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Chlorhexidine Derivatives Registration Review: Final Work Plan September 2011

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Case # 3038

Approved By:

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Supporting documents for the Chlorhexidine Derivatives Case may be found in the registration review docket EPA-HQ-OPP-2011-0069 located on the internet at www.regulations.gov.

Introduction

This is the Final Work Plan (FWP) of the Environmental Protection Agency (EPA or "the Agency") for the registration review of chlorhexidine derivatives (Case 3038). The work plan includes the expected registration review timeline. The work plan also addresses public comments received concerning the Preliminary Work Plan (PWP) in the Summary Document which was posted in the chlorhexidine derivatives registration review docket, and any other comments concerning the initial docket postings. The Summary Document provided information on what EPA knows about the pesticide and what additional risk analyses and data or information the Agency believes are needed to make a registration review decision.

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. Changes in science, public policy and pesticide use practices will occur over time. 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 that statutory standard. The public phase of registration review begins when the initial docket is opened for each case. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

The Chlorhexidine Derivatives Case (Case Number 3038) includes three active ingredients, chlorhexidine diactetate (PC Code 045502), chlorhexidine digluconate (PC Code 045504) and chlorhexidine dihydrochloride (PC Code 481700). When EPA created the schedule for evaluating chemicals under the registration review program, chlorhexidine dihydrochloride (PC Code 481700) was identified as being part of the chlorhexidine derivatives registration review case. After further review, the Agency has determined that there are no registered pesticide products containing chlorhexidine dihydrochloride as an active ingredient (AI) and, thus, chlorhexidine dihydrochloride is not subject to evaluation under registration review and will be removed from Case 3038.

Chlorhexidine diacetate is registered for use as hard surface-treatment disinfectants, sanitizers, bactericides and virucides. Chlorhexidine diacetate is also registered to control bacteria in agricultural premises and equipment and to control certain viruses in animal premises and equipment, egg handling and packing equipment, and meat processing plants. Chlorhexidine digluconate is registered for use as a disinfectant for hard, non-porous surfaces (wheelchairs, metal bed frames, exteriors of toilets, countertops, metal surfaces, imaging equipment surfaces, glass, acrylic, and porcelain) in hospitals, restrooms, schools, offices, gyms, and homes. Chlorhexidine digluconate is also registered for use to control microbial contamination in dental unit waterlines. There are no tolerances or exemptions from requirements of a tolerance established for either chlorhexidine diacetate or chlorhexidine digluconate used as a pesticide.

The first products containing chlorhexidine diacetate and chlorhexidine digluconate as active ingredients were registered in the United States in 1955 and 1987, respectively. A reregistration eligibility decision (RED) for chlorhexidine diacetate was completed in 1996. Chlorhexidine digluconate was first registered after November 1, 1984, and; therefore, was not subject to the reregistration program. Currently, there are four chlorhexidine diacetate and one chlorhexidine

diglucaonate products registered with EPA. The Chlorhexidine Derivatives Preliminary Work Plan (PWP) was published on March 30, 2011 and the 60-day comment period ended on May 31, 2011. Documents associated with the registration review of chlorhexidine derivatives can be viewed at www.regulations.gov in docket EPA-HQ-OPP-2011-0069.

Comments Received on the Preliminary Work Plan

EPA received one comment during the public comment period on the initial docket, described below. In the PWP, EPA also solicited comments on three specific topics: environmental justice; water body impairment; and trade irritants. No comments or information were received during the public comment period concerning these issues.

> Comment: The FIFRA Endangered Species Task Force (FESTF) submitted a comment requesting that the lead technical registrants for chlorhexidine derivates, Fort Dodge Animal Health and Procter & Gamble Company, who are not a members of the FESTF (or a company having met its data compensation obligations), provide a formal offer-to-pay to FESTF for reliance on their data or be required to develop substantially similar data on their own.
>
> Response: The Agency thanks FESTF for its comment and will consider this information as it conducts the registration review and makes its registration review decisions for chlorhexidine derivates.

The comment received during the initial public comment period did not affect the data needs, work plan and timeline described in the PWP and they remain as they were presented initially in the PWP. Further, this document makes final the work plan for the chlorhexidine derivates registration review process.

Risk Assessments and Anticipated Data Needs

The Agency will conduct a comprehensive ecological risk assessment, including an endangered species risk assessment, for all uses of chlorhexidine derivatives. The Agency will also conduct a human health risk assessment. The Agency will require additional data for use in conducting the registration review for chlorhexidine derivatives.

Ecological Risk Assessment Status and Data Needs

- Based on ecotoxicity studies submitted to the Agency, chlorhexidine diacetate was found to be slightly toxic to practically nontoxic to avian species, moderately toxic to cold water fish, and highly toxic to warm water fish and aquatic invertebrates. Chlorhexidine digluconate is slightly toxic to avian species and highly toxic to cold water fish, warm water fish and aquatic invertebrates.

- An environmental fate assessment has not been completed due to the lack of data on the chlorhexidine derivatives.

- The Agency has not conducted a risk assessment that supports a complete endangered species determination for chlorhexidine derivatives. The ecological risk assessment planned during registration review will allow the Agency to determine whether chlorhexidine derivatives' uses have '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 Services (the Services), as appropriate.

- The Agency anticipates conducting ecological risk and environmental fate assessment for the registration review of chlorhexidine derivatives based on use in disinfectant/sanitizers used in animal premises and dental unit water lines that may potentially pass through waste water treatment plants and be discharged into terrestrial and aquatic environments.

- The Agency anticipates the need to require the following additional ecological data for use in conducting the registration review of chlorhexidine derivatives.

  850.5400 -- Algal Toxicity (Tier II) Using Freshwater Green Alga, *Selenastrum capricornutum*

- The Agency anticipates the need to require the following additional environmental fate data for use in conducting the registration review of chlorhexidine derivatives.

  835.2120 -- Hydrolysis
  835.2240 -- Photodegradation in water
  850.6800 -- Modified activated sludge, respiration inhibition test
  835.1110 -- Activated Sludge Sorption Isotherm
  835.3110 -- Ready Biodegradability

- For more information, please refer to *Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for the Chlorhexidine Derivatives Registration Review Decision Document*, located in the docket.

Human Health Risk Assessment Status and Data Needs

- The most recent human health risk assessment for chlorhexidine diacetate was conducted in support of the 1996 RED. The most recent human health risk assessment for chlorhexidine digluconate was completed in 2010 in support of its use in dental unit waterlines.

- The Agency has identified one product that is registered "for dipping teats as an aid in controlling bacteria that causes mastitis." EPA will examine this use as part of the registration review process.

Dietary Assessment

- A dietary risk assessment was not conducted for the 1996 RED because at that time, the U.S. Department of Agriculture and the EPA agreed that disinfectants, when applied to federally

inspected meat, poultry, egg, and rabbit processing plants, did not present dietary exposure risks (USDA, FSIS publication# 1419, "List of Proprietary Substances and Nonfood Compounds"). This publication was no longer updated after 1998 and this policy is now referred to as a "former" guideline or "former requirement;" therefore, the Agency anticipates conducting a dietary risk assessment for the registration review of chlorhexidine derivatives.

Tolerances and International Harmonization

- There are no tolerances or exemptions from requirements of a tolerance established for either chlorhexidine diacetate or chlorhexidine digluconate used as a pesticide.

Occupational and Residential Assessment and Risk

- An occupational risk assessment was conducted for chlorhexidine diacetate in the 1996 RED based on potential exposures from its use as a non-porous, hard surface disinfectant in various agricultural and veterinary settings. Risks exceeded EPA's level of concern for the wet mist fogging use scenario assessed in the Chlorhexidine Diacetate RED. This exceedance was addressed by label language requiring ventilation prior to re-entry into the treated area. The Agency determined all registered uses of chlorhexidine diacetate were eligible for reregistration.

- The most recent human health risk assessment for chlorhexidine digluconate was conducted in 2010. Due to the small amount of product used per treatment, the high dilution of the active ingredient in the product, and the method of application, the Agency determined that the occupational exposures would be minimal in comparison to the toxicology endpoints; therefore, an occupational risk assessment was not completed.

- A residential risk assessment has not been conducted for chlorhexidine derivatives.

- The Agency anticipates conducting residential and occupational exposure risk assessments for the registration review of chlorhexidine derivatives based on current use patterns.

Aggregate and Cumulative Exposure and Risk

- The Agency has not previously conducted an aggregate risk assessment for chlorhexidine derivatives.

- The Agency anticipates conducting an aggregate risk assessment for the registration review of chlorhexidine derivatives.

- EPA does not have, at this time, available data to determine whether chlorhexidine derivatives have a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this Registration Review, EPA has assumed that chlorhexidine derivatives do not have a common mechanism of toxicity with other substances when used as an antimicrobial as registered.

Human Health Data Needs

- The Agency anticipates the need to require the following additional human health data to conduct the registration review of chlorhexidine derivatives.

  870.3465 -- 90-day inhalation toxicity (rat)
  870.5100 -- Bacterial reverse mutation assay
  870.5395 -- Mammalian erthrocyte micronucleus test
  875.1200 -- Dermal indoor exposure
  875.1400 -- Inhalation indoor exposure
  875.1600 -- Application exposure data reporting and calculations
  875.1700 -- Product use information
  875.2300 -- Indoor surface residue dissipation

- For more information, please refer to *Chlorhexidine Derivatives (Chlorhexidine Diacetate and Chlorhexidine Digluconate): Human Health Assessment Scoping Document in Support of Registration Review*, located in the docket.

Product Chemistry:

- The Agency does not anticipate the need to require additional product chemistry data for this registration review at this time.

- For more information, please refer to *Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for the Chlorhexidine Derivatives Registration Review Decision Document*, located in the docket.

Incidents

Ecological:

- There were seven animal incidents associated with chlorhexidine exposure reported in the OPP Incident Data System (IDS). There were seven domestic animal incidents reported involving cats and dogs exposure to chlorhexidine diacetate from pesticidal uses. For cats, the symptoms following exposure to a chlorhexidine diacetate solution were skin redness, inflammation at the site of exposure, weakness, central nerve system signs, apnea, respiratory arrest, comatose-like state and death. For dogs, the symptoms after chlorhexidine exposure were facial paralysis and deafness.

Human Health:

- There were three human incidents associated with chlorhexidine exposure reported in the OPP Incident Data System (IDS). The three human incidents reported to be associated with chlorhexidine exposure from pesticidal uses included: (1) tracheal edema in a woman following her visit to a veterinarian's office where a chlorhexidine solution had been used, (2) severe cold-like symptoms that progressed to bronchitis in a woman running a cattery housing six cats who used a chlorhexidine solution to disinfect cages,

and (3) dermal sensitization symptoms occurring in one person after dermal exposure to a chlorhexidine cleaning solution.

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 the 1996 chlorhexidine diacetate reregistration decision and the 2010 chlorhexidine digluconate registration, 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), chlorhexidine derivatives are 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. Chlorhexidine derivatives were 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 chlorhexidine derivatives. 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 chlorhexidine derivatives registration review:

Anticipated Schedule

Activities	Estimated Month/Year
Phase 1: Opening the docket	
Open Public Comment Period for Docket	Completed March 2011
Close Public Comment Period for Docket	Completed May 2011
Phase 2: Case Development	
Develop Final Work Plan (FWP)	Completed September 2011
Issue DCI	September 2012
Data Submission	September 2014
Open Public Comment Period for Preliminary Risk Assessments	March 2016
Close Public Comment Period for Preliminary Risk Assessments	June 2016
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	September 2017
Close Public Comment Period for Proposed Reg. Review Decision	December 2017
Final Decision and Begin Post-Decision Follow-up	March 2017
Total (years)	6

Next Steps

A DCI will be developed regarding the data needs listed under the “Risk Assessments and Data Needs” section of this document. The Agency anticipates issuing the DCI in September 2012 and conducting human health, environmental fate and ecological risk assessments for all uses.

Summary of Anticipated Data Requirements – Chlorhexidine Derivatives

The table below summarizes anticipated data needs for the Chlorhexidine Derivatives Case**.**

Table 1. Summary of Anticipated Data Requirements – Chlorhexidine Derivatives

Active Ingredient	Guideline Number	Anticipated Data Requirement	Test Material	Estimated Timeframe (Measured in Months from DCI Receipt)
045502 or 045504	835.2120	Hydrolysis	TGAI	12
045502 or 045504	835.2240	Photodegradation in water	TGAI	12
045502 or 045504	850.6800	Modified Activated Sludge Respiration Inhibition	TGAI	12
045502 or 045504	835.1110	Activated Sludge Sorption Isotherm	TGAI	12
045502 or 045504	835.3110	Ready Biodegradability	TGAI	12
045502 or 045504	850.5400	Aquatic growth, Tier II green algae	TGAI	12
045502 or 045504	870.3465	90-day Inhalation Toxicity	TGAI	24
045502 or 045504	870.5100	Bacterial Reverse Mutation Test	TGAI	8
045502 or 045504	870.5395	Mammalian Erythrocyte Micronucleus Test	TGAI	8
045502 and 045504	875.1200	Dermal Exposure - Indoor	TGAI	24
045502 and 045504	875.1400	Inhalation Exposure - Indoor	TGAI	24
045502 and 045504	875.1600	Data Reporting and Calculations	TGAI	24
045502 and 045504	875.1700	Product Use Information	TGAI	12
045502 or 045504	875.2300	Indoor surface residue dissipation	TGAI/TEP	24