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EPA Registration Division contact: EPA Registration Division (7505T)

TEMPLATE:

Gowan Company LLC

Pesticide Petition 4F9135

EPA has received a pesticide petition ([insert petition number]) from **Gowan Company, LLC, P.O. Box 556 Yuma, AZ 85366** requesting, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180

By amending the existing tolerance with regional registration for **Hexythiazox, (trans-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2- oxothiazolidine-3-carboxamide)** in or on the raw agricultural commodities of **Citrus Crop Group 10-10 at 0.6 parts per million (ppm), to include a national tolerance for Crop Subgroup 10-10B lemon/lime.** EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition.

A. Residue Chemistry

1. Plant metabolism. **The nature of the residues in plants is adequately understood for purposes of this tolerance petition. Metabolism studies in fruit crops, radish, tea and corn have been completed. The Agency has determined that the residues of concern are hexythiazox and its metabolites containing the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety calculated as the stoichiometric equivalent of hexythiazox.**

2. Analytical method. **The methodology, Morse Laboratories, LLC, Analytical Method# Meth-220, Original, titled "Determination of Hexythiazox In/On Various Matrices," dated May 6, 2013 with method modifications dated May 16, 2013 was reviewed by the Agency in the study, Magnitude of the Residue of Hexythiazox in or on Citrus Raw Agricultural Commodities Following One Application of Onager® 1E Miticide—2013 (Wyatt, D.) MRID: 49591801. The same method was used in the new residue data generated to amend the crop subgroup 10-10B lemon/lime tolerance, nationally.**

3. *Magnitude of residues.* **This study was conducted to determine the magnitude of residues of GWN-8020 (hexythiazox) in or on lemon raw agricultural commodities (RAC) following one foliar application of GWN-10666 (Onager Optek) Miticide at the maximum label use rate of 0.1875 lb ai/A (0.210 kg ai/ha) with a 7-day and 14-day preharvest interval (PHI). After one application of GWN-10666 applied at 0.1875 lb ai/A, eight samples per pre-harvest timing were taken at 7 and 14 day were analyzed for residues. At 7 days after application (DAA), residues ranged from 0.164-0.285 parts per millionth (ppm). At 14 DAA, residues ranged from 0.169-0.200 ppm.**

B. Toxicological Profile

1. Acute toxicity. **A battery of acute toxicity studies places technical grade hexythiazox in Toxicity Category IV for acute oral toxicity (LD50 > 5,000 mg/kg), Category IV for acute dermal toxicity (LD50 >5,000 mg/kg), Category IV for acute inhalation toxicity (LC50 >2.0 mg/L), Category III for primary eye irritation (showed mild irritation (reddened conjunctiva) and Category IV for dermal irritation (non irritant). Hexythiazox is a non-sensitizer.**

2. Genotoxicity. **A number of mutagenicity studies were conducted. These are a mammalian erythrocyte micronucleus test [MRID 45480101], a mammalian cell forward gene mutation assay [MRID 00155154], a rat primary hepatocyte unscheduled DNA synthesis assay [MRID 00156893], a clastogenic evaluation in an in vitro cytogenetic assay measuring chromosomal aberration in Chinese hamster ovary cells [MRID 00156894], and an Ames study with Salmonella [MRID 44955710]. All these mutagenicity tests were negative.**

3. Reproductive and developmental toxicity. **In a developmental toxicity study with rats [MRID 44955711], the fetotoxicity NOAEL was 240 mg/kg/day, and the compound was not embryotoxic at the highest dose tested, 2160 mg/kg/day. In a developmental toxicity study with rabbits [MRID 00146555], no developmental toxicity was observed at the highest dose tested, 1080 mg/kg/day. In a two generation reproduction study with rats [MRID 00147578], no reproductive effects were observed at 2400 ppm in the diet (>180.67 M and >207.67 F mg/kg/day).**

4. Subchronic toxicity. **In a 90-day oral toxicity rat study the NOEL was 8.1 M / 5.4 F mg/kg/day and the NOAEL was 58.6 M / 38.1 F 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.**

5. Chronic toxicity. **In a 1-year feeding study in dogs, the NOAEL was 2.5 mg/kg/day and the LOAEL was 12.5 mg/kg/day, based on increased alkaline phosphatase, increased adrenal and liver weights, and liver and adrenal lesions. In a carcinogenicity study in mice, the NOAEL was 41.6 M / 51.2 F mg/kg/day and the LOAEL was 267 M / 318 F mg/kg/day. Effects were decreased bodyweight in males and increased hepatocellular carcinomas and combined adenoma/carcinomas.**

In a chronic feeding/carcinogenicity study in rats, the NOAEL (systemic) was 23 M / 29 F mg/kg/day and the LOAEL (systemic) was 163 M / 207 F mg/kg/day based on decreased body weight gain and increased liver weights in both sexes.

The Agency has concluded that quantification of cancer risk using a non-linear approach; i.e., RfD, for hexythiazox will adequately account for all chronic toxicity, including carcinogenicity from exposure to hexythiazox.

6. Animal metabolism. **The metabolism of hexythiazox has been studied in goats, hens and rats. Metabolic pathways in the animal are similar to those in plants.**

7. Metabolite toxicology. **There are no metabolites of toxicological concern based on a differential metabolism between plants and animals.**

8. Endocrine disruption. **Information concerning possible endocrine effects of hexythiazox similar to effects produced by a naturally occurring estrogen, or other endocrine effects is available from the two-generation rat reproduction study, the rat and rabbit developmental studies and the rat and dog chronic studies. There is no evidence from these studies that hexythiazox induces estrogenic or other endocrine effects.**

C. Aggregate Exposure

1. Dietary exposure. **Dietary Exposure from food. A dietary risk assessment for all registered crops has been completed by the Agency (Federal Register, July 17, 2013, pages 42693-42699).**

i. Food. Acute Exposure. **No acute endpoint has been identified in the 4 toxicological studies for hexythiazox; therefore, a quantitative acute dietary exposure assessment is unnecessary.**
Chronic Exposure. The Agency comprehensively evaluated potential dietary exposure resulting from the currently registered uses of hexythiazox in the July 17, 2013 Federal Register. The Agency concluded that chronic exposure to hexythiazox from food and water would utilize 97% of the cPAD (for children 1-2 years old). The Agency's assessment employed tolerance residue values, the assumption of 100% crop treated and default processing factors. The proposed national use of hexythiazox in crop subgroup 10-10B lemon/lime will not significantly affect dietary risk. A tier 1 chronic assessment shows a negligible percentage of the cPAD will be utilized by any population subgroup for the proposed use in crop subgroup 10-10B lemon/lime.

ii. Drinking water. **The Agency has previously used screening level surface-water exposure models in dietary exposure analysis and risk assessment for hexythiazox in drinking water. Based on the Pesticide Root Zone Model /Exposure**

Analysis Modeling System (PRZM/EXAMS), the estimated drinking water concentration (EDWC) of hexythiazox for chronic assessment was estimated to be 4.3 parts per billion (ppb). (Federal Register, July 17, 2013, pages 42693-42699)

2. Non-dietary exposure. **EPA has previously determined that potential residential exposures to hexythiazox are below levels of concern.**

D. Cumulative Effects

EPA has not found that hexythiazox shares a common mechanism of toxicity with any other substances.

E. Safety Determination

1. U.S. population. **Acute risk. No adverse effect resulting from a single oral exposure to hexythiazox has been identified, thus hexythiazox is not expected to pose an acute risk.**
Short-and intermediate term risk. EPA has previously concluded that there are no short term or intermediate term risks of concern from exposure to hexythiazox.
Chronic risk. The Agency previously concluded that 97% of the cPAD would be utilized from the currently registered uses (food and water). The proposed amendment is in line with the existing citrus group 10-10 tolerance utilizing a negligible percentage of the cPAD. Chronic residential exposure to the residues of hexythiazox is not expected.

2. Infants and children. **The Agency has previously determined 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.**

F. International Tolerances

The following maximum residue levels for hexythiazox on crop subgroup 10-10B lemon/lime commodities have been established.

Country	Commodity	Tolerance (PPM)
Codex	Citrus, Fruit	0.5
EU	Citrus Fruits, Grapefruit, Oranges, Lemons, Limes, Mandarins, Others	1.0
Japan	Citrus (NATSUDAIDAL, whole), Lemon, Orange (Including navel orange), Grapefruit, Lime, Other Citrus Fruits	1.0
Taiwan	Citrus (Including whole Taiwan Crop Group for Citrus	1.0