toxicity study, a dermal absorption factor is not necessary to estimate risk. The LOC = 100 (10X to account for interspecies extrapolation and 10X to account for intra-species variation).

Occupational Inhalation (Short- and Intermediate-term): The inhalation study was recommended to be waived, therefore, no additional UFs are needed to account for missing data. The 13-week feeding study in the rat was selected for the short- and intermediate-term inhalation risk assessment. The LOAEL (49.7 and 58.0 mg/kg/day for males and females, respectively) is based on male reproductive effects and lung effects (NOAEL of 16.3 mg/kg/day). Toxicity by the inhalation route is considered equivalent to toxicity by the oral route of exposure. The LOC = 100 (10X to account for interspecies extrapolation and 10X to account for intra-species variation).

A summary of the toxicological endpoints and doses selected for ethaboxam is provided in Tables 4.5.1. and 4.5.2

4.4 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational exposures to a pesticide, the risk assessment must address exposures from two major routes (dermal and inhalation) and determine whether the individual exposures from these routes can be combined. If routes of exposure have endpoints based on the same target organ or system, they can be combined. For ethaboxam, the dermal and inhalation exposure estimates were not combined since the endpoints are not based on the same toxicological effects.

4.5 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.1. Toxicological Doses and Endpoints for Ethaboxam for Use in Non-Occupational Human Health Risk Assessment.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD	Study and Toxicological Effects
Acute Dietary (All Populations)	No appropriate endpoint attributable to a single exposure identified.			
Chronic Dietary (All Populations)	NOAEL= 5.5 mg/kg/day	UF_A= 10X UF_H = 10X FQPA SF = 1X	cRfD = 0.055 mg/kg/day cPAD = 0.055 mg/kg/day	Combined Chronic/Carcinogenicity-Rat (MRID 46387811) LOAEL = 16.4 mg/kg/day based on decreased epididymal weight, seminiferous tubule atrophy, abnormal spermatogenic cells in the epididymal duct, and absent sperm.
Cancer (Oral, Dermal, Inhalation)	Classification: "Suggestive Evidence of Carcinogenic Potential" in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (2005) based on an increased incidence of benign Leydig cell tumors in males (TXR 0054172; J. Kidwell; 23-MAR-2006).			

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. FQPA SF = Food Quality Protection Act safety factor. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). PAD = population adjusted dose (c = chronic). RfD = reference dose (c = chronic).

Table 4.5.2. Summary of Toxicological Doses and Endpoints for Ethaboxam for Use in Occupational Human Health Risk Assessment.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days); Intermediate -Term (1-6 months)	NOAEL = 300 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	28-day dermal toxicity-Rat (MRID 48535645) LOAEL = 1000 mg/kg/day based on decreased body weight (10%) and body weight gains (41%).
Inhalation Short-Term (1-30 days); Intermediate -Term (1-6 months)	NOAEL = 16.3 mg/kg/day Inhalation toxicity is assumed to be equivalent to toxicity via the oral route.	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	13 week – Rat Oral Toxicity (MRIDs 46387805; 48535644) LOAEL = 49.7 mg7mg/kg/day based on testicular/epididymal effects in males (abnormal spermatids in the testes and abnormal spermatogenic cells in the epididymides), lung effects (alveolar septal congestion and focal alveolar hemorrhage).

Table 4.5.2. Summary of Toxicological Doses and Endpoints for Ethaboxam for Use in Occupational Human Health Risk Assessment.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (Oral, Dermal, Inhalation)	Classification: "Suggestive Evidence of Carcinogenic Potential" in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (2005) based on an increased incidence of benign Leydig cell tumors in males (TXR# 0054172; J. Kidwell; 23-MAR-2006).			

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). LOC = level of concern. MOE = Margin of Exposure.

Body Weight: The standard body weight for the general population (80 kg) was used for all occupational exposure scenarios covered in this risk assessment since the endpoints selected were not based on developmental and/or fetal effects.

5.0 Dietary Exposure and Risk Assessment

A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 4.02. This software uses 2005-2010 food 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).

5.1 Residues of Concern Summary and Rationale

Data have been submitted and reviewed depicting the metabolism of ethaboxam in livestock and crops, as well as its degradation in the environment. HED has determined the residues of concern (ROC) in primary and rotational crops for tolerance enforcement and risk assessment, and in drinking water for risk assessment. In all cases, the ROC is parent ethaboxam only (D429263, J. Cowins, 10-NOV-2016).

Table 5.1. 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**
Crops	Primary Crop	Ethaboxam	Ethaboxam
	Rotational Crop	Ethaboxam	Ethaboxam
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Ethaboxam	Not Applicable

5.2 Food Residue Profile

The residue chemistry database for ethaboxam is complete. The nature of the residue is adequately understood with parent ethaboxam being the residue of concern in plants. Adequate field trial data are available for determining the magnitude of ethaboxam residues in/on greenhouse-grown celery. Sufficient storage stability data are available to support the sample storage intervals incurred in the celery field trials. Residues are quantifiable and tend to decline with increasing pre-harvest intervals (PHIs). HED concluded that the submitted residue chemistry studies were generally well conducted and are adequate for supporting regulatory conclusions, establishing appropriate tolerance levels for enforcement, and for purposes of risk assessment.

Analysis of residues can be accomplished through standard analytical techniques. An adequate analytical method is available for tolerance enforcement.

The predominant residue observed in crops is the parent compound ethaboxam. Based on the current and proposed uses and use patterns, quantifiable residues of ethaboxam are not expected in rotational crops or in livestock commodities.

5.3 Water Residue Profile

Estimates of ethaboxam in surface and groundwater sources of drinking water were provided by the Environmental Fate and Effects Division (EFED) for use in the chronic dietary risk assessment (D460984, I. Abdel-Saheb, 06-OCT-2021). The EDWCs for ethaboxam were modeled using conservative assumptions for registered foliar uses. The highest chronic exposure resulted from groundwater in the Florida citrus scenario, where the maximum seasonal application rate was 0.5 lb ai/A. EFED confirmed that the previously calculated EDWCs remain unchanged for the proposed new uses on Leaf Petiole Vegetables, Subgroup 22B. The EDWCs reflect the very conservative assumption that ethaboxam is stable to all routes of metabolism and degradation. The ethaboxam EDWCs were modeled with EFED's surface water model *Pesticide in Water Calculator* (PWC), and groundwater model *Pesticide Root Zone Model for GroundWater* (PRZM-GW). The models and their descriptions are available at the EPA internet site https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

For the chronic dietary assessment, HED used the higher chronic EDWC in groundwater calculated for the Florida citrus scenario (0.0074 ppm). This EDWC was incorporated directly into the chronic dietary assessment via the food categories "water, direct, all sources" and "water, indirect, all sources."

Table 5.3. Ethaboxam EDWCs Used in the Chronic Dietary Exposure Assessment.

Residue Source (Model)	Use Rate (lb ai/A)	Chronic EDWC (µg/L)
Surface Water (PWC)	0.5	3.91
Groundwater (PRZM-GW)	0.5	**7.4***

* The higher EDWC for the evaluated use scenarios is shown in bold.

5.4 Dietary Risk Assessment

HED completed an updated dietary risk assessment in support of the proposed new uses (Leahigh, A. D468316, 16-JUL-2024).

5.4.1 Description of Residue Data Used in Dietary Assessment

The chronic dietary analysis is a conservative assessment that provides overestimates of residues that people will be exposed to in their diets. HED based the assessment on tolerance-level residues and 100 PCT assumptions, which are both very conservative. In addition, conservative processing factors were used for several commodities. Finally, the EDWCs are overestimates of residues in drinking water. EFED made the very conservative assumption that ethaboxam is stable to all routes of metabolism and degradation. For these reasons, HED is confident that dietary exposure and risk are not being underestimated.

5.4.2 Percent Crop Treated Used in Dietary Assessment

HED assumed 100 PCT for all commodities in the chronic dietary assessment.

5.4.3 Acute Dietary Risk Assessment

An acute endpoint attributable to a single dose exposure was not identified; therefore, an acute dietary risk assessment was not conducted.

5.4.4 Chronic Dietary Risk Assessment

The US population and all population subgroups have risk estimates that are below the LOC of 100 %cPAD. Chronic dietary (food plus drinking water) risk estimates are 8.6% of the cPAD for the general U.S. population and 39% of the cPAD for children 1-2 years old, the population subgroup with the highest exposure estimate (Table 5.4.6).

5.4.5 Cancer Dietary Risk Assessment

Ethaboxam is classified as showing “suggestive evidence of carcinogenicity,” based on increased incidence of Leydig cell tumors in males. The Agency determined that quantification of cancer risk using a nonlinear approach would adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to ethaboxam. Therefore, HED considers the noncancer chronic reference dose protective of cancer dietary risk and a separate cancer dietary risk assessment was not conducted.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food plus Drinking Water) Exposure and Risk Estimates for Ethaboxam.		
Population Subgroup	Chronic	
	Exposure (mg/kg/day)	% cPAD
US Population (total)	0.004501	8.2
All infants (<1 year)	0.006852	13
Children 1-2 years	**0.021662**	**39***
Children 3-5 years	0.012519	23
Children 6-12 years	0.005321	9.7
Youth 13-19 years	0.002225	4.0
Adults 20-49 years	0.003254	5.9
Adults 50-99 years	0.003919	7.1
Females 13-49 years	0.003563	6.5

* Population subgroup with the highest exposure and risk estimate shown in bold.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no existing or proposed residential uses associated with ethaboxam. Therefore, residential exposures were not assessed.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

Acute aggregate risk from exposure to ethaboxam results from exposure to residues in food and drinking water alone. An acute dietary risk assessment was not conducted since effects attributable to a single exposure were not observed in the available toxicity studies.

7.2 Short-Term Aggregate Risk

Short-term aggregate risk assessments are needed for adults and children exposed in residential settings and through food and drinking water. Since there are no registered or proposed residential uses for ethaboxam, the short-term aggregate risk estimates are equivalent to the chronic dietary risk estimates and are below HED's LOC.

7.3 Chronic Aggregate Risk

Chronic aggregate risk from exposure to ethaboxam results from exposure to residues in food and drinking water alone; therefore, chronic aggregate risk estimates are equivalent to the chronic dietary

risk estimates, which are not of concern for the general U.S. population or any population subgroup.

7.4 Cancer Aggregate Risk

Ethaboxam is classified as "suggestive evidence of carcinogenicity," based on an increased incidence of benign Leydig cell tumors in males. The Agency determined that quantification of cancer risk using a nonlinear approach would adequately account for all chronic toxicity, including carcinogenicity, which could result from exposure to ethaboxam. Therefore, HED considers the noncancer chronic reference dose protective of cancer aggregate risk, and a separate cancer aggregate risk assessment was not conducted.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

The proposed ethaboxam use is for applications in greenhouses. These uses are not likely to result in spray drift.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

The proposed ethaboxam use is for applications in greenhouses. These uses are not likely to result in post-application inhalation exposure to individuals nearby greenhouse pesticide applications.

10.0 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 as to ethaboxam and any other substances and ethaboxam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that ethaboxam has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[4] and conducting cumulative risk assessments (CRA).[5] During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for ethaboxam suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

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

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

11.0 Occupational Exposure/Risk Characterization

HED completed an occupational exposure and risk assessment for the proposed new uses (D468066, K. Chan, 16-JUL-2024).

11.1 Occupational Handler Exposure and Risk Estimates

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

Based on the anticipated use patterns, current labeling, and types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed new uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios presented in Table 11.1.1.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

MOEs with baseline attire (i.e., no gloves) ranged from 1,800 to 21,000 and 1,300 to 630,000 for dermal and inhalation exposure, respectively. All MOEs are greater than the LOC of 100 and, therefore, are not of concern.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethaboxam.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Level of PPE	Inhalation Unit Exposure (µg/lb ai)[1]	Level of PPE	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation	
								Dose (mg/kg/day)[4]	MOE[5] (LOC = 100)	Dose (mg/kg/day)[6]	MOE[7] (LOC = 100)
Mixer/Loader											
Liquid, Chemigation, Broadcast Liquid, Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	220	SL/No G	0.219	No-R	0.25 lb ai/acre	60 acres	0.041	7,300	0.000041	400,000
Applicator											
Spray (all starting formulations), Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	78.6	SL/No G	0.34	No-R	0.25 lb ai/acre	60 acres	0.015	20,000	0.000064	260,000
Mixer/Loader/Applicator											
Liquid, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	13,200	SL/No G	140	No-R	0.0125 lb ai/gallon solution	7 gallons solution	0.015	21,000	0.00015	110,000
Liquid, Manually-pressurized Handwand, Broadcast		100,000		23.6				0.11	2,800	0.000026	630,000
Liquid, Mechanically-pressurized Handgun, Broadcast Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed		5,950		448			175 gallons solution	0.16	1,800	0.012	1,300

1. Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (Occupational Pesticide Handler Unit Exposure Surrogate Reference Table 2021 (epa.gov); level of PPE: SL/No G = single layer, no gloves; No-R = no respirator).
2. Based on registered or proposed label (EPA Reg. No. 59639-211). See Table 3.3.
3. Exposure Science Advisory Council Policy #9.2.
4. Dermal Dose: Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
5. Dermal MOE: Dermal MOE = Dermal POD (300 mg/kg/day) ÷ Dermal Dose (mg/kg/day). LOC = 100.
6. Inhalation Dose: Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
7. Inhalation MOE = Inhalation MOE = Inhalation POD (16.3 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Level of concern (LOC) = 100.

11.2 Post-Application Exposure and Risk Assessment

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

11.2.1 Dermal Post-Application Exposure and Risk Estimates

Occupational Post-application Dermal Exposure Data and Assumptions

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

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from the ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[6]" which, along with additional information about the ARTF data, can be found at the Agency website.[7]

Application Rate: The ethaboxam quantitative exposure/risk assessment developed for occupational post-application workers is based on the proposed application rates listed in Table 3.3.

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

Dislodgeable Foliar Residue (DFR): Chemical-specific DFR data have not been submitted for ethaboxam. Therefore, this assessment uses HED's default assumption that 25% of the application is available for transfer on day 0 following the application, and the residues dissipate at a rate of 10% each following day.

Occupational Post-application Non-Cancer Dermal Risk Estimates

There are no occupational post-application risks of concern on the day of application on 0-DAT using default residue assumptions (i.e., all MOEs on day 0 ≥ the LOC).

[6] Available: https://www.epa.gov/sites/production/files/2021-03/documents/usepa-opp-hed_exposac_policy_3_march2021_0.pdf

[7] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Table 11.2.1.1 Occupational Post-application Non-Cancer Exposure and Risk Estimates for Ethaboxam on 0-DAT.						
Crop/Site	**Activities**	**Transfer Coefficient (cm^2/hr)**	**Application Rate (lb ai/A)**	**DFR[1]**	**Dermal Dose (mg/kg/day)[2]**	**MOE (LOC = 100)[3]**
Greenhouse vegetable	Harvesting, Hand Pinching Pruning, Hand Scouting Weeding, Hand	1,200	0.25	0.70	0.084	3,600
	Transplanting	230			0.016	19,000

1. DFR = Application Rate (0.25 lb ai/A) × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day.
2. Daily Dermal Dose (mg/kg/day) = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ¸ BW (80 kg).
3. MOE = POD (300 mg/kg/day) / Daily Dermal Dose (mg/kg/day). Level of concern (LOC) = 100

Restricted Entry Interval (REI)

Ethaboxam is classified as Toxicity Category IV via the dermal route and skin and eye irritation potential. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 immediately following application for all post-application activities. Under 40 CFR 156.208(c)(2), ai's classified as Acute III or IV for acute dermal, eye irritation, and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Standard (WPS) interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to ethaboxam. HED supports the proposed REI of 12 hours. This is the REI listed on the proposed label and is considered protective of post-application exposure.

11.2.2 Inhalation Post-Application Exposures and 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.[8] The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis.[9] 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 ethaboxam.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the ARTF. 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.

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

[8] Available: https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037
[9] Available: https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0219-0002

12.0 References

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Appendix A. Toxicology Profile

A.1 Toxicology Data Requirements

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

Table A.1. Toxicology Data Requirements.

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
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 .....28/90-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
870.5375 ..... Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 ..... Mutagenicity—Erythrocyte Micronucleus-mammalian	yes	yes
870.6100a .....Acute Delayed Neurotoxicity (hen)	no	-
870.6100b..... 90-Day Neurotoxicity (hen)	no	-
870.6200a ..... Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b ..... 90 Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 ..... Developmental Neurotoxicity	no	-
870.7485 ..... General Metabolism	yes	yes
870.7600 ..... Dermal Penetration	no	yes
870.7600 ..... Immunotoxicity	yes	yes

* The Hazard Science Policy Council (HASPOC) recommended that the subchronic inhalation study be waived for ethaboxam at this time (TXR 0056543, K. Rury, 20-MAR-2013).

A.2 Toxicity Profile Tables for Ethaboxam

Table A.2.a. Acute Toxicity Profile for Ethaboxam.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral (rat)	46378518	LD_{50} > 5000 mg/kg (M & F)	IV
870.1200	Acute Dermal (rat)	48535632	LD_{50} > 5000 mg/kg (M & F)	IV
870.1300	Acute Inhalation (rat)	48535633	LC_{50} > 4.89 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	48535634	No corneal involvement or iritis observed. No positive conjunctival irritation in 1/3 rabbits at 24 hrs. (a score of 1 for redness) All irritation cleared by 48 hours.	IV
870.2500	Primary Skin Irritation (rabbit)	48535635	Not a dermal irritant	IV
870.2600	Dermal Sensitization (guinea pig)	48535636	Not a skin sensitizer (	N/A

Table A.2.b. Subchronic, Chronic, and Other Toxicity Studies Ethaboxam Technical.

Guideline/ Type of Study	Study Title/ Classification /Doses	MRID	Results
870.3100 28-DAY FEEDING- RAT (LGC-3523 metabolite)	ppm = 0, 650, 2000, 13000 mg/kg/day = M: 0, 56.5, 170.9, or 1104.1 F: 0, 56.5, 70.7, or 1155.8 Acceptable/Nonguideline	48535691	NOAEL= 1104/1156 mg/kg/day [M/F]. LOAEL = not established
870.3100 (2003) 13 WEEK FEEDING- RAT	ppm = 0, 200, 650, 2000 mg/kg/day = M: 0, 16.3, 49.7, 154 F: 0, 17.9, 58, 164 Acceptable/Guideline	48535644 46387805	NOAEL = 16.3/ 17.9 mg/kg/day [M/F] LOAEL = 49.7/58.0 mg/kg/day [M/F] based on decreased mean absolute epididymides weight in males with correlating histopathology, increased incidence of abnormal spermatids in occasional tubules of the testes in males, and lung effects (alveolar septal congestion and focal alveolar hemorrhage).
870.3100 (2002) 13 WEEK FEEDING- MOUSE	ppm = 0, 200, 450, 1000 mg/kg/day = M: 0, 33, 74, 163, 405 F: 0, 41, 93, 195, 483 Acceptable/Guideline	46387802	NOAEL = 405/483 mg/kg/day [M/F] LOAEL = not established
870.3150 (2001) 13 WEEK FEEDING- DOG	mg/kg/day = 0, 15, 40, 100 Acceptable/Guideline	46387803	NOAEL = 15 mg/kg/day LOAEL= 40 mg/kg/day based on decreased body weight and body weight gain in females.

Table A.2.b. Subchronic, Chronic, and Other Toxicity Studies Ethaboxam Technical.			
Guideline/ Type of Study	**Study Title/ Classification /Doses**	**MRID**	**Results**
870.3200 28-DAY DERMAL- RAT	mg/kg/day = 0, 100, 300, or 1000 Acceptable/Nonguideline	48535645	NOAEL = 300 mg/kg/day LOAEL=1000 mg/kg/day based on decreased body weight and body weight gains. At 300 mg/kg/day- dermal irritation in the form of hyperkeratosis, scabbing, and dermal inflammation at the application site
870.3700 (1997) DEVELOPMENTAL TOXICITY- RAT	mg/kg/day = 0, 10, 30, 100, 300 Acceptable/Guideline mg/kg/day = 0, 100, 300, 1000 Acceptable/Guideline	46387808 46488701	First study Maternal: NOAEL = 300 mg/kg/day Maternal LOAEL = not established Developmental: NOAEL= 300 mg/kg/day Developmental LOAEL = not established Second study Maternal: NOAEL = 100 mg/kg/day Maternal LOAEL = 300 mg/kg/day based on increased salivation Developmental: NOAEL= 300 mg/kg/day Developmental LOAEL = 1000 mg/kg/day based on thin diaphragm with liver protrusion, decreased fetal body weight, misshapen pituitary, diaphragmatic hernia, and skeletal anomalies (incomplete or irregular ossification of the pelvic girdle, digits, sternebrae, and thoracic vertebral centra).
870.3700 (1997) DEVELOPMENTAL TOXICITY- RABBIT	mg/kg/day = 0, 25, 75, 125 Acceptable/Guideline	46490401	Maternal NOAEL= 75 mg/kg/day LOAEL = 125 mg/kg/day based on inappetence, decreased food consumption, and body weight loss. Developmental NOAEL= 125 mg/kg/day LOAEL = not established
870.3800 (2002) 2-GENERATION REPRODUCTION- RAT	ppm = 0, 65, 200, 650 mg/kg/day = M: 0, 5.2, 16.2, 52.6 F: 0, 5.7, 17.6, 56.1 Acceptable/Guideline	46387804	Parental: NOAEL = 16.2/17.6 mg/kg/day [M/F] LOAEL = 52.6/56.1 mg/kg/day [M/F] based on decreased premating body weight gain of the F_0 and F_1 generation adult males and decreased premating body weight of the F_1 adult males and females. Reproductive: NOAEL = 16.2/56.1 mg/kg/day [M/F] LOAEL = 52.6 mg/kg/day based on small epididymides and testes, abnormal spermatogenic cells in the epididymal ducts, impaired sperm

Table A.2.b. Subchronic, Chronic, and Other Toxicity Studies Ethaboxam Technical.			
Guideline/ Type of Study	**Study Title/ Classification /Doses**	**MRID**	**Results**
			mobility, abnormal sperm, and reduced fertility in males. Offspring: NOAEL = 16.2/17.6 mg/kg/day [M/F] LOAEL = 52.6/56.1 mg/kg/day [M/F] based on decreased body weight in male and female F_1 pups and decreased viability of the F_1 and F_2 males during lactation. Delay in sexual maturation.
870.4300 (2002) 104-WEEK COMBINED CHRONIC TOXICITY/CARCINOGENICITY- RAT	ppm = 0, 100, 300, 650 mg/kg/day = M: 0, 5.5, 16.4, 35.8 F: 0, 7, 21, 45.5 Acceptable/Guideline	46387811	NOAEL = 5.5/7 mg/kg/day [M/F] LOAEL = 16.4/21 mg/kg/day [M/F] based on adverse effects seen in male reproductive organs- decreased epididymal weight, seminiferous tubule atrophy, abnormal spermatogenic cells in epididymal duct, and absent sperm. Evidence of carcinogenicity: Interstitial/Leydig cell adenoma at the highest dose tested (35.8/45.5 mg/kg/day [M/F])
870.4100 (2001) 52-WEEK FEEDING- DOG	mg/kg/day = 0, 5, 10, 30 Acceptable/Nonguideline	46387809	NOAEL = 30 mg/kg/day LOAEL = not established
870.4200 (2003) 78-WEEK CARCINOGENICITY- MICE	ppm = 0, 100, 300, 900 mg/kg/day = M: 0, 12, 35, 117 F: 0, 14, 44, 135 Acceptable/Guideline	46387810	NOAEL= 35/44 mg/kg/day [M/F] LOAEL = 117/135 mg/kg/day [M/F] based on decreased body weight gain and food efficiency in both sexes, and liver toxicity in males. No evidence of carcinogenicity.
870.5100 (2004) BACTERIAL REVERSE MUTATION ASSAY	Acceptable/Guideline	46378529	Negative
870.5300 (2001) *IN VITRO* MAMMALIAN CELL GENE MUTATION TEST	Acceptable/Guideline	46378530	Negative
870.5375 (2001) *IN VITRO* MAMMALIAN CELL CHROMOSOME ABERRATION TEST	Unacceptable/Guideline	46378531	Induced significant increases in chromosome aberrations and a marked increase in the mitotic index at a concentration of 250 µg/mL (-S9) after a 3-hour exposure and at 100 µg/mL after 19 hours of continuous exposure.

Table A.2.b. Subchronic, Chronic, and Other Toxicity Studies Ethaboxam Technical.			
Guideline/ Type of Study	**Study Title/ Classification /Doses**	**MRID**	**Results**
870.5550 (2006) *In Vitro* Micronucleus Test in Cultured Human Lymphocytes	0, 25, 50, 75, 100, 125, 150, 175, 200, 250, 500, 800, or 1000 µg/mL Acceptable/Guideline	46989601	Induced a positive and significant ($p< 0.01 - 0.001$) response in the absence of S9 activation in lymphocytes stimulated with PHA for 24 hours.
870.5395 (2001) MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST (XDE-750)	Acceptable/Guideline	46378532	Negative
870.6200 (2011) ACUTE NEUROTOXICITY- RAT	mg/kg/day = 0, 300, 1000, or 2000 Acceptable/guideline	48535643	NOAEL = 2000 mg/kg LOAEL = not established
870.6200 (2009) SUBCHRONIC NEUROTOXICITY- RAT	ppm = 250, 600, or 1,500 mg/kg/day=0, 18.0/21.0, 43.0/50.0, 106.0/122.0 mg/kg bw/day [M/F] Acceptable/guideline	48535646	NOAEL = 43/50 mg/kg/day [M/F] LOAEL = 122 mg/kg/day based on reduction in body weights, body weight gains and food consumption in males.
870.7485 (2003) METABOLISM AND PHARMOKINETICS- RAT	Thiazole or Thiophene radiolabeled mg/kg/day = Low dose: 10 High dose: 150 Thiazole radiolabeled mg/kg/day = 10 Daily for 14 days Acceptable/Guideline	46378533	Excretion-Majority of the radiolabeled compound was excreted in the feces or urine within 48 hours of administration, regardless of radiolabel, dose, or sex. For both radiolabels, fecal and urinary excretion combined accounted for 96-104% of the administered dose. The main route of excretion was feces (66-74% of single or repeated administered low-dose), followed by urine (23-30% of the administered low-dose).
870.7600 (2003) DERMAL PENETRATION- RAT	2 µg/cm² or 1 mg/cm² for 6 hrs. Acceptable/Guideline	48535712	Total absorption (absorbed and absorbable dose) was 7.5% after 6 hours.
870.7800 (2011) IMMUNOTOXICITY- RAT	ppm = 0, 250, 650, or 1500 mg/kg/day = 0, 21, 52, or 121 mg/kg/day Acceptable/Guideline	48535688 48535655	Systemic toxicity NOAEL = 21 mg/kg/day Systemic toxicity LOAEL = 52 mg/kg/day based on reduced body weight gain and food consumption. Immunotoxicity NOAEL = 121 mg/kg/day Immunotoxicity LOAEL = not established

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of the Technical Grade Test Compound: Ethaboxam.

Parameter	Value				Reference
Melting Point/Range	Decomposes on melting at 185°C				MRID 46378504
pH	6.8 (1% w/v suspension)				MRID 46378502
Density	1.28 at 24°C				
Water Solubility	12.4 mg/L at 25°C				MRID 46378508
Solvent Solubility at 20°C	Solvent	Solubility			MRID 46378502
	n-Heptane	0.00039 g/L			
	Xylene	0.14 g/L			
	n-Octanol	0.37 g/L			
	1,2-Dichloroethane	2.9 g/L			
	Ethyl Acetate	11 g/L			
	Methanol	18 g/L			
	Acetone	40 g/L			
Vapor Pressure at 25ºC	6.1 x 10^{-7} mm Hg (8.1 x 10^{-5} Pascals)				MRID 46378504
Dissociation Constant, pK_a	3.6				
Octanol/Water Partition Coefficient, Log(K_{OW})	2.73 at pH 4; 2.89 at pH 7; 2.91 at pH 10				
UV/Visible Absorption Spectrum	Solvent System[1]	λmax (nm)	Absorbance	Є (dm^3/mol/cm)	
	Water:ACN	231 (shoulder)	0.696	11,200	
		311	1.144	18,400	
	0.125M HCl:ACN	235	0.794	12,800	
		284	1.006	16,200	
	0.125M NaOH:ACN	252	0.678	10,900	
		262 (shoulder)	0.622	10,000	
		289	0.647	10,400	
		335	1.098	17,700	
	No absorption maxima at wavelengths >400 nm				

[1] ACN = acetonitrile; all ratios were 4:1, v:v.

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1, the AHETF database, and the ARTF database are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website.[10]

[10] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure