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Pyriproxyfen Summary Document
Registration Review: Initial Docket
September 2011

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Case No. 7424

Approved By:

Richard P Keigwin, Jr

Richard P. Keigwin, Jr., Director
Pesticide Re-evaluation Division

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Date

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Please Note

This Preliminary Work Plan (and Fact Sheet) summarizes the Environmental Protection Agency's current position on pyriproxyfen based on the following documents:

1. Registration Review Problem Formulation for Pyriproxyfen. July 13, 2011.
2. Pyriproxyfen: Human Health Risk Scoping Document in Support of Registration Review. September 8, 2011.
3. Pyriproxyfen: Review of Human Incidents. May 17, 2011.
4. BEAD Chemical Profile for Registration Review: Pyriproxyfen (PC code: 129032). August 16, 2011.
5. Screening Level Use Analysis (SLUA) for Pyriproxyfen. November 30, 2010.
6. Appendix A for Pyriproxyfen. April 20, 2011.

Supporting documents for pyriproxyfen may be found in the docket (EPA-HQ-OPP-2011-0677) located on the internet at www.regulations.gov.

I. Preliminary Work Plan – Pyriproxyfen

Introduction:

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides sold or distributed in the United States (U.S.) generally must be registered by the Environmental Protection Agency (EPA or the Agency), based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

The Agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop and commit to a final work plan and schedule for the registration review of pyriproxyfen.

Pyriproxyfen is an insect growth regulator registered for use in various agricultural, commercial, residential, and aquatic settings. Agricultural use sites include orange, pear, cotton, almond, and apple as well as other fruits, vegetables, and nuts. Commercial uses include applications in and around food storage/handling establishments and other structures. Residential uses include applications inside the home (including on pets and in pet living quarters) or outside on gardens, lawns, ornamentals, patios, and other structures to control mosquitoes and other insects. Aquatic use sites include ornamental ponds, waste water and settling ponds, catch basins/sewers, and other water-holding sites that do not drain into natural water bodies. Pyriproxyfen was first registered in 1995 and, therefore, was not subject to reregistration.

Anticipated Risk Assessment and Data Needs:

The Agency anticipates conducting a comprehensive ecological risk assessment, including an endangered species assessment, and a revised human health risk assessment for all uses of pyriproxyfen. The following is a summary of the issues relevant to the registration review of pyriproxyfen.

Ecological Risk:

- The most recent comprehensive ecological risk assessment for pyriproxyfen was completed in 2009 for several new uses on root/tuber and leafy vegetables, artichoke, asparagus, vine-climbing fruits, and watercress.

- The Agency has not conducted a risk assessment that supports a complete endangered species determination for pyriproxyfen. The ecological risk assessment planned during registration review will allow the Agency to determine whether pyriproxyfen's use has "no effect" or "may affect" federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide's use "may affect" a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Service (the Services), as appropriate.

- On January 19, 2011, the Center for Biological Diversity and the Pesticide Action Network North America filed a lawsuit in the United States District Court for the Northern District of California, against the Environmental Protection Agency (EPA) for allegedly failing to undergo consultation with the United States Fish and Wildlife Service and the National Marine Fisheries Service regarding the effects of over 350 pesticides, including pyriproxyfen, on over 200 endangered and threatened species throughout the United States (Center for Biological Diversity, et al. v. EPA, et al., No. C 11-00293 (N.D.Cal.)).

- The primary environmental degradates for pyriproxyfen (*i.e.*, those that appear as 10% or more in the environment) are 2-(2-pyridyloxy)propionic acid (PYPAC) and 4-(4'-hydroxyphonoxy)phenyl-2-(2-pyridyloxy)-propyl ether (4'-OH-PYR).

- The ecological fate database for pyriproxyfen is largely complete with the exception of data on the environmental fate of the degradates 4'-OH-PYR and PYPAC. The Agency is seeking additional information to better understand how these degradates behave in the environment. In the absence of additional information, the Agency may consider requiring specific fate data.

- Based upon the use pattern and the current available database on pyriproxyfen, the Agency anticipates requiring the following ecological effects data for use in conducting a complete ecological risk assessment, including an endangered species assessment:

GLN 850.4100	Seedling Emergence, tier II (with TEP)
GLN 850.4150	Vegetative Vigor, tier II (with TEP)
GLN 850.1710	Oyster bioconcentration
Non-guideline*	Chronic sediment toxicity (special study; with freshwater benthic invertebrate)
Non-guideline	Acute honey bee larvae feeding study (special study)

*See problem formulation for a discussion regarding this data requirement.

- Certain pyriproxyfen labels are unclear with respect to application parameters like the maximum seasonal application rate, or maximum applications per crop cycle. In the absence of clear label information, the Agency must employ conservative assumptions to complete the human health and ecological risk assessments. The Agency encourages clear and consistent label language for the sake of all stakeholders and encourages the technical registrants to review the product labels for clarity. Please refer to the problem formulation for a discussion of uncertainties on certain products.

- Environmental exposure estimates from certain pyriproxyfen uses (e.g., indoor uses or ant mound uses) could be refined with additional information such as total production volume, or use rates for unique use sites, if provided to the Agency. Please refer to the problem formulation for information needed to support accurate environmental exposure calculations.

- Please refer to the document, *Registration Review Problem Formulation for Pyriproxyfen,* dated July 13, 2011, located in the docket for a detailed discussion of the anticipated risk assessment and information/data needs.

Human Health Risk:

- The most recent human health risk assessment for pyriproxyfen was completed in 2009 for several new uses on various root/tuber and leafy vegetables, small vine-climbing fruits, artichoke, asparagus, and watercress.

- The human health toxicity database is adequate to support registration review with the exception of immunotoxicity and neurotoxicity data. The Agency anticipates requiring the following data for use in the registration review of pyriproxyfen:

GLN 870.6200a	Rat acute neurotoxicity
GLN 870.6200b	Rat subchronic neurotoxicity
GLN 870.7800	Immunotoxicity

- The Agency anticipates revising the dietary risk assessment (including a revised drinking water assessment) for registration review. A revised dietary assessment will incorporate any revised endpoints and any changes to safety factors or uncertainty factors.

- For the human health risk assessment, the residues of concern for dietary exposure (food and water) is pyriproxyfen *per se* and the degradate 4'-OH-PYR.

- The tolerance expression for pyriproxyfen will be reviewed during registration review to ensure that it appropriately covers the metabolites and degradates of pyriproxyfen and that it specifies the residues to be measured for each commodity.

- The Agency anticipates updating the residential risk assessment to reflect current policy and to include inhalation exposure to handlers pending the selection of an inhalation end point from an existing subchronic inhalation study.

- The Agency anticipates revising the aggregate exposure assessment to incorporate any changes to the residential exposure assessment and any updates to the dietary assessment.

- The Agency anticipates updating the occupational risk assessment (short term exposure) to reflect current policy and to include an assessment of potential inhalation risks pending selection of an inhalation point of departure from an existing subchronic inhalation toxicity study.

- A large number of human health incidents have been recorded in the Agency's Incident Data System (IDS) that involved pyriproxyfen, indicating the potential for exposure. Very few incidents involved pyriproxyfen alone. The Agency will continue to monitor and review the incident database during the registration review of pyriproxyfen.

- Please refer to the document, *Pyriproxyfen: Human Health Risk Scoping document in Support of Registration Review,* dated September 8, 2011, located in the docket for a detailed discussion of the anticipated risk assessment and data needs for human health.

Endocrine Disruptor Screening Program

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

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required

determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Pyriproxyfen is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Accordingly, as part of registration review, EPA will issue future EDSP orders/data call-ins, requiring the submission of EDSP screening assays for pyriproxyfen. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Timeline:

EPA has created the following estimated timeline for the completion of the pyriproxyfen registration review:

Registration Review for Pyriproxyfen – Projected Registration Review Timeline	
Activities	**Estimated Date**
Opening the Docket	
Open Docket and Public Comment Period	2011 – September
Close Public Comment	2011 – November
Case Development	
Final Work Plan	2012 – February
Issue DCI	2012 – Oct. – Dec.
Data Submission	2014 – Oct. – Dec.
Open Public Comment Period for Draft Risk Assessments	2016 – April – June
Close Public Comment Period	2016 – July – Sept.
Registration Review Decision	
Open Public Comment Period for Proposed Registration Review Decision	2016 – Oct. – Dec.
Close Public Comment Period	2017 – Jan. – March
Registration Review Decision and Begin Post-Decision Follow-up	2017
Total (years)	6

Guidance for Commenters:

The public is invited to comment on EPA's preliminary work plan and rationale. The Agency will carefully consider all comments as well as any additional information or data provided in a timely manner prior to issuing a final work plan for pyriproxyfen.

Trade Irritants:

Through the registration review process, the Agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. Growers and other stakeholders are asked to comment on any trade irritant issues resulting from lack of Maximum Residue Limits (MRLs) or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

Water Quality:

Pyriproxyfen is not identified as a cause of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act[1]. No Total Maximum Daily Load (TMDL) criteria have been developed for pyriproxyfen[2]. More information on impaired water bodies and TMDLs can be found at the Agency's website[3]. The Agency invites submission of water quality data for this pesticide. To the extent possible, data should conform to the quality standards in Appendix A of the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process*[4] in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

Environmental Justice:

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to pyriproxyfen, compared to the general population. Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.

Other Information:

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[1] http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885

[2] http://iaspub.epa.gov/tmdl_waters10/attains_nation.tmdl_pollutant_detail?p_pollutant_group_id=885&p_pollutant_group_name=PESTICIDES

[3] http://www.epa.gov/owow/tmdl/

[4] http://www.epa.gov/oppsrrd1/registration_review/water_quality_sop.htm

Stakeholders are also specifically asked to provide information and data that will assist the Agency in refining the ecological and human health risk assessments, including any species-specific effects determinations. The Agency is interested in receiving the following information:

1. data on postharvest agricultural use and usage of pyriproxyfen
2. suggestions from stakeholders on ways to reduce non-target organism exposures to pyriproxyfen
3. confirmation on the following label information
    a. maximum application rates
    b. geographic limitations on use
4. use or potential use distribution (e.g., acreage and geographical distribution of relevant crop)
5. use history
6. median and 90th percentile reported use rates (lbs. a.i./acre) from usage data – national, state, and county
7. application timing (date of first application and application intervals) by crop – national, state and municipality
8. sub-municipality crop location data
9. directly acquired municipality-level usage data (not derived from state level data)
    a. maximum reported use rate (lbs. a.i./acre) from usage data – county
    b. percent crop treated – county
    c. median and 90th percentile number of applications – county
    d. total pounds per year – county
    e. the year the pesticide was last used in the county/sub-county area
    f. the years in which the pesticide was applied in the county/sub-county area
10. state or local use restrictions
11. ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
12. monitoring data
13. usage data such as pounds AI applied, area treated, typical use rates, and typical number of applications would be useful for the agricultural crops that are not covered in the usage section of the BEAD chemical profile for pyriproxyfen (located in the docket)
14. usage data for indoor/outdoor consumer use (residential)
15. usage data for use in and around food handling establishments/food processing establishments, and commercial and institutional facilities

Next Steps:

After the 60-day comment period closes, the Agency will review and respond to any comments received in a timely manner, and then issue its Final Work Plan (FWP) for the registration review of pyriproxyfen.

II. FACT SHEET

Background Information:

- Pyriproxyfen PC Code: 129032, CAS#: 95737-68-1
- Technical registrants:
  - McLaughlin Gormley King Co (Company No. 1021)
  - Makhteshim Chemical Works, LTD (Company No. 11678)
- First registered for use in 1995 and therefore was not subject to reregistration.
- There are 150 active FIFRA section 3 registrations (technical and end use) and 8 special local need section 24c registrations.
- Tolerances for residues of pyriproxyfen in or on acerola, almond hulls, animal feed, apple, artichoke, asparagus, atemoya, avocado, banana, and other fruits, nuts, vegetables, and food handling establishments are codified in 40 CFR § 180.510.
- Pesticide Re-evaluation Division Chemical Review Manager (CRM): Khue Nguyen nguyen.khue@epa.gov
- Registration Division Contact: Kevin Sweeney: sweeney.kevin@epa.gov

Use & Usage Information: (For additional details, please refer to the *BEAD Chemical Profile for Registration Review: Pyriproxyfen*, dated August 16, 2011, and Appendix A document, dated April 20, 2011 in the pyriproxyfen docket.)

- Pyriproxyfen is a broad spectrum pyridine insecticide (insect growth regulator) registered for various agricultural and non-agricultural uses. Agricultural uses include various row crops, fruits, nuts, and vegetables, including oranges, pears, cotton, and almonds. Non-agricultural uses include indoor and outdoor residential and industrial establishments, pets, and water-holding sites such as ornamental ponds and catch basins.

- Pyriproxyfen is formulated as a granular, dust, pelleted/tableted, microencapsulated, impregnated, water soluble packs, emulsifiable concentrate, ready-to-use solution, and as pressurized gas, liquid, and dust forms.

- The major use of pyriproxyfen is on fruits, with oranges as the single crop with the highest annual usage.

Recent Actions:

- In June 2011, the Agency granted experimental use permits for use of pyriproxyfen to control Asian tiger mosquitoes in urban areas of Florida and New Jersey.

- In August 2010, there were two FIFRA section 3 registrations granted for pyriproxyfen as the active ingredient in two new mosquito larvicide products (Sumilarv) for use in catch basins, temporary water-holding sites, and natural/artificial water-holding containers.

- New uses were registered for pyriproxyfen in 2009 for application on various root/tuber vegetables, leafy vegetables, artichoke, asparagus, vine-climbing fruits (except grapes), and watercress (FR 74 No. 205, 10/26/09).

Ecological Risk Assessment Status:

The following are key findings of the most recent pyriproxyfen ecological risk assessment. Please refer to the *Registration Review Problem Formulation for Pyriproxyfen*, dated July 13, 2011, for a detailed discussion of the anticipated ecological risk assessment needs.

- The most recent comprehensive ecological risk assessment for pyriproxyfen was completed in 2009 for new use registrations on various root/tuber/leafy vegetables, artichoke, asparagus, vine-climbing fruits, and watercress.

- Pyriproxyfen is a juvenile insect growth regulator whose mode of action involves inhibition of metamorphosis in target insects. Due to its mode of action, ecological risks to many non-target taxa did not exceed the Agency's level of concern. Risks above the Agency's level of concern were identified for freshwater invertebrates and estuarine/marine invertebrates in the 2009 assessment.

Human Health Risk Assessment Status:

The following are key findings of the most recent pyriproxyfen human health risk assessment. Please refer to the *Pyriproxyfen: Human Health Risk Scoping Document in Support of Registration Review*, dated September 8, 2011, for a detailed discussion of the anticipated human health risk assessment needs.

Hazard Characterization:

- The primary target organs identified in subchronic and chronic toxicity studies were the liver and kidneys. Pyriproxyfen does not demonstrate any evidence of cancer and, therefore, is classified as a Group E chemical – no evidence of carcinogenicity to humans.

- Pyriproxyfen does not demonstrate any evidence of developmental/reproductive toxicity or quantitative or qualitative susceptibility.

Dietary (Food and Water):

- The most recent dietary assessment (screening level, food and drinking water) was conducted in 2009 in support of new use registrations on various vegetables, artichoke, asparagus, vine-climbing fruits, and watercress. Acute dietary risks were not estimated because acute toxicity endpoints were not identified in the database. Chronic dietary

risks were estimated and found to be not of concern for the general US population or any population subgroup.

Residential:

- A residential handler exposure assessment was not conducted for the 2009 assessment because short-term dermal and inhalation endpoints were not available in the toxicity database for the relevant durations (short and intermediate exposures). However, oral post-application risk (e.g., hand-to-mouth) to children was assessed and found not to be of concern.

Aggregate:

- At the time of the 2009 assessment, children were the only population subgroup identified with potential aggregate exposure (i.e., dietary and residential post-application); no risks of concern were identified.

Occupational:

- The Agency did not conduct an occupational assessment in 2009 because occupational exposures were expected to be short-term, for which no toxicity endpoint (dermal or inhalation) was identified in the database.

- An occupational handler exposure assessment (2011) for the registration of an experimental use permit to control Asian tiger mosquitoes did not indicate risks above the Agency's level of concern for dermal and inhalation exposure scenarios.

Human Studies:

- Past pyriproxyfen risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED) and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies supporting these multi-pesticide generic exposure databases, and has found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

Cumulative

- The Agency does not have data that indicates pyriproxyfen shares a common mechanism of toxicity with other chemical substances. If, in the future, new information on pyriproxyfen is available that could potentially impact a cumulative risk assessment and result in a risk of concern, the Agency will revisit the need for a cumulative risk assessment.

Incidents:

- The Office of Pesticide Programs Incident Data System (IDS) was reviewed for reports of pyriproxyfen human incidents. In general, there were a moderately large number of incidents involving pyriproxyfen. From 2006 to 2011, there were 454 incidents involving products containing pyriproxyfen. Very few reported cases (4) were for exposure to pyriproxyfen alone—all 4 cases were moderately severe. The frequency and severity of incidents indicate a high potential for exposure and merit further analysis for risk assessment purposes.

- A review of the Agency's Ecological Incident Information System (EIIS) did not identify any ecological incidents attributed to pyriproxyfen. A review of the Avian Monitoring Information System (AIMS), which is maintained by the American Bird Conservancy, also did not identify any bird incidents associated with pyriproxyfen.

Data Call-In (DCI) Status:

- There have been no data call-in notices issued for pyriproxyfen.

Tolerances and International Harmonization:

- Tolerances are established under 40 CFR 180.510 for residues that result from agricultural uses and from use in food handling establishments.

- Where possible, EPA encourages the harmonization of U.S. tolerances and Maximum Residue Limits (MLRs) in key export markets. A table noting the U.S. tolerances, Canadian MRLs, and Codex MRLs for pyriproxyfen is located in the document, *Pyriproxyfen: Human Health Assessment Scoping Document in Support of Registration Review*. The Agency will work to harmonize tolerances/MRLs, where possible, during registration review.

Labels:

- There are 3 technical products, 1 manufacturing use product, and 146 end-use products.

- The labels for pyriproxyfen can be obtained from the Pesticide Product Label System (PPLS) website: http://oaspub.epa.gov/pestlabl/ppls.home.