OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: July 16, 2024

SUBJECT: **Ethaboxam**. Petition for the Establishment of Permanent Tolerances and Registration for Use on Leaf Petiole Vegetables, Subgroup 22B. Summary of Analytical Chemistry and Residue Data.

PC Code: 090205
CAS No.: 162650-77-3
Decision No.: 591231
Petition No.: 3E9052
Risk Assessment Type: NA
TXR No.: NA
MRID No.: 52082401

DP Barcode: D468315
Task Group No.: 00484701
Parent Case No.: 00475265
Registration No.: 59639-185, 59639-211
Regulatory Action: Section 3
Reg. Review 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

Ethaboxam (with CAS name N-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide, and IUPAC name (RS)-N-[cyano(2-thienyl)methyl]-4-ethyl-2-(ethylamino)thiazole-5-carboxamide) is a systemic thiazole carboxamide fungicide with preventative activity used for the control of downy mildew, Pythium seed decay, and seedling dieback. 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], and sugar beets). An import tolerance (i.e., tolerance without US registration) has been established for ethaboxam residues in grapes.

The nature of the residue in primary crops, rotational crops, livestock, and drinking water is adequately understood. The residue definition/residue of concern (ROC) for risk assessment and tolerance enforcement is the parent compound in primary and rotational crops. The ROC for risk assessment is the parent compound in drinking water. HED has not yet established the ROC in livestock commodities.

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.

The proposed end-use product (EP), 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. 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).

Scientifically acceptable crop field trial studies were submitted on celery. The number of trials was adequate, and the use pattern was consistent with the proposed use patterns regarding maximum application rate and timing. This residue study supports registration of the proposed uses on subgroup 22B, and establishment of tolerances for residues of ethaboxam, as listed in Table 2.2.2.

There are no processed commodities associated with subgroup 22B. Therefore, a processing study is not required.

Suitable methods for tolerance enforcement have been developed and independently validated, which are adequate to determine residues arising from the proposed new uses. The Food and Drug Administration (FDA) multi-residue methods (MRMs) are not adequate for determining residues of ethaboxam.

Adequate storage stability data were submitted to support the storage durations and conditions of

samples from the submitted field trial studies.

The commodities in subgroup 22B are not considered significant livestock feedstuffs. Therefore, the requested new uses will not increase dietary burdens, and will not result in the need for establishment of tolerances in livestock commodities.

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 subgroup 22B. Therefore, there are no harmonization issues with Codex nor PMRA regarding the proposed new uses.

An International Residue Limit Status sheet for ethaboxam is appended to this document as Attachment 1.

2.0 Regulatory Recommendations

HED has examined the residue chemistry database for ethaboxam. There are no residue chemistry issues that would preclude granting the requested new uses of ethaboxam. The specific tolerance recommendations are discussed in Section 2.2, below.

2.1 Data Deficiencies/Data Needs

None.

2.2 Tolerance Considerations

The tolerance expression for ethaboxam currently established under 40CFR §180.622 complies with HED's Final Guidance on Tolerance Expressions (D. Wilbur; 12-JUL-2022). The current tolerance expression is adequate and includes both coverage and compliance statements for enforcement purposes.

2.2.1 Enforcement Analytical Method

Residue Chemistry Summary Document: D429263, J. Cowins, 10-NOV-2016

Method RM-49C-1

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 (for which a separate method based on Method RM-49P is available), samples were extracted twice using a mixture of acetonitrile (ACN)/water (7:3, v:v), centrifuged, and filtered. An aliquot of the extract was diluted with ACN, and partitioned twice with hexane. The ACN was removed by rotary evaporation, and the residue was re-dissolved in 5% sodium chloride solution, then partitioned twice with dichloromethane (DCM). The DCM phase was 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) with electrospray ionization (ESI) in positive ion mode. Separation was achieved via gradient elution, starting with water mixed with 0.1% formic acid transitioning to methanol mixed with 0.1% formic acid. The ethaboxam ion transition

m/z 321.1 → 200.1 was used for quantitation, and m/z 321.1 → 183.1 was used for confirmation. Calibration curves were created using external standards.

Method RM-49R
Method RM-49R, titled Ethaboxam: Determination of Ethaboxam, EEO and EEHO in Crops, is also a validated tolerance enforcement method. This method was used for the determination of ethaboxam and its metabolites in samples from previously submitted rotational crop studies.

Briefly, samples were extracted twice with acetone/water (3:1, v:v) and centrifuged to separate solids. For analysis of ethaboxam, the combined extracts were diluted with methanol or an internal standard solution and water, then filtered through a syringe filter for analysis via LC/MS/MS with ESI in positive ion mode. Separation was achieved by gradient elution, starting with water mixed with 0.05% formic acid transitioning to methanol mixed with 0.05% formic acid. The ethaboxam ion transition m/z 321.1 → 200.1 was used for quantitation, and m/z 321.1 → 183.1 was used for confirmation. Calibration curves were created using external standards.

Conclusions: The analytical methods for enforcement have passed both independent laboratory validation (ILV) and Agency validation, and are adequate to determine residues arising from the proposed new uses. The methods are adequate for enforcement purposes. 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] situation). Therefore, a tolerance enforcement method is not needed for livestock commodities at this time.

2.2.2 Recommended Tolerances

Table 2.2.2. Tolerance Summary for Ethaboxam.

Commodity	Established/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

2.2.3 Revisions to Petitioned-For Tolerances

None.

2.2.4 International Harmonization

Neither Codex Alimentarius nor Canada's PMRA have established MRLs for ethaboxam in commodities

that are members of Leaf petiole vegetable subgroup 22B. Therefore, there are no harmonization issues with Codex nor PMRA regarding the proposed new uses.

An International Residue Limit Status sheet for ethaboxam is appended to this document as Attachment 1.

2.3 Label Recommendations

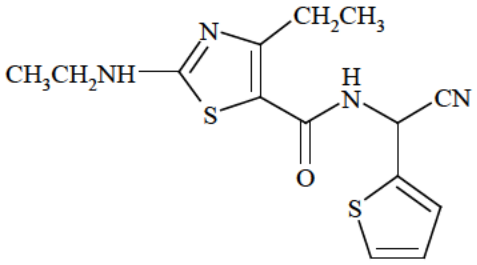
None.

3.0 Introduction

Ethaboxam is a systemic thiazole carboxamide fungicide that controls various diseases caused by the Oomycete class of fungi, including two genera of plant pathogens, *Pythium* and *Plasmopara halstedii*. These fungi cause seed decay, seedling dieback, and downy mildew. Ethaboxam's pesticidal mode of action is an interference with beta-tubulin assembly, mitosis, and cell division. The chemical structure and nomenclature of ethaboxam are listed in Table 3.1, and its physicochemical properties are presented in Table 3.2 (below).

3.1 Chemical Identity

Table 3.1. Ethaboxam Nomenclature.

Compound	Chemical Structure
	
Common name	Ethaboxam
Company experimental name	LGC-30473
IUPAC name	(RS)-N-[cyano(2-thienyl)methyl]-4-ethyl-2-(ethylamino)thiazole-5-carboxamide
CAS name	N-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide
CAS #	162650-77-3
End-use product/EP	V-10208 4 SC Fungicide (also referred to as Elumin Fungicide); 42.5% ai by weight; 4 lb ai/gal (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.

Table 3.2. Physicochemical Properties of Technical Grade Ethaboxam.		
Parameter	Value	Reference
Molecular weight (g/mole)	320.43	MRID 49490202
Melting point/range (°C)	185°C	MRID 46378504
pH	6.8 (1% w/v suspension)	MRID 46378502
Density (g/cm^3)	1.28 at 24°C	
Water solubility (mg/L at 25°C)	4.8	MRID 49490202
Solvent solubility (mg/L at 20°C)	n-Heptane 0.39 mg/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	MRID 46378502
Vapor pressure at 25°C (Pa)	8.1 x 10-5	MRID 49490202
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	

3.3 Pesticide Use Pattern/Directions for Use (860.1200)

The proposed directions for of ethaboxam on Leaf petiole vegetable subgroup 22B were provided in the petition materials, and they are summarized in Table 3.3 (below).

Table 3.3.1. Summary of Directions for Proposed Use of Ethaboxam on Leaf Petiole Vegetable 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	Make two soil drench applications to seedlings (that have at least two true leaves). RTI[1] = 14 days. REI[2] = 12 hours. PHI[3] = N/A. PPE[4] = chemical- resistant gloves made of any waterproof material, socks and shoes.
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]).

[1] RTI = Re-Treatment Interval.

[2] REI = Restricted Entry Interval.

[3] PHI = Pre-Harvest Interval.
[4] PPE = Personal Protective Equipment

Conclusions.

The submitted label directions for ethaboxam use on Leaf Petiole Vegetable subgroup 22B are adequate to allow evaluation of the residue data relative to the proposed new uses.

4.0 Metabolite/Degradate Residue Profile

4.1 Nature of the Residue

4.1.1 Summary of Plant Metabolism (860.1300)

Residue Chemistry Summary Document D313733, M. Doherty, 27-APR-2006
Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

The nature of the residue is adequately understood, based on acceptable metabolism studies conducted on grape, potato and tomato. Ethaboxam was the major residue component identified in all reviewed plant metabolism studies. A significant portion of extractable radioactivity was shown to be incorporated in carbohydrates such as glucose and starch. The only other metabolite identified was LGC-35523, a keto-carboxylic acid derivative of thiophene-labeled ethaboxam which the petitioner stated is identical to a photo-degradate present in an aqueous photolysis study. Metabolite LGC-35523 comprised 11-18% of the total radioactive residues (TRR) in grapes, and 2-4% TRR in tomatoes; this metabolite was not detected in potatoes. Translocation studies with grapes and tomatoes indicate that ethaboxam does not appear to be readily translocated in treated crops (D313733, M. Doherty, 27-APR-2006).

4.1.2 Summary of Livestock Metabolism (860.1300)

Residue Chemistry Summary Document D313733, M. Doherty, 27-APR-2006
Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

Data depicting the metabolism of ethaboxam in laying hens and lactating goats were submitted. In both laying hens and lactating goats, the majority of orally dosed ethaboxam was excreted. Aside from goat fat, ethaboxam was, at most, a minor residue in edible livestock commodities.

Desethylethaboxam and cyanoformamide consistently made up the majority of residues in all livestock commodities. HED notes that for future submissions of livestock commodities, the metabolites of concern, EEO (4-ethyl-2-(ethylamino)-1,3-oxazol -5-(4H)-one) and EEHO (4-ethyl-2-(ethylamino)-4-hydroxy-1,3-oxazol -5-(4H)-one), should be analyzed for determination of the ROC in livestock commodities.

4.1.3 Summary of Confined Rotational Crops (860.l850)

Residue Chemistry Summary Document D313733, M. Doherty, 27-APR-2006
Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

A confined rotational crop study was conducted on lettuce, radish, sorghum and wheat planted after a

single application of radiolabeled [14C]-ethaboxam (thiazole and thiophene labels) at 1.10 lb ai/acre (roughly 2X the current maximum use rate) to bare soil in test plot boxes. The crops were planted into the plots at 30, 120 and 365 days after soil treatment. The confined rotational crop studies indicated that residues of ethaboxam and its metabolites generally decrease with increasing plant-back intervals (PBIs). These studies, when coupled with the field accumulation studies, demonstrate that residues of ethaboxam, EEO and EEHO are not expected in rotational crops at a 30-day PBI. Therefore, the data support the existing 30-day PBI.

Conclusions.

The nature of the residue in primary crops, rotational crops, and livestock has been adequately delineated.

4.2 Residues of Concern Summary and Rationale

Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

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 ROC in primary and rotational crops for tolerance enforcement and risk assessment, and in drinking water for risk assessment, is the parent ethaboxam (see Table 4.2, below).

Table 4.2. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Ethaboxam	Ethaboxam
	Rotational Crop	Ethaboxam	Ethaboxam
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Ethaboxam	Ethaboxam

5.0 Residue Profile

5.1 Residue Analytical Methods (860.1340)

5.1.1 Data Collection Methods

MRID 52082401

Samples from the celery trials were analyzed for residues of ethaboxam via LC/MS/MS, using a working method very similar to the reference method, “Determination of Ethaboxam in Crops”, RM-49C-1,. This method was previously deemed acceptable for tolerance enforcement in crop commodities (D429263, J. Cowins, 10-NOV-2016). The LOQ, determined as the lowest level of method validation (LLMV), was

0.010 ppm. Acceptable concurrent recoveries were obtained from field trial samples of mustard greens fortified with ethaboxam at 0.010-5.0 ppm. The fortification levels adequately represented measured residue levels in celery samples. The total mean residues of ethaboxam were in the range <0.01 to 0.0601 ppm in samples taken at 78-144 days PHI.

Conclusions.

The method has been adequately validated as a data collection method.

5.1.2 Multi-Residue Methods (860.1360)

Residue Chemistry Summary Document D313733, M. Doherty, 27-APR-2006

Ethaboxam has been determined to have low volatility (vapor pressure of 8.1 x 10-5 Pascals at 25°C), and it is thermally unstable (decomposes on melting at 185°C). FDA's Pesticide Analytical Methods (PAM) Volume I involve gas chromatographic analyses. Since ethaboxam is thermally unstable under these conditions, the PAM protocols are not suitable for the analysis of ethaboxam. The QuEChERS multi-residue method appears to be suitable for the analysis of ethaboxam (Collaborative Validation of the QuEChERS Procedure for the Determination of Pesticides in Food by LC-MS/MS.; J. Ag. Food Chem. 59(12):6383-6411; Sack et al; 2011).

5.1.3 Tolerance Enforcement Methods

Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

Suitable methods for ethaboxam tolerance enforcement have been developed and independently validated. For all matrices, the LOQ, defined as the LLMV, was determined to be 0.010 ppm. The LOD was defined to be 50% of the LOQ (that is, 0.005 ppm).

Conclusions.

The available methods are considered suitable for tolerance enforcement purposes.

5.1.4 Submittal of Analytical Reference Standards (860.1650)

The analytical reference standard for ethaboxam is currently available in EPA's National Pesticide Standards Repository (NPSR), with an expiration date of 07/16/2024, per email communication from Craig Vigo of the Biological and Economic Analysis Division's (BEAD's) Analytical Chemistry Branch (ACB) on 12/13/2025. As long as tolerances remain published in 40CFR §180.622, the registrant is required to maintain reasonable amounts of the reference standard for ethaboxam in the NPSR. When necessary, a new reference standard, or updated certificate of analysis (COA), should be sent to the ACB, which is located at Fort Meade, MD. It should be sent to the attention of either Craig Vigo or Thuy Nguyen at the address listed below, along with a letter of transmittal. **Please note that the full 9-digit ZIP Code is required, or the mail will be returned to the registrant.**

USEPA
National Pesticide Standards Repository
Analytical Chemistry Branch/BEAD/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

The letter of transmittal should include the assay of the standard, name of the analytical method used, a statement of principal impurities, purification procedures employed, storage requirements, and special precautions for safe handling. Replacement of standards may be required periodically if supplies are exhausted, if the standards expire, or if decomposition occurs during storage. Material Safety Data Sheets (MSDSs) must accompany all analytical standards as specified in 29CFR §1910.1200 by the Occupational Safety and Health Administration (OSHA).

5.2 Storage Stability (860.1380)

MRID 52082401

To support sample storage durations, freezer storage stability data for ethaboxam were generated concurrently with the celery trials. Samples of untreated celery were fortified with ethaboxam at 0.10 ppm, and placed into frozen storage at -20°C.

For the celery trial study, the maximum storage duration for samples between harvest and extraction for analysis was 16.5 months. These data adequately support the sample storage conditions and durations from the submitted studies.

The recoveries for the storage stability samples were in the range 81 to 86%, which were consistent with the results of the zero-day storage stability analysis where recoveries ranged from 83 to 87%. Concurrent recoveries for spikes analyzed along with the storage stability samples were in the range 71 to 90%.

A summary of the storage conditions and durations for the celery trial samples is presented in Table 5.2, below.

Table 5.2. Summary of Storage Conditions.

Commodity	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Celery	-20	16.5 months	19.4 months

Conclusions.

The six celery trials had sample storage intervals no longer than 16.5 months. HED concludes that the available storage stability data for celery (19.4 months) are adequate to support the sample storage conditions and durations from the celery trial studies.

5.3 Residue Data

5.3.1 Crop Field Trials (860.1500)

MRID 52082401

Magnitude of residue data have been collected from six field trials located in the United States. At each trial, two soil drench applications of the test substance 13-14 days apart were made to the treated trays. The application rates were in the range 0.250 to 0.256 lb ai/100 gal per application for a total rate range of 0.500 to 0.512 lb ai/100 gal per season. All applications were made using either appropriate spray equipment or by drenching the trays using a watering can. The targeted volume of 1-2 pints per square foot of soil surface was sufficient to provide adequate dispersal of the test substance.

After the second application was made, the plants were transplanted from the greenhouse to the field and were allowed to reach commercial maturity before sampling. Sampling started in the untreated control plot and ended in the treated plot. At all the field trials, samples were harvested 78-144 days after the last application.

The samples were analyzed using a working method very similar to the reference method, "Determination of Ethaboxam in Crops", RM-49C-1, Valent USA Corporation, April 5, 2012.
The total mean residues of ethaboxam were in the range <0.01 to 0.0601 ppm in samples taken at 78-144 days PHI.

Table 5.3.1. Summary of Residues from Field Trials with Ethaboxam.

Crop Matrix	Applic. Rate (lb ai/100 gal)	PHI (days)	n*	Residues (ppm)						
				Min.†	Max.†	LAFT*	HAFT*	Median*	Mean*	SD*
CROP 1; Proposed Use = xxx lb ai/A total application rate, y-day PHI.										
Celery	0.500 to 0.512	78-144	6	<0.01	0.0658	<0.01	0.0601	0.0109	0.0270	0.0238

n = number of independent field trials
LAFT = Lowest Average Field Trial
HAFT = Highest Average Field Trial
SD = Standard Deviation.
† Values based on individual samples
* For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ are assumed to be at the LOQ.

Conclusions.

The submitted field trials for ethaboxam on celery reflected the proposed use pattern. The studies are supported by adequate analytical methods and storage stability data; therefore, they are adequate for regulatory purposes. The numbers of trials are sufficient, and the geographic distributions of the trials capture the growing regions in the US for celery, per OCSPP Residue Chemistry Test Guideline 860.1500. Residues from the trials are representative of worst-case situations expected to result from application of ethaboxam according to the proposed use pattern.

5.3.2 Field Rotational Crops (860.1900)

Residue Chemistry Summary Document D429263, J. Cowins, 10-NOV-2016

The previously submitted and reviewed rotational crop study is adequate, and the PBI listed on the label is sufficient.

5.3.3 Processed Food and Feed (860.1520)

There are no processed commodities associated with commodities within crop subgroup 22B. Therefore, a processing study is not required.

5.3.4 Meat, Milk, Poultry and Eggs (860.1480)

The commodities in Leaf Petiole Vegetables, Subgroup 22B are not considered significant livestock feedstuffs, so the dietary burdens have not changed from the previous residue chemistry summary document for ethaboxam (D452226, W. Drew, 8-OCT-2020). Therefore, the requested new uses will not result in the need for establishment of tolerances in livestock commodities.

5.3.5 Food Handling (860.1460)

There are no proposed uses that are relevant to this guideline topic.

5.3.6 Water, Fish, and Irrigated Crops (860.1400)

There are no proposed uses that are relevant to this guideline topic.

5.4 Food Residue Profile

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.

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.

6.0 Tolerance Derivation

HED based the recommended tolerance of 0.15 ppm in/on Leaf Petiole Vegetables, Subgroup 22B on the Organization for Economic Cooperation and Development (OECD) Calculator on IR-4 greenhouse celery residue data.

An International Residue Limit Status sheet is appended to this document as Attachment 1. The datasets and results from the OECD MRL/tolerance calculation procedure for celery is appended as Attachment 2.

Attachment 1. International Residue Limits Table

Ethaboxam (PC Code 090205)					
Summary of US Tolerances and International Maximum Residue Limits.					
Residue Definitions					
US (40CFR §180.578)[1]		**Canada**		**Codex[1]**	
Crops: *N*-(cyano-2-thienylmethyl)-4-ethyl-2-(ethlyamino)-5-thiazolecarboxamide.		**All food crops:** *N*-(cyano-2-thienylmethyl)-4-ethyl-2-(ethlyamino)-5-thiazolecarboxamide.			
Commodity[2]	**Tolerance (ppm)[3]**	**Commodity**	**MRL (mg/kg)**	**Commodity**	**MRL (mg/kg)**
Leaf Petiole Vegetables, Subgroup 22B	0.15				
Completed: A. Leahigh on 11/15/2023.					

Attachment 2. OECD MRL Calculation Procedure Inputs/Outputs

Ethaboxam
Celery
USA
0.25 lb ai/100 gal (2X)

Residues (mg/kg)	
0.010	*
0.015	
0.060	
0.057	
0.010	*
0.010	*

Reset | Select frame | Gener

Ethaboxam
Celery
USA
0.25 lb ai/100 gal (2X)

Total number of data (n)	6
Percentage of censored data	50%
Number of non-censored data	3
Lowest residue	0.010
Highest residue	0.060
Median residue	0.013
Mean	0.027
Standard deviation (SD)	0.024
Correction factor for censoring (CF)	0.667

Proposed MRL estimate

- Highest residue	0.060
- Mean + 4 SD	0.125
- CF x 3 Mean	0.054
Unrounded MRL	0.125
Rounded MRL	0.15

High uncertainty of MRL estimate.
[Small dataset]

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Celery

Document ID: MRID No. 52082401

Report: Pike, T. (2022) Ethaboxam. Magnitude of the Residue on Celery (GH).

Guidelines: EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996)

GLP Compliance: No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

Acceptability: The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, A. Leahigh, 090205_TG00484701_CHEMR_2024-07-16.

Scientific Integrity: 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.pdff. 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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EXECUTIVE SUMMARY

Six field trials for ethaboxam on celery were conducted in the United States (California, Florida, and Wisconsin) during the 2019 growing season.

At each trial, two soil drench applications of the test substance 13-14 days apart were made to the treated trays. The application rates were in the range 0.250 to 0.256 lb ai/100 gal per application for a total rate range of 0.500 to 0.512 lb ai/100 gal per season. All applications were made using either appropriate spray equipment or by drenching the trays using a watering can. The targeted volume of 1-2 pints per square foot of soil surface was sufficient to provide adequate dispersal of the test substance.

After the second application was made, the plants were transplanted from the greenhouse to the field and were allowed to reach commercial maturity before sampling. Sampling started in the untreated control plot and ended in the treated plot. At all the field trials, samples were harvested 78-144 days after the last application.

The samples were analyzed using a working method very similar to the reference method, "Determination of Ethaboxam in Crops", RM-49C-1, Valent USA Corporation, April 5, 2012.

The total mean residues of ethaboxam were in the range <0.01 to 0.0601 ppm in samples taken at 78-144 days PHI.

The nature of the residues of ethaboxam is adequately understood, and an acceptable analytical method is available for enforcement purposes.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Ethaboxam.	
Common name	Ethaboxam
Identity	N-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide
CAS no.	162650-77-3
Company experimental name	LGC-30473
Other synonyms (if applicable)	V-10208 4 SC Fungicide (also referred to as Elumin Fungicide); 42.5% ai by weight; 4 lb ai/gal (EPA Reg. No. 59639-211)

B. Study Design

1. Test Procedure

A total of six residue trials in/on celery were conducted with a V-10208 4 SC Fungicide (also referred to as Elumin Fungicid; 42.5% ai by weight; 4 lb ai/gal) during the 2019 growing season (Table B.7.6.1.1-2).

All trials were found to be independent based on the criteria described in 568_Criteria for Independence of Trials 4/23/2013 (EPA and PMRA).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.

Crop	Region														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Celery			1		1					4					6

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3. At each trial, two soil drench applications of the test substance 13-14 days apart were made to the treated trays.

Table B.7.6.1.1-3. Study Use Pattern.

Location: City, State/Province; Year (Trial ID)	End-use Product (% ai)	Method of Application/ Timing of Application	Volume (pints/ft^2)	Rate per Application (lbs ai/100 gal)	Retreatment Interval (days)	Total Rate (lbs ai/100 gal)	Surfactant Or Adjuvant
Salinas, CA 2019 (CA*42)	Elumin	1. Vegetative, 4-5 true leaves	1.33	0.253	-	0.506	None
		2. 6-7 true leaves	1.31		13		
Salinas, CA 2019 (CA*43)	Elumin	1. 4-5 true leaves	1.45	0.253	-	0.506	None
		2. 6-7 true leaves	1.14		13		
Riverside, CA 2019 (CA44)	Elumin	1. Vegetative, 2 true leaves	1.5	0.250	-	0.500	None
		2. Vegetative	1.5		14		
Riverside, CA Thermal, CA 2019 (CA45)	Elumin	1. Vegetative, 2 true leaves	1.5	0.250	-	0.500	None
		2. Vegetative	1.5		14		
Citra, FL 2019 (FL135)	Elumin	1. 3-4 true leaves	1.5	0.250	-	0.500	None
		2. 3-4 true leaves	1.5		13		
Arlington, WI 2019 (WI414)	Elumin	1. Vegetative, >2 true leaves	1.5	0.256	-	0.512	None
		2. Vegetative	1.5		14		

Celery was grown and maintained according to typical agricultural practices. Irrigation was used. No unusual weather conditions were reported during the study.

Sample Handling and Preparation

The samples were shipped to the analytical laboratory frozen by ACDS freezer truck. All samples arrived frozen and intact at the analytical laboratory. The samples were checked in, ground with dry ice and then stored frozen until extraction and analysis.

2. Description of Analytical Procedures

The samples were analyzed using a working method very similar to the reference method, "Determination of Ethaboxam in Crops", RM-49C-1, Valent USA Corporation, April 5, 2012.

Celery samples (5 g) were extracted two times using 20 mL acetonitrile: water mixture (7:3, v/v) by shaking on a reciprocating shaker for 30 minutes. After each period of shaking, extracts were centrifuged to remove solids, filtered through glass wool, and collected to a volumetric cylinder and combined. The extract was brought to 50 mL using acetonitrile: water (7:3, v/v). An aliquot was then partitioned twice against acetonitrile/hexane. The acetonitrile phase was evaporated to dryness under nitrogen in RapidVap. The dried extract was reconstituted with an aliquot of 5% sodium chloride solution and then partitioned twice with dichloromethane. The dichloromethane phase was evaporated to dryness under nitrogen in RapidVap. The dried extract was reconstituted with water (0.5% acetic acid): acetonitrile (8:2, v/v) and diluted as necessary for LC-MS/MS analysis.

Method suitability was evaluated both prior to sample analysis and concurrently with sample analysis. Recoveries were in the range 71-104%.

The lowest level of method validation (LLMV) for celery (GH) was 0.01 ppm for ethaboxam. Analytical sets typically consisted of calibration standards, unfortified controls, fortified controls, and treated samples. A calibration standard was injected at the beginning and end of each analytical set.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples of celery fortified with ethaboxam at 0.01 and 0.1 ppm. Recoveries were within the acceptable range of 70-120%; therefore, the method is considered valid for the determination of residues of ethaboxam in celery (Table B.7.6.1.3-4). The fortification levels were adequate to represent the measured residues.

Concurrent recoveries were not corrected for apparent residues in/on controls. Concurrent recoveries for spikes analyzed along with the storage stability samples were in the range 71 to 90%. This data indicates that ethaboxam is stable under the conditions which the samples were held between harvest and analysis.

Table B.7.6.1.1-4. Summary of Procedural/Concurrent Recoveries of Ethaboxam from Celery.

Matrix	Fortification Level (ppm)	Recoveries (%)		Mean ± Std. Dev. (%)
Celery	0.01	MV	75	83±11
		MV	76	
		MV	77	
		SSCR	71	
		CR	71	
		CR	95	
		CR	98	
		CR	83	
		CR	102	
		CR	82	
		SSCR	80	
Celery	0.1	MV	76	89±10
		MV	77	
		MV	72	
		SSCR	90	
		CR	89	
		CR	99	
		CR	104	
		CR	92	
		CR	90	
		CR	99	
		SSCR	87	

The maximum storage interval for field-treated samples in this study was 503 days (Table B.7.6.1.1-5). Storage stability samples were fortified with ethaboxam at 0.1 ppm soon after the receipt of the samples by the analytical laboratory. A set of storage stability samples was analyzed immediately in order to generate zero-day storage stability results. The rest of the storage stability samples were held in frozen storage under similar conditions to the field generated samples. After 590 days of freezer storage, the remaining storage stability samples were analyzed for ethaboxam.

The recoveries for the storage stability samples were in the range 81 to 86%, which were consistent with the results of the zero-day storage stability analysis where recoveries ranged from 83 to 87%.

The available freezer storage stability data indicate that residues of ethaboxam were stable when stored frozen at ≤-20°C in celery for up to 590.

Table B.7.6.1.1-5. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration (days/months)	Limit of Demonstrated Storage Stability (days)	Storage Stability Recoveries (%)
Celery	-20	NA[1]	0	83
				87
				86
Celrey	-20	503	590	81
				84
				86

[1]Zero day storage stability samples

The total mean residues of ethaboxam were in the range <0.01 to 0.0601 ppm in samples taken at 78-144 days PHI.

The results from these trials showed that when harvested 78-144 days after the last of two application(s) at a rate of 0.250 to 0.256 lb ai/100 gal per application for a total rate range of 0.500 to 0.512 lb ai/100 gal per season, residues of ethaboxam in celery ranged from <0.01 ppm to 0.0601 ppm (Tables B.7.6.1.1-6 and B.7.6.1.1-7).

Due to the very low levels of observed residues, no decline trend could be determined in celery.

Table B.7.6.1.1-6. Residue Data from [Crop] Field Trials with [Active Ingredient].								
Location: City, State/Province ; Year (Trial ID)	Region	Crop (Variety)	End-Use Product	Rate (lb ai/100 gal)[1]	PHI (days)	Residues (ppm)		
						Ethaboxam		Mean Residue[2]
Salinas, CA 2019 (CA*42)	10	Celery (Merengo)	Elumin	0.506	100	<0.01	<0.01	<0.01[3]
Salinas, CA 2019 (CA*43)	10	Celery (Sonora)		0.506	144	0.0118	0.0172	0.0145
Riverside, CA 2019 (CA44)	10	Celery (Tango)		0.500	104	0.0609	0.0593	0.0601
Riverside, CA Thermal, CA 2019 (CA45)	10	Celery (Tango)		0.500	105	0.0488	0.0658	0.0573
Citra, FL 2019 (FL135)	3	Celery (Tano)		0.500	78	<0.01	<0.01	<0.01[3]
Arlington, WI 2019 (WI414)	5	Celery (Dutchess)		0.512	109	<0.01	<0.01	<0.01[3]

[1] 2 soil drench applications of Elumin.
[2] Mean residue; for residues <0.01 ppm, a value of 0.01 ppm is used to calculate the mean.
[3] All residues in samples from this trial are below the Lowest Level of Method Validation.

Table B.7.6.1.1-7. Summary of Residues from [Crop] Field Trials with [Active Ingredient].											
Crop Matrix	Analyte	Total Application Rate (lb ai/100 gal)	PHI (days)	n	Residues[1] (ppm)						
					Max.[1]	LAFT[2]	HAFT[2]	Median[2]	Mean[2]	SD[2]	
Celery	Ethaboxam	0.500-0.512	78-144	12	0.0658	<0.01	0.0601	0.0123	0.270	0.0238	

[1] Values based on total number of samples.
[2] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ are assumed to be at the LOQ (0.01 ppm).
n = number of field trials.

III. CONCLUSIONS

The celery field trials are considered scientifically acceptable. The results from these trials showed that when harvested 78-144 days after the last of two application(s) at a rate of 0.250 to 0.256 lb ai/100 gal per application for a total rate range of 0.500 to 0.512 lb ai/100 gal per season, residues of ethaboxam in celery ranged from <0.01 ppm to 0.0601 ppm. Due to the very low levels of observed residues, no decline trend could be determined in celery. Adequate storage stability data are available to support sample storage durations and conditions.

REFERENCES

A. Leahigh, 090205_TG00484701_CHEMR_2024-07-16