UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 07/08/2020

Subject: **Hexythiazox**. Human Health Risk Assessment for Amended Tolerances on Caneberry Subgroup 13-07A and Dates, Dried Fruit and Establishment of a Tolerance Without U.S. Registration for Residues in Tea.

PC Code: 128849	DP Barcodes: D452458 and D453375
Decision Nos.: 549928 and 548644	Registration No.: EPA Reg. No. 10163-337
Petition No.: 9F8737 and 9E8756	Regulatory Action: Section 3 & Tolerance without U.S. Registration
Risk Assessment Type: Single Chemical	Case No.: NA
TXR No.: NA	CAS No.: 78587-05-0
MRID No.: NA	40 CFR: §180.448

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1.0 Executive Summary

Hexythiazox, (4*R*,5*R*)-*rel*-5-(4-chlorophenyl)-*N*-cyclohexyl-4-methyl-2-oxo-3-thiazolidinecarboxamide, is an ovicide/miticide used to control spotted spider mites on a variety of crops and outdoor residential settings (i.e., ornamental landscaping, ornamental lawns and turf, residential gardens). Hexythiazox is a contact pesticide which achieves control of eggs or immature mites via direct contact or contact with treated surfaces. The Registration Division (RD) has asked the Health Effects Division (HED) to provide a review of the human health exposure and risk estimates associated with the proposed amendment to the Onager EW Miticide (EPA Reg. No. 10163-337, micro-emulsion formulation) label for use on Caneberry subgroup 13-07A and dates as well as the establishment of a tolerance without U.S. registration for residues in/on tea.

The most recent human health risk assessment for hexythiazox was completed in 2019 for an amended use on Berry, Low Growing subgroup (13-07G) (S. Shelat, D448711, 7/2/2019). For the current action, Gowan Company has submitted a proposed amended label for the use of Onager EW Miticide on dates and caneberry subgroup 13-07A and petitioned for tolerance without U.S. registration for residues in/on tea. The tea action is not associated with a US registration; therefore, no associated occupational exposure assessment is conducted for tea. For dates and caneberry subgroup 13-07A, the product is applied via ground, aerial or chemigation equipment. The proposed label directs applicators and other handlers to wear baseline attire (i.e., long-sleeved shirt, long pants, shoes, and socks) and chemical-resistant gloves. Short-and intermediate-term occupational handler and post-application exposures are anticipated from the proposed new uses.An updated chronic dietary assessment has also been conducted to assess all registered and proposed uses. Additionally, no updates were made to the previous residential assessment however, an updated aggregate exposure and risk assessments are conducted to incorporate the updated dietary exposure estimates.

The proposed label amendments have been considered under current HED policy. The toxicology database for hexythiazox is complete. All toxicity studies required under 40 CFR part 158 data requirements have been submitted or formally recommended to be waived by the Hazard and Science Policy Council (HASPOC) (K. Rury, TXR# 0056434, 10/18/2012).

The primary target organs of hexythiazox are the adrenals and liver following subchronic and chronic exposure to dogs, rats, and mice. Hexythiazox is not considered to be a developmental, reproductive, neurotoxic or immunotoxic chemical nor a mutagen. Hexythiazox is classified as "Likely to be Carcinogenic to Humans". HED also concluded that quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity from exposure to hexythiazox. The Food Quality Protection Act (FQPA) Safety Factor is reduced to 1X since there is no evidence of increased susceptibility to *in utero* and/or postnatal exposure to hexythiazox.

Hexythiazox has low acute toxicity via the oral, dermal, or inhalation route of exposure (Toxicity Category IV). It is a mild eye irritant (Toxicity Category III), but not a skin irritant or a skin sensitizer.

The submitted residue data on raspberry and date are adequate in terms of both number, geographic representation, and application scenario to support the proposed amended use on caneberry subgroup 13-07A and dates. In addition, adequate data have been submitted to support a tolerance for residues in/on tea without a U.S. registration.

An acute dietary risk assessment is not required since no endpoint attributable to a single oral exposure was identified from the available toxicity database. An unrefined chronic dietary risk assessment was conducted using tolerance-level residues, modeled drinking water estimates, assuming 100% crop treated, and using HED's 2018 default and empirical processing factors. The highly conservative risk assessment showed no risk estimates of concern for the U.S. population or any population subgroup. The estimated exposure to the U.S. general population resulted in a risk equivalent to 23% of the chronic population adjusted dose (cPAD). The estimated exposure to children 1 – 2 years old, the most highly exposed population subgroup, resulted in a risk estimate equivalent to 97% of the cPAD. Hexythiazox is classified as "Likely to be Carcinogenic to Humans." A quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to hexythiazox. Therefore, a separate cancer assessment was not conducted, and the chronic exposure assessment is considered protective of any cancer exposures.

In previous human health risk assessments for hexythiazox, inhalation exposure and risk to residential handlers was assessed; however, all currently registered hexythiazox product labels with residential use sites require that handlers wear specific clothing and personal protective equipment (PPE). Therefore, HED has made the assumption that these products are not for homeowner use, and, for all current and future assessments, a quantitative residential handler assessment will not be conducted. Residential post-application exposures from applications in residential settings were addressed in previous assessments. Due to lack of a dermal endpoint, only the incidental oral exposures from use on residential turf were assessed previously and were not of concern, Margins of exposure (MOEs) were greater than the Level of Concern (LOC).

The aggregate risk assessment has been updated to reflect the new dietary exposure assessment. The short-term and intermediate-term aggregate assessment resulted in no risk estimates of concern when aggregating residential post-application exposures previously assessed with the updated chronic dietary exposures. MOEs were 1,100 and 1,200 for the short and intermediate-term aggregate assessments, respectively (Level of Concern (LOC) = 100).

No dermal endpoint was selected for hexythiazox therefore only the occupational handler inhalation exposure and risk estimates were calculated for the proposed uses of hexythiazox at the label-required PPE (i.e., no respirator). Occupational handler MOEs for the proposed new uses range from 22,000 to 5,600,000 (LOC = 100).

No dermal hazard was identified for hexythiazox therefore a quantitative occupational post-application assessment was not conducted. The restricted entry interval (REI) specified on the proposed label is based on the acute toxicity of hexythiazox and the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to hexythiazox.

2.0 HED Recommendation

The Agency has found no chronic dietary (food plus drinking water), short- and intermediate-term aggregate, nor occupational risks of concern from the proposed uses of hexythiazox.

There are no residue chemistry or occupational exposure considerations that would preclude granting the requested label amendment for use on caneberry subgroup (13-07A) and dates, dried fruit as well as the establishment of a tolerance without U.S. registration for residues in/on tea.

2.1 Data Deficiencies/Data Needs

An analytical reference standard for metabolite PT-1-3 moiety (minimum of 1 gram) should be submitted. For mailing information, see Appendix C.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate HPLC/UV analytical method is available for the enforcement of tolerances for residues of hexythiazox and its metabolites containing the PT-1-3 moiety in crop and livestock commodities. This method is listed in the U.S. EPA Index of Residue Analytical Methods under hexythiazox as method AMR-985-87.

Hexythiazox has been tested FDA Multiresidue protocols C through E and the findings have been forwarded to the FDA. Hexythiazox metabolites were not recovered through protocols C through E.

2.2.2 Recommended Tolerances

Tolerances are currently established for hexythiazox under 40 CFR §180.448 and comply with the HED *Interim Guidance on Tolerance Expressions* (S. Knizner, 05/27/2009). Table 2.2.2 below summarizes the recommended tolerance levels which were derived using the Organization for Economic Cooperation and Development Maximum Residue Level (OECD MRL) calculation procedure.

Table 2.2.2. Tolerance Summary for Hexythiazox

Commodity	Proposed Tolerance (ppm)	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Caneberry, Subgroup 13-07A	3.0	1	3	Corrected value to be consistent with HED Rounding Class Practice
Date, dried	3.0	1.0	3	Corrected value to be consistent with HED Rounding Class Practice
Tea, dried[1]	15.0	--	15	Corrected value to be consistent with HED Rounding Class Practice

[1] Tolerance without U.S. registration

2.2.3 Revisions to Petitioned-For Tolerances

A revised section F should be submitted removing the trailing zero as recommended in Table 2.2.2.

2.2.4 International Harmonization

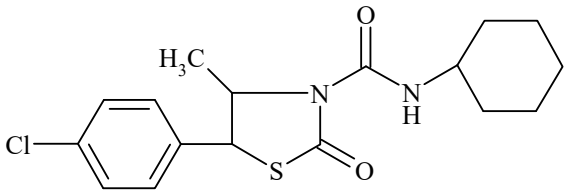
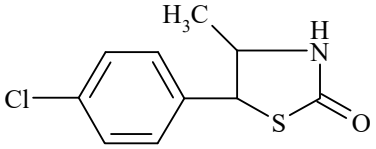
There is no Canadian maximum residue limit (MRL) on tea; however, there are Canadian MRLs on berries (raspberry, blackberry, and loganberry) at 1.5 ppm and dates at 2 ppm. Codex has established MRLs on tea at 15 ppm and date at 2 ppm; however, Codex has not established an MRL for residues of raspberry. The U.S. residue definition for hexythiazox is not harmonized with Canada and Codex. The Codex plant residue definition is for the parent compound, hexythiazox, only as opposed to the U.S. definition which includes hexythiazox plus metabolites containing the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety. The HED-recommended tea tolerance value is harmonized with the Codex tea MRL value; however, HED does not recommend harmonizing with the Codex or Canadian date MRL as a result of different use patterns. In addition, HED does not recommend lowering the tolerance for berries to harmonize with Canadian MRL. A summary of MRLs can be found in Appendix B.

2.3 Label Recommendations

There are no label recommendations at this time.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Nomenclature of Hexythiazox.	
Compound	
Common name	Hexythiazox
Company experimental names	Savey® 50 DF
IUPAC name	(4*RS*,5*RS*)-5-(4-chlorophenyl)-*N*-cyclohexyl-4-methyl-2-oxo-1,3-thiazolidine-3-carboxamide
CAS name	*trans*-5-(4-chlorophenyl)-*N*-cyclohexyl-4-methyl-2-oxo-3-thiazolidinecarboxamide
CAS #	78587-05-0
End-use product/EP	1 lb gal EW (EPA Reg. No. 10163-337; Onager Optek™ Miticide (EW))
Compound (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety	
Common name	PT-1-3 moiety
Chemical name	5-(4-chlorophenyl)-4-methyl-thiazolidin-2-one

3.2 Physical/Chemical Characteristics

Table 3.2 Physicochemical Properties of Hexythiazox.		
Parameter	Value	Reference[1]
Melting point/range	108.0-108.5 °C	00143533
pH	Not applicable	
Density	1.289 at 25 °C	00143533
Water solubility	0.12 ppm	44006301
Solvent solubility	g/L chloroform 1379 xylene 362 acetone 160.0 acetonitrile 28.6 n-hexane 3.9 methanol 20.6	00143533
Vapor pressure	$<10^{-8}$ mm Hg at 25 ºC	44006301
Dissociation constant, pK_a	Not applicable	
Octanol/water partition coefficient Log (P_{OW})	560 (average)	0143533, 00146531
UV/visible absorption spectrum (molecular absorption coefficients)	Maximum at 223 nm in acetonitrile, no absorption in the visible range.	Not available

D. Drew, D396862, 18-JUN- 2012

3.3 Pesticide Use Pattern

Gowan Company has submitted a proposed amended label for the use of Onager Optek Miticide (EPA Reg. No. 10163-337, micro-emulsion formulation) on dates and caneberry subgroup 13-07A. Caneberry subgroup 13-07A and dates are currently registered on Savey® 50 DF (EPA Registration #10163-250), a dry-flowable (DF) formulation, at a lower maximum rate of 0.1875 lb ai/acre. For the proposed use, the product is applied via ground, aerial or chemigation equipment. The proposed label directs applicators and other handlers to wear baseline attire (i.e., long-sleeved shirt, long pants, shoes, and socks) and chemical-resistant gloves. The newly proposed use pattern has been summarized in Table 3.3.1. The available label information for the petition for a tolerance without U.S. registration for residues in/on tea is provided in Table 3.3.2.

Table 3.3.1. Summary of Directions for Use of Hexythiazox.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Dates						
Groundboom, Airblast, Aerial, Chemigation, Mechanically-pressurized Handgun	Onager EW Miticide [EPA Reg. No. 10163-337]	0.094 - 0.25 lb ai/acre 0.0125 lbs ai/gallon[a] [12 – 32 oz/acre]	Do not make more than one application per year. Do not apply more than 32 oz per acre per calendar year.	0.25 lb ai/acre [32 oz/acre[b]]	90	Apply at first signs of egg deposition, but no later than first observation of mite webbing on dates. Do not make more than one application of Onager EW or any other hexythizox product to the same crop per year. Do not plant rotational crops other than those on this label within 120 days of this application.
Caneberry Subgroup 13-07A						
Groundboom, Airblast, Aerial, Chemigation, Mechanically-pressurized Handgun	Onager EW Miticide [EPA Reg. No. 10163-337]	0.094 - 0.25 lb ai/acre 0.0125 lbs ai/gallon[a] [12 – 32 oz/acre]	Do not make more than one application per year. Do not apply more than 32 oz per acre per calendar year.	0.25 lb ai/acre [32 oz/acre[b]]	3	Application may be made post-harvest. Do not make more than one application of Onager EW or any other hexythiazox product to the same crop per year. Do not plant rotational crops other than those on this label within 120 days of this application.

a. calculated assuming 20 gallons of finished spray per acre for ground applications
b. calculated from 1 lb ai/gal stated on product label

Table 3.3.2 Summary of Directions for Proposed Use for Hexythiazox on Imported Tea

Country	Proposed Use	Formulation	Application	Maximum Seasonal Application Rate	Max. no. of Treatment	PHI (days)
India	Tea	5% EC	Foliar	0.0223 lb ai/A (0.025 kg ai/ha)	2	NS

NS: not specified
* Although an India label was provided in the petition, the use direction was taken from Joint FAO/WHO Meeting on Pesticide Residue (JMPR)

review.

3.4 Anticipated Exposure Pathways

Humans may be exposed to hexythiazox in food and drinking water, since hexythiazox may be applied directly to growing crops. There are residential uses of hexythiazox; and non-occupational exposure to hexythiazox via spray drift is possible. There is the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from contact with previously treated turf. Occupational exposures are expected from the application (dermal and inhalation) of hexythiazox and from reentry into previously treated areas. This risk assessment considers the relevant exposure pathways based on all of the proposed uses of hexythiazox.

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

As noted above, the most recent quantitative risk assessment for hexythiazox was completed in 2019 (S. Shelat, D448711, 7/2/2019), and is relied upon here. In that assessment the Agency noted that the toxicology database for hexythiazox is complete. All toxicity studies required under 40 CFR part 158 data requirements have been submitted or formally waived by the HASPOC (K. Rury, 10/18/2012, TXR# 0056343). The HASPOC recommended that acute neurotoxicity, subchronic neurotoxicity, and subchronic inhalation toxicity study are not required at this time. A 28-day dermal toxicity study was not available; however, after evaluating the

entire toxicity database, the Agency determined that conducting another 28-day dermal toxicity study would not provide additional information for risk assessment purposes (D368015, 8/26/2009). Therefore, a 28-day dermal toxicity study is not required at this time.

The primary target organs of hexythiazox are the adrenals and liver following subchronic and chronic exposure to dogs, rats, and mice. In a subchronic toxicity study in rats, increased liver and adrenal weights, as well as adrenal histopathology (fatty degeneration of the adrenal zona fasciculata) were seen. In the chronic feeding/carcinogenicity studies in rats and mice, effects included decreased body weight gain and increased liver weights. Hexythiazox is not considered to be a developmental, reproductive, neurotoxic or immunotoxic chemical nor a mutagen. Hexythiazox is classified as "Likely to be Carcinogenic to Humans" based upon increased incidences of malignant and combined benign/malignant liver tumors in female mice, and benign mammary gland tumors observed in male rats. HED also concluded that quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity from exposure to hexythiazox.

Hexythiazox has low acute toxicity via the oral, dermal, or inhalation route of exposure (Toxicity Category IV). It is a mild eye irritant (Toxicity Category III), but not a skin irritant or a skin sensitizer.

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

The hexythiazox risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X because (1) there is an adequate toxicity database for hexythiazox; (2) the prenatal developmental studies in rabbits and rats and the two-generation reproduction study in rats showed no indication of increased susceptibility to *in utero* and/or postnatal exposure to hexythiazox; (3) there is no concern for neurotoxicity following exposure to hexythiazox, and (4) there are no residual uncertainties identified in the exposure databases.

4.2 Residual Uncertainty in the Exposure Database

The residential exposure assessment assumes maximum label use rate as well as other conservative assumptions. The dietary exposure estimates are unrefined and reflect tolerance-level residues in food, 100% crop treated (CT), and upper-bound drinking water estimates based on modeling. Therefore, the Agency does not believe that exposure to hexythiazox will be under-estimated.

4.3 Toxicity Endpoint and Point of Departure Selections

The endpoints selected for hexythiazox remain unchanged from the 2019 assessment (S. Shelat, 06/27/2019, D448711). A summary of the points of departure and toxicity endpoints for hexythiazox is below in Table 4.0.a and 4.0.b

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

Acute Dietary Endpoint for the General Population including females 13+: No endpoint attributable to a single exposure was identified from the available oral toxicity database; therefore, an acute dietary risk assessment for hexythiazox is not required. In a rat developmental toxicity study, delayed ossification is not considered an appropriate endpoint attributable to a single exposure. No other endpoint attributable to a single exposure was identified from the available oral toxicity database, and an acute dietary risk assessment for females 13+ is not required.

Chronic Dietary Endpoint for the General Population: A one-year toxicity feeding study in dogs was selected with a NOAEL of 2.5 mg/kg/day and the LOAEL of 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology. A Safety Factor (SF) of 100X (10X for interspecies extrapolation and 10X for intraspecies variation, and 1X for FQPA SF) is applied to obtain a chronic reference dose (cRfD) of 0.025 mg/kg/day. The cPAD is 0.025 mg/kg/day.

Incidental and Adult Oral Exposure (Short- and intermediate-Term): A two-generation reproduction study in rats was selected with a NOAEL of 30 mg/kg/day and the LOAEL of 180 mg/kg/day based on decreased pup body weights during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights were observed. In the rat subchronic toxicity study, the NOAEL (5.4 mg/kg/day) was lower than that from the reproduction study (30 mg/kg/day); however, this is considered to be due to dose-spacing rather than to a real difference in the effect level, as evidenced by the fact that the NOAEL in the chronic toxicity study in the rat (23/29 mg/kg/day, M/F) is comparable to the NOAEL from the reproduction study. Additionally, the endpoints (organ weight and adrenal histopathology) observed in the subchronic study were assessed in the reproduction study.

Dermal Exposure (Short- and Intermediate-Term): No dermal toxicity study is available. However, a quantitative dermal risk assessment for short- and intermediated-term dermal exposure is not necessary. The estimated dermal absorption factor is 2%, based on the NOAEL of 30 mg/kg/day from the reproduction study, the oral equivalent dose for this dermal exposure scenario is 1.5-fold greater than the limit dose. There is no evidence of increased quantitative or qualitative susceptibility of the young following *in utero* and pre-and post-natal exposure to hexythiazox.

Inhalation Exposure (Short and Intermediate-Term): Other than an acute inhalation study (Toxicity Category IV), no data from a subchronic inhalation study is available. The HASPOC recommended that a 28-day inhalation study is not required (TXR# 0056434, 10/18/2012). Accordingly, a two-generation reproduction study in rats was selected with a NOAEL of 30 mg/kg/day and the LOAEL of 180 mg/kg/day, based on decreased pup body weight during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights. Inhalation toxicity is assumed to be equal to oral (100% of oral).

4.3.1 Recommendation for Combining Routes of Exposures for Risk Assessment

For all durations, incidental oral and inhalation exposures can be combined since the same target organ was the basis for the selected endpoints.

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

Table 4.3.1.1 Toxicological Doses and Endpoints for Hexythiazox for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	An acute dietary risk assessment is not required since no endpoint attributable to a single exposure was identified from the available oral toxicity database.			
Chronic Dietary (All Populations)	NOAEL = 2.5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	cRfD = 0.025 mg/kg/day cPAD = 0.025 mg/kg/day	One-year feeding toxicity – dogs (MRID 00151359, 00146556, 00156895) LOAEL = 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology.
Incidental and Adult Oral Short- and intermediate-Term	NOAEL = 30 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	2-Generation Reproduction Study – Rat (MRID 001475478) LOAEL = 180 mg/kg/day, based on decreased pup body weight during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights.
Dermal Short- and Intermediate-Term	A quantitative dermal risk assessment for short- and intermediated-term dermal exposure is not necessary since no dermal hazard is anticipated. There is no evidence of increased quantitative or qualitative susceptibility of the young following *in utero* and pre-and post-natal exposure to hexythiazox.			
Inhalation Short- and Intermediate-Term	Oral NOAEL = 30 mg/kg/day Inhalation absorption is assumed to be equal to oral	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	2-Generation Reproduction Study – Rat (MRID 001475478) LOAEL = 180 mg/kg/day, based on decreased pup body weights during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights.
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans". A quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to hexythiazox.			

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). FQPA = FQPA Safety Factor. RfD= Reference dose. PAD = population adjusted dose (a = acute, c = chronic). LOC = level of concern.

Table 4.3.1.2 Summary of Toxicological Doses and Endpoints for Hexythiazox for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-term (1-30 days)	A quantitative dermal risk assessment for short- and intermediate-term dermal exposure is not necessary since no dermal hazard is anticipated. There is no evidence of increased quantitative or qualitative susceptibility of the young following *in utero* and pre-and post-natal exposure to hexythiazox.			
Inhalation Short- and Intermediate-term (1-30 days)	Oral NOAEL = 30 mg/kg/day Inhalation absorption is assumed to be equal to oral	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	2-Generation Reproduction Study – Rat (MRID 001475478) LOAEL = 180 mg/kg/day, based on decreased pup body weights during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights.
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans". A quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to hexythiazox.			

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). MOE = margin of exposure. LOC = level of concern.

5.0 Dietary Exposure and Risk Assessment

5.1. Summary of Plant and Animal Metabolism Studies

No new plant or livestock metabolism data were submitted in support of this petition. The nature of the residue in plants (apple, citrus, grape, pear, radish, tea and corn) and ruminants (goat) and poultry are adequately understood based on acceptable metabolism studies. The residues of concern in plants and livestock for both tolerance expression and risk assessment are the parent hexythiazox and its metabolites which contain the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety (also called PT-1-3).

Field rotational crop data have been previously submitted and reviewed. The Agency has concluded that a 120-day plant-back (PBI) interval for all crops not listed on the hexythiazox label is appropriate. For the proposed uses, no additional data are required for rotational crops as berries and dates are not considered to be rotated crop and the proposed tea tolerances are for imported commodities and no direct uses are being proposed for hexythiazox on tea crops grown in the U.S.

Table 5.1.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression[2]			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Hexythiazox and metabolites[1]	Hexythiazox and metabolites[1]
	Rotational Crop	Hexythiazox and metabolites[1]	Hexythiazox and metabolites[1]
Livestock	Ruminant	Hexythiazox and metabolites[1]	Hexythiazox and metabolites[1]

Table 5.1.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression[2]			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
	Poultry	Hexythiazox and metabolites[1]	Hexythiazox and metabolites[1]
Drinking Water		Hexythiazox and metabolites[1]	NA

[1] Metabolites of concern are those of hexythiazox that contain the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety, also known as the PT-1-3 moiety.
NA: Not Applicable
[2] Residue chem memo, D430498, D429132, D. Hrdy, 12/20/2016; Residue chem memo, D452584, W. Drew, 07/02/2019.

5.2 Food Residue Profile

Adequate residue chemistry data have been provided for the proposed uses of hexythiazox. The submitted residue data on raspberry and dates are adequate in terms of both number, geographic representation, and application scenario to support the proposed amended use on caneberry subgroup 13-07A and dates. An acceptable method was used for residue quantitation, and adequate storage stability data are available to support sample storage durations and conditions. The submitted field trial shows that residues of hexythiazox on raspberries (representative commodity for caneberry subgroup 13-07A) were 0.519-1.43 ppm and 0.424-1.70 ppm following a single foliar application of the EW formulation at 0.233-0.241 and 0.250-0.259 lb ai/A. For dates, residues were 0.297-1.25 ppm and 0.167-1.56 ppm following a single foliar application of the EW formulation at 0.234-0.235 and 0.250-0.251 lb ai/A. In addition, adequate data in the submitted JMPR review have been provided to support a tolerance for residues in/on tea without a U.S. registration.

5.3 Water Residue Profile

No new drinking water estimates were provided for the proposed action. EFED has determined in the memo *"Hexythiazox: Streamlined Environmental Fate and Ecological Risk Assessment and Drinking Water Assessment for Proposed Increased Application Rate on Caneberry Subgroup 13-07A and Dates"* (D453377, K. Jones, 12-FEB-2020) that the EDWCs from the previous drinking water assessment were adequate for the proposed new uses because EDWCs for this new action would not exceed those calculated in the last hexythiazox drinking water assessment. The highest EDWCs, when considering all currently registered and proposed hexythiazox uses, result from modeled surface water concentrations from use on soybeans and sorghum. These surface water EDWCs are referenced in the latest hexythiazox drinking water assessment on Low Growing Berry Subgroup 13-07G (D452255, A. Shelby, 06-JUN-2019). Therefore, EFED has recommended HED to reference the 2019 drinking water assessment for the appropriate EDWCs for use in the human health dietary assessment. EDWCs from the last drinking water assessment are **7.75 µg/L** for the 24-hour average (acute) concentration **4.3 µg/L** for 1-in-10-year annual average (chronic), and **3.5 µg/L** for the simulation average (cancer). Drinking water estimates are presented in Table 5.3.1 below, the model and its description are available at the EPA intranet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment.

Table 5. 3.1: EDWCs produced from highest PWC output from previous drinking water assessments and for the increased application rate on Crop Subgroup 13-07G.			
PWC Scenarios	**1 in 10 year annual peak concentration (µg/L)**	**1-in-10 year annual average (µg/L)**	**30 year annual average (µg/L)**
Mississippi Soybeans[1]	7.26	**4.31**	**3.48**
Texas Sorghum[1]	**7.75**	2.09	1.35
Oregon Berries[2]	2.34	1.20	1.06

1 Modeling results reproduced from original DWA in which they appeared (DP 404023, 1/17/2012).

2 Previous modeling conducted to represent Crop Subgroup 13-07G.

5.4 Dietary 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 3.16. This software uses 2003-2008 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). This analysis was conducted in support of a human-health risk assessment for the requested tolerance increase and amended uses of existing label Onager Optek for caneberry subgroup 13-07A and dates; and a tolerance without U.S. registration for residues of hexythiazox in/on tea.

5.4.1 Acute Dietary Assessment

An acute dietary risk assessment is not required since no endpoint attributable to a single oral exposure was identified from the available toxicity database.

5.4.2 Chronic Dietary Assessment

The estimated exposure to the U.S. general population resulted in a risk equivalent to 23% of the chronic population adjusted dose (cPAD). The estimated exposure to children 1 – 2 years old, the most highly exposed population subgroup, resulted in a risk estimate equivalent to 97% of the cPAD. The results are presented in Table 5.4.4.1.

5.4.3 Cancer Dietary Assessment

Hexythiazox is classified as "Likely to be Carcinogenic to Humans." A quantification of risk using a non-linear approach; *i.e.,* RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to hexythiazox. Therefore, a separate cancer assessment was not conducted, and the chronic exposure assessment is considered protective of any cancer exposures.

5.4.4 Summary of Dietary Assessment

Table 5.4.4.1 Summary of Dietary (Food and Drinking Water) Exposure and Risk for

Hexythiazox.				
Population Subgroup*	**Chronic Dietary**		**Cancer Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD**	**Dietary Exposure (mg/kg/day)**	**Risk**
General U.S. Population	0.005695	23	·	
All Infants (< 1 year old)	0.008827	35		
Children 1-2 years old*	0.024122	**97**		
Children 3-5 years old	0.016431	66		
Children 6-12 years old	0.008045	32	N/A	N/A
Youth 13-19 years old	0.004312	17		
Adults 20-49 years old	0.004112	16		
Adults 50-99 years old	0.004285	17		
Females 13-49 years old	0.004119	17		

*The subpopulation with the highest risk estimates is **bolded.**

6.0 Residential Exposures/Risks

Hexythiazox. Occupational and Residential Exposure Assessment for a Proposed Use on Tea, Dates, and Caneberry Subgroup 13-07A, V. Kurker, D456354, 7/6/2020

6.1 Residential 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 tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

In previous human health risk assessments for hexythiazox, inhalation exposure and risk to residential handlers was assessed and resulted in no risks of concern (Alexandra LaMay, D404018, 5/6/2013). However, all previously registered hexythiazox product labels with residential use sites require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use PPE (e.g., gloves). Therefore, HED has made the assumption that these products are not for homeowner use, and, for all current and future assessments, a quantitative residential handler assessment will not be conducted unless PPE is removed from labels with residential use sites. The residential handler scenarios from previous human health assessments will no longer be considered for the aggregate assessment.

6.2 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in

an environment that has been previously treated with hexythiazox. All proposed new uses of hexythiazox are occupational and do not impact the previous residential post-application assessment.

In the previous residential post-application assessment (Alexandra LaMay, D396864, 9/25/2012), child incidental oral exposure to treated turf was assessed for hexythiazox. Risk estimates range from 11,000 for hand-to-mouth short-term exposure to 4,700,000 for incidental soil ingestion short- and intermediate-term exposure. Risk estimates are not of concern (MOEs > LOC) for all scenarios.

6.3 Residential Post-Application Exposure and Risk Estimates

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for hexythiazox.

- The recommended residential exposure for use in the children 1<2 years old aggregate assessment reflects incidental oral exposures from post-application exposure to treated turf.

Table 6.3.1. Recommendations for the Residential Exposures for the Hexythiazox Aggregate Assessment.[1]

Lifestage	Post-application Exposure (mg/kg/day)[2]			Residential Post-application Total Exposure (mg/kg/day)	Residential Post-application MOE[3]
	Dermal	Inhalation	Oral		
Short-Term					
Children 1 to <2 years old	N/A	N/A	0.0029	0.0029	**10,000[4]**
Intermediate-Term[5]					
Children 1 to <2 years old	N/A	N/A	0.0000063	0.0000063	**4,700,000**

[1] Bolded risk estimates should contribute to the residential exposure portion of the aggregate assessment.
[2] Post-application exposure represents high-end dermal, inhalation and/or incidental oral exposure for the relevant exposure duration
[3] Total MOE = 1/((1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental oral MOE)). Dermal NOAEL = N/A, Inhalation NOAEL = 30 mg/kg/day; Incidental oral NOAEL = 30 mg/kg/day.
[4] The Residential Post-application MOE for Short-Term exposure was copied over from the previous assessment's aggregate assessment table. The previous assessment states that the MOE = 11,000 but this is a typo and it should be rounded to 10,000. The value of 10,000 will be carried forward for the aggregate assessment in Section 7.0.
[5] Intermediate-term incidental oral ingestion comes from 2012 risk assessment (Alexandra LaMay, D396864, 9/25/2012) which states, "As the aerobic soil metabolism half-life for hexythiazox is 145.2 days, intermediate-term exposure is also possible for incidental soil ingestion exposure."

7.0 Aggregate Risk Assessments and 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

No toxic effects attributable to a single dose of hexythiazox were observed in the toxicology database; therefore, a quantitative acute aggregate risk assessment for this chemical is not required.

7.2 Short- and Intermediate-Term Aggregate Risks

A separate short-term and intermediate-term aggregate assessment was completed for hexythiazox. No residential handler scenarios were assessed and the lack of dermal endpoint selected resulted in the only the incidental oral route of exposure for consideration in the aggregate. For adults, the short-/intermediate-term aggregate is equivalent to the dietary exposure and risk estimates and is not of concern. For the short-term assessment, the children (1 to <2 year old) hand-to-mouth scenario was considered for the aggregate. Due to the long aerobic soil metabolism half -life for hexythiazox, the incidental soil ingestion scenario was considered for the intermediate-term aggregate exposure. Both these oral scenarios were combined with the chronic dietary exposures for the aggregate assessment.

Table 7.2.1 Short-Term and/or Intermediate Term Aggregate Risk Calculations.

Population	LOC for Aggregate Risk[1]	MOE Dietary[2]	MOE Oral Residential Exposure[3]	MOE Dermal Residential Exposure[4]	MOE Inhalation Residential Exposure[5]	Aggregate MOE (food, water, and residential)[6]
Short-Term Scenario						
Children (incidental oral, hand-to-mouth)	100	1,200	10,000	NA	NA	1,100
Intermediate-Term Scenario						
Children (soil ingestion)	100	1,200	4,800,000	NA	NA	1,200

[1] 10X for inter- and 10X for intra- species uncertainty factors totaling 100
[2] MOE dietary = [30 mg/kg/day (short- or intermediate-term oral NOAEL)/(chronic dietary exposure (0.024122 mg/kg/day))]. Chronic dietary exposure for children (1 to <2) from Table 5.4.4.
[3] MOE oral = [30 mg/kg/day (short- or intermediate-term oral NOAEL)/(hand-to-mouth residential exposure)]. Short-term incidental oral exposure and intermediate-term soil ingestion exposure from Table 6.3.1.
[4] MOE dermal = N/A, no dermal endpoint selected
[5] MOE inhalation = NA, no inhalation exposure assessed for the current use pattern.
[6] MOE Aggregate = 1/[(1/MOE dietary) + (1/MOE oral) + (1/MOE dermal) + (1/MOE inhalation)].

7.3 Chronic Aggregate Risks

As there are no long-term residential exposures, the chronic aggregate risk estimates are equivalent to the chronic dietary risk estimates as presented in Section 5.4 (Table 5.4.4) and result in no risks of concern.

7.4 Cancer Aggregate Risks

A cancer aggregate assessment was not conducted since hexythiazox is classified as “Likely to be Carcinogenic to Humans” and a non-linear approach will adequately account for all chronic

toxicity, including carcinogenicity.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for hexythiazox. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [2] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

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

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).
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 hexythiazox.

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 hexythiazox and any other substances and hexythiazox does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that hexythiazox 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-

[2] Available: http://www.epa.gov/reducing-pesticide-drift

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)[3] and conducting cumulative risk assessments (CRA)[4]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for hexythiazox 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.

11.0 Occupational Exposures and Risk

Hexythiazox. Occupational and Residential Exposure Assessment for a Proposed Use on Tea, Dates, and Caneberry Subgroup 13-07A, V. Kurker, D456354, 7/6/2020

11.1 Short-/Intermediate -Term 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 and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixer/Loader Liquid for Aerial, Airblast, Chemigation, and Groundboom Application
- Applicator Spray for Aerial, Airblast, and Groundboom Application
- Flagger Spray for Aerial Application
- Mixer/Loader/Applicator Liquid for Mechanically-pressurized Handgun Application

Application Rate:
The single maximum application rates are 0.25 lb ai/acre and 0.0125 lb ai/gallon (EPA Reg. No. 10163-337) as detailed in Table 4.1.

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for "baseline," defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc.). The hexythiazox product labels direct mixers, loaders, applicators and other handlers to wear baseline attire (e.g., long-sleeved shirt, long pants, shoes plus socks) and chemical-resistant gloves.

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

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Occupational handler inhalation exposure and risk estimates were calculated for the proposed uses of hexythiazox at the label-required PPE (i.e., no respirator). Occupational handler MOEs for the proposed new uses range from 22,000 to 5,600,000 (LOC = 100). A summary of the occupational handler risk estimates is provided below in Table 11.0.1.

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

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation	
					Dose (mg/kg/day)[4]	MOE (LOC = 100)[5]
Mixer/Loader						
Liquid, Aerial, Broadcast	Orchard/Vineyard[6]	0.219	0.25 lb ai/ acre	350 acres	0.00024	130,000
Liquid, Airblast, Broadcast				40 acres	0.0000274	1,100,000
Liquid, Chemigation, Broadcast				350 acres	0.00024	130,000
Liquid, Groundboom, Broadcast				40 acres	0.0000274	1,100,000
Applicator						
Spray, Aerial, Broadcast	Orchard/Vineyard[6]	0.0049 (EC)	0.25 lb ai/ acre	350 acres	0.00000536	5,600,000
Spray, Airblast, Broadcast		4.71		40 acres	0.000589	51,000
Spray, Groundboom, Broadcast		0.34			0.0000425	710,000
Flagger						
Spray, Aerial, Broadcast	Orchard/Vineyard[6]	0.35	0.25 lb ai/ acre	350 acres	0.000383	78,000
Mixer/Loader/Applicator						
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Orchard/Vineyard[6]	8.68	0.0125 lb ai/gallon	1000 gallons	0.00136	22,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (June 2018); Level of mitigation: No Respirator, EC= Engineering Controls

2 Based on proposed new uses on the label (Reg. No. 10163-337).

3 Exposure Science Advisory Council Policy #9.1.

4 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 (A or gal/day) ÷ BW (80 kg).

5 Inhalation MOE = Inhalation NOAEL (30 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

6 Dates and caneberry subgroup 13-07A are both considered orchard/vineyard crops

11.2 Short-/Intermediate-Term Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are

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

11.2.1 Dermal Post-Application Exposure and Risk Estimates

No dermal hazard was selected for hexythiazox, so no dermal post-application exposure/risk was assessed. In accordance with the updated Part 158 data requirements (2007), one or more dislodgeable foliar residue (DFR) studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. However, as quantification of dermal risk is not required for hexythiazox, a DFR study is not required for hexythiazox at this time.

Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of hexythiazox. Hexythiazox is classified as Toxicity Category IV for acute dermal toxicity, Toxicity Category IV for acute dermal irritation, and Toxicity Category III for eye irritation. It is not a skin sensitizer. Under WPS for agricultural pesticides, active ingredients classified as Acute Toxicity Category III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the REI on the label of 12 hours is adequate to protect agricultural workers from post-application exposures to hexythiazox.

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 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). 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 hexythiazox.

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

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

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application is not of concern (i.e., MOE > 100).

12.0 References

A. Habtemichael, D456356, 07/07/2020	**Hexythiazox**. Petition for Amendment of Established Permanent Tolerances in/on Caneberry Subgroup 13-07A and Dates, Dried Fruit; and the Establishment of a Tolerance without U.S. Registration in/on Imported Tea. Summary of Analytical Chemistry and Residue Data
A. Habtemichael, D456357, 07/07/2020	**Hexythiazox**. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for Amendment of Onager Optek Label and Established Permanent Tolerance in/on Caneberry Subgroup 13-07A and Dates, dried; and the Establishment of a Tolerance without U.S. Registration in/on imported Tea.
K. Jones, D453377, 2/12/2020	**Hexythiazox:** Streamlined Environmental Fate and Ecological Risk Assessment and Drinking Water Assessment for Proposed Increased Application Rate on Caneberry Subgroup 13-07A and Dates
S. Shelat, D448711, 7/2/2019	Hexythiazox. Human Health Risk Assessment for Amended Use on Berry, Low Growing Subgroup (13-07G)
V. Kurker, D456354, 7/6/2020	Hexythiazox. Occupational and Residential Exposure Assessment for a Proposed Use on Tea, Dates, and Caneberry Subgroup 13-07A
K. Rury, TXR # 0056434, 10/18/2012	Hexythiazox: Summary of Hazard and Science Policy Council (HASPOC) Meetings: Recommendations on the need for inhalation, and acute and subchronic neurotoxicity studies.

13.0 Appendices

Appendix A. Toxicology Assessment

The toxicology data requirements (40 CFR 158.500) for the food uses of hexythiazox are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Toxicology Data Requirements

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	no
870.3250	90-Day Dermal	no	no
870.3465	90-Day Inhalation	CR	waived[a]
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
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	Waived[a]
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	Waived[a]
870.6300	Develop. Neurotoxicity	CR	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes
870.7800	Immunotoxicity	yes	yes

[a]HASPOC recommended that acute and subchronic neurotoxicity and inhalation studies are not required (TXR# 0056343, 10/18/2012).

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Data on Hexythiazox Technical			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	00146549	LD_{50} = >5000 mg/kg	IV
870.1200 Acute dermal toxicity	00146550	LD_{50} = >5000 mg/kg	IV
870.1300 Acute inhalation toxicity	00146554	LC_{50} = >2.0 mg/L	IV
870.2400 Primary eye irritation	00146551	Reddened conjunctiva	III
870.2500 Acute dermal irritation	00146552	Non irritant	IV
870.2600 Skin sensitization	00146553	Non sensitizer	N/A

Table A.2.2. Subchronic and Chronic Toxicity Profile of Hexythiazox		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rat	45067101 (1983) Acceptable/guideline 0, 10, 70, 500, or 3500 ppm M: 0, 1.2, 8.1, 58.6, or 397.5 mg/kg/day F: 0, 0.8, 5.4, 38.1 or 257.6 mg/kg/day	NOAEL = 8.1/5.4 mg/kg/day, males/females LOAEL = 58.6/38.1 mg/kg/day, males/females, based on increased absolute and relative liver weights in both sexes, increased relative ovarian and kidney weights, and fatty degeneration of the adrenal zona fasciculata. High dose 397.5/257.6 mg/kg/day, decreased body-weight gain in females, slight swelling of hepatocytes in central zone (both sexes), increased incidence of glomerulonephrosis in males, increased adrenal weights
870.3700a Prenatal developmental toxicity rat	44955711 (1984) Acceptable/guideline 0, 240, 720, or 2160 mg/kg/day	Maternal NOAEL = 240 mg/kg/day LOAEL = 720 mg/kg/day based on decreased maternal body weight gain, and decreased food consumption. Developmental NOAEL = 240 mg/kg/day LOAEL = 720 mg/kg/day based on delayed ossification.
870.3700b Prenatal developmental toxicity rabbit	00146555 (1984) Acceptable/guideline 0, 120, 360, or 1080 mg/kg/day	Maternal NOAEL ≥1080 mg/kg/day LOAEL >1080 mg/kg/day Developmental NOAEL ≥1080 mg/kg/day LOAEL >1080 mg/kg/day
870.3800 Two-Generation reproduction and fertility effects rat	00147578 (1985) Acceptable/guideline 0, 60, 400, or 2400 ppm Average doses across generations: M: 0, 4.45, 29.73, or 180.67 mg/kg/day F: 0, 5.27, 34.77, or 207.67 mg/kg/day	Parental/Systemic NOAEL = 29.73/34.77 mg/kg/day, males/females LOAEL = 180.67/207.67 mg/kg/day, males/females, based on decreased body weight gain and increased absolute and relative liver, kidney, and adrenal weights. Reproductive NOAEL ≥180.67/207.67 mg/kg/day, males/females LOAEL >180.67/207.67 mg/kg/day, males/females Offspring NOAEL = 29.73/34.77 mg/kg/day, males/females LOAEL = 180.67/207.67 mg/kg/day, males/females, based on decreased pup body weight during lactation, and delayed hair growth and/or eye opening.
870.4100b Chronic toxicity dog	00151359, 00146556, 00156895 (1984) Acceptable 0, 100, 500, or 5000 ppm (0, 2.5, 12.5, or 125 mg/kg/day) M: 0, 2.87, 13.1, or 153 mg/kg/day	NOAEL = 2.5 mg/kg/day LOAEL = 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology (adrenal cortex hypertrophy). @ 125 mg/kg/day, relative adrenal weights and associated adrenal cortex hypertrophy (more pronounced)

Table A.2.2. Subchronic and Chronic Toxicity Profile of Hexythiazox		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
	F: 0, 3.17, 13.9, or 148 mg/kg/day 4-week: 0, 125, 500, 2000, 8000 ppm	4-week range-finding: relative adrenal weight increased at 2000 ppm (50 mg/kg/day) and 8000 ppm (200 mg/kg/day)
870.4300 Chronic Toxicity/ Carcinogenicity rat	00146559 (1984) Acceptable/guideline 0, 60, 430, or 3,000 ppm M: 0, 3, 23, or 163 mg/kg/day F: 0, 4, 29, or 207 mg/kg/day	NOAEL = 23/29 mg/kg/day, males/females LOAEL =163/207 mg/kg/day, males/females based on decreased body weight and body weight gain and increased absolute and relative liver weights in both sexes. No evidence of carcinogenicity
870.4300 Carcinogenicity mice	00147577, 00156896 (1985) Acceptable/guideline 0, 40, 250, or 1500 ppm M: 0, 6.72, 41.6, or 267 mg/kg/day F: 0, 8.38, 51.2, or 318 mg/kg/day	NOAEL = 41.6/51.2 mg/kg/day, males/females LOAEL = 267/318 mg/kg/day, males/females) based on decreased male body weight and body weight gain, and increased absolute and relative liver weights in both sexes. Evidence of carcinogenicity (causes liver tumors in females).
Gene Mutation 870.5100 *(Salmonella typhimurium* and *Escherichia coli* reverse gene mutation assay)	44955710 (1983) Acceptable	The test was negative up to the highest dose tested (6400 µg/plate +/-S9.
Gene Mutation 870.5300 (*In vitro* mammalian cell forward gene mutation assay in CHO cells)	00155154 (1985) Acceptable	Independently performed trials were negative up to precipitating doses (≥60 µg/mL) and severely cytotoxic concentrations (200 µg/mL -S9; 400 µg/mL +S9).
Cytogenetics 870.5375 *In vitro* mammalian cell cytogenetic assay in CHO cells	00156894 (1986) Acceptable	The test was negative up to precipitating doses accompanied by severe cytotoxicity (≥167 µg/mL +/-S9).
Cytogenetics 870.5395 *In vivo* mouse micronucleus assay	44955708 Unacceptable There's an update	The results were inconclusive because a positive response, which was within the wide range of historical background data, was recorded for female mice at the mid-and high-doses (500 and 1000 mg/kg). The assay should be repeated to confirm or refute the equivocal results.
Other Effects 870.5550 *In vitro* UDS assay in primary rat hepatocytes	00156893 (1985) Acceptable	The test was negative up to a lethal dose (250 µg/mL).
870.6200b 28-day neurotoxicity Crj:CD(SD)IGS(SPF) rats	48657401 (2004) Acceptable/non-guideline 0, 100, 1000, or 10000 ppm Males: 0, 8.8, 88.7, or 868.2 mg/kg/day	NOAEL = 1000 ppm (males 88 mg/kg/day; females 90 mg/kg/day). LOAEL = 10000 ppm (males 868 mg/kg/day; females 892 mg/kg/day), based on decreased motor activity in both sexes, decreased body weight in males, increased adrenal weight in females, and increased liver weight in both sexes.

Table A.2.2. Subchronic and Chronic Toxicity Profile of Hexythiazox		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
	Females: 0, 9.5, 90.1, or 892.7 mg/kg/day (28 days)	HASPOC (D0056434): 28-day duration is sufficient to assess sub-chronic neurotoxicity from hexythiazox exposure
870.7485 Metabolism and pharmacokinetics	00146558 (1985) Acceptable/guideline Single oral dose at 10 mg/kg (Group B); 14 daily oral doses (10 mg/kg) of unlabeled material followed by one dose (10 mg/kg) of [^{14}C] test material (Group C); and a single oral dose of 880 mg/kg (Group D).	Absorption and distribution of dosed radioactivity were rapid. The radioactive material was rapidly eliminated in the urine and feces; the majority of the radioactivity was eliminated within 24 hours. There were no observable differences in the total elimination between male and female rats. The major route of elimination in both the male and female rats was by fecal excretion. The major metabolite found, PT-1-8 (cis), accounted for 8-12% of the administered radioactivity in the low dose groups. Approximately 11-20% and 65-69% of the dosed radioactivity was identified as unchanged NA-73 in the low-dose and high-dose groups, respectively. All other metabolites were present at low concentrations (<2%). There was no apparent sex difference in metabolite formation. Significant levels of NA-73 equivalent [^{14}C]-residues were detected in the fat, liver, and adrenals. A sex-related difference in the residue levels of all tissues was observed, with residues in female tissues being two-fold higher than those found in male tissues.
870.7485 Metabolism and pharmacokinetics	0146557 (1983) Acceptable/non-guideline Single low dose (10 mg/kg/day)	Total recovery of radioactivity 72 hours after treatment accounted for 101.9-103% of the dose. The distribution of radioactivity 72 hours after dosing was as follows: 1) 30% (male and female) was excreted in the urine, 2) 60% (female) to 67% (male) was excreted in the feces, and 3) about 4% (male) to 10% (female) of the administered radioactivity remained in the tissues, with the highest concentration in the fat (2.3 ppm, males; 5.4 ppm, females). Significant sex differences existed for the pharmacokinetics of NA-73 in these rats, with females exhibiting slower elimination rats and higher tissue residues (about double) than males. NA-73 was metabolized to a large number of metabolites that were excreted both in the urine and feces. Seven metabolites were structurally identified in addition to the parent compound in both excreta of both sexes, with the major fecal metabolite, PT-1-8 (cis) accounting for 10% of the dosed radioactivity. The others were all minor metabolites accounting for less than 1.4%. About 20% of the dose was excreted as unchanged NA-73 (97% of which was in the feces). No significant sex difference was apparent with respect to metabolite formation.
870.7600 Dermal penetration	40608402, 40787901 (1985) Unacceptable/guideline	The total percent of dose absorbed averaged 2%, 1%, and 1.1% for cannulated rats (10-hour sacrifice) and 0.8%, 0.2%, and 0.2% for non-cannulated rats (1-hour sacrifice) at the low, medium, and high dose levels, respectively. The amount of radioactivity in the blood, carcass, urine and other organs totaled <2% of the applied dose.

Table A.2.2. Subchronic and Chronic Toxicity Profile of Hexythiazox		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		The HIARC determined that the results of this study (2% dermal absorption) can be used for risk assessment purposes (HED DOC # 014022, 3/1/2000).
870.7800 Immunotoxicity	48685201 (2012) Acceptable/guideline	Immunotoxicity NOAEL is 4500 ppm (equivalent to 904 mg/kg/day). A LOAEL was not established.

Appendix B. International Residue Limits Table

Table B.1. Summary of US and International Tolerances and Maximum Residue Limits for Hexythiazox

Residue Definition:

US	Canada	Mexico[1]	Codex
40 CFR 180.448: Hexythiazox and its metabolites containing the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety	Hexythiazox		Plants: Hexythiazox Livestock: sum of hexythiazox and all metabolites containing the trans-5-(4-chlorophenyl)-4-methyl-2-oxothiazolidine-moiety (PT-1-3-), expressed as hexythiazox. The residue is fat-soluble.

Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex[2]
Caneberry Subgroup 13-07A	3	1.5 (raspberries, blackberries, loganberries)		--
Date, dried	3	2		2
Tea	15	--		15
Completed: A. Habtemichael; 12/17/19				

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

Appendix C. Submittal of Analytical Reference Standards

Analytical standard for hexythiazox (expires on 06/12/2021), is currently available in the EPA National Pesticide Standards Repository; however analytical standard for its metabolite PT-1-3 moiety is not available [email communication from T. Cole to A. Habtemichael, 12/18/2019]. Reference standard supplies need to be replenished as requested by the Repository. The reference standards for metabolite PT-1-3 moiety (minimum of 1 gram) should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of Theresa Cole at the following address:

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

Note: The full 9-digit zip code is mandatory, or the mail will be returned.