US EPA ARCHIVE DOCUMENT

Clofentezine Summary Document: Registration Review

March 2007

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Docket Number: EPA-HQ-EPA- OPP-2006-0240-0003
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Clofentezine Summary Document Registration Review: Initial Docket March 2007

Approved By:

Debra Edwards 3/23/07

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Director, Special Review and
Reregistration Division

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I. Preliminary Work Plan - clofentezine

Introduction:

The Food Quality Protection Act of 1996 mandated a new program: **registration review**. All pesticides distributed or sold in the United States generally must be **registered** by the U.S. Environmental Protection Agency (USEPA; EPA; The Agency), based on scientific data showing that they will not cause unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The new 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. Changes in science, public policy, and pesticide use practices will occur over time. Through the new 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 has begun to implement the new Registration Review program, and plans to review each registered pesticide every 15 years to determine whether it continues to meet the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration. 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 clearly 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.

Anticipated Risk Assessment and Data Needs:

Ecological Risk:

- Ecological risk assessments for most clofentezine uses were completed several years ago, and the Agency has not conducted a risk assessment that supports a complete endangered species determination. Please refer to Section III, Ecological Risk Assessment Problem Formulation, for a detailed discussion of the anticipated risk assessment needs.

- The Agency anticipates needing the following data in order to conduct a complete ecological risk assessment, including an endangered species assessment, for all uses:

    - (GLNs 830.7840 & 830.7860) Solubility in water study
    - (GLNs 835.1230 & 835.1240) Mobility in Soil Data
    - (GLNs 835.4300 & 835.4400) Anaerobic and Aerobic Aquatic Metabolism Studies
    - (GLN 850.1035) Estuarine/marine Invertebrate acute
    - (GLN 850.1350) Estuarine/marine Invertebrate Life-Cycle, or a better quality freshwater Invertebrate Life Cycle

Human Health Risk:

- Additional drinking water assessments are needed to verify that the application to ornamentals, a currently labeled use, will not result in aggregate risks that exceed the Agency's level of concern.
- Occupational risk assessments will be needed for several scenarios including: handler dermal and inhalation assessments for Christmas trees and ornamentals (greenhouse and outdoor), which were not previously assessed; handler inhalation assessments for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons and walnuts based on use patterns (airblast equipment); and a post-application assessment for ornamentals.
- Please refer to Section IV of this document, HED Scoping Document, for a detailed discussion of the anticipated risk assessment needs for human health.

Timeline:

EPA has created the following estimated timeline for the completion of the clofentezine registration review. The Agency may conduct the occupational assessment uses much earlier in the process, allowing mitigation (if necessary) to occur well before the 5.5 years elapse.

Activities	**Estimated Month/Year**
Phase 1: Opening the docket	
Open Public Comment Period for Clofentezine Docket	March 2007
Close Public Comment Period	June 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	July 2007
Issue DCI	May 2008
Data Submission	May 2010
Open Public Comment Period for Preliminary Risk Assessments	Sept. 2011
Close Public Comment Period	Nov. 2011
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	Feb. 2012
Close Public Comment Period	April 2012
Final Decision and Begin Post-Decision Follow-up	August 2012
Total (years)	5.5

Guidance for Commenters:

The public is invited to comment on EPA's preliminary registration review work plan and rationale. The Agency will carefully consider all comments as well as any additional information or data provided prior to issuing a final work plan for the clofentezine case.

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. Please see the docket for a listing of the differences among the U.S., Canada, Codex, and Mexico tolerances.

Stakeholders are also specifically asked to provide information and data in the following areas.

- There is specific information that will assist the Agency in refining the ecological risk assessment, including any species-specific effects determinations. The Agency is very much interested in obtaining the following information:

    1. confirmation on the following label information
        a. sites of application
        b. formulations
        c. application methods and equipment
        d. maximum application rates
        e. frequency of application, application intervals, and maximum number of applications per season
        f. geographic limitations on use
    2. use or potential use distribution (e.g., acreage and geographical distribution of relevant crops)
    3. use history
    4. median and 90th percentile reported use rates (lbs ai/acre) from usage data – national, state, and county
    5. application timing (date of first application and application intervals) by crop – national, state, and county
    6. sub-county crop location data
    7. usage/use information for non-agricultural uses (e.g., forestry, residential, rights-of-way)
    8. directly acquired county-level usage data (not derived from state level data)
        a. maximum reported use rate (lbs ai/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
    9. typical interval (days)
    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

- Clofentezine is not identified as a cause of impairment for any waterbodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at http://oaspub.epa.gov/tmdl/waters_list.impairments?p_impid=3. The Agency invites submission of any other existing water quality data for clofentezine and its degradates (please see http://www.epa.gov/oppsrrd1/registration_review/water_quality.htm for further instruction).

Next Steps:

After the comment period closes in June 2007, the Agency will prepare a Final Work Plan for this pesticide.

II. FACT SHEET

Background Information:

- Clofentezine Registration Review case number: 7602
- Clofentezine PC code: 125501 CAS #: 704115-24-5
- Technical Registrant: Irvita Plant Protection N.V.
- First approved for use in 1989
- Not subject to reregistration; thus no Reregistration Eligibility Decision (RED) exists.
- Tolerance Reassessment Eligibility decision released on April 19, 1999 through publication in the Federal Register (Volume 64, Number 74). No formal TRED document was produced.
- CRM: Joy Schnackenbeck: Schnackenbeck.joy@epa.gov
- PM: Dani Daniel: Daniel.Dani@epa.gov

Use & Usage Information: (For additional details, please refer to the BEAD Appendix A document in the clofentezine docket.)

- Clofentezine is a miticide used on almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons, prunes, plums, walnuts, and ornamentals.
- Clofentezine is used on less than 5 % of the total crop treated for almonds, apricots, cherries, peaches, persimmons, prunes & plums and walnuts. It is used on less than 10% of the crop for apples, nectarines and peaches and less than 15% of the crop for grapes.
- Pests controlled include: European red mites, two-spotted spider mites, McDaniel mites, Pacific spider mites, Eriophyes, and yellow spider mites.
- Approximately 9,000 pounds of clofentezine are used annually.

Recent Actions:

- A Rule for clofentezine was issued on 3/9/05 (70 FR 11563) which established tolerances for residues in or on grapes and persimmons. Fina Makhteshim-Agan of North America, Inc. and the Interregional Research Project Number 4 (IR-4) requested these tolerances.
- A Rule for clofentezine was issued on 4/19/1999 (FR 99-9710), which established tolerances for residues on apples and apple pomace. This FR notice also included the tolerance reassessment for almonds, apricots, cherries, nectarines, peaches, pears, prunes and plums and walnuts.

Ecological Risk Assessment Status:

The Agency currently plans to prepare a comprehensive ecological risk assessment, including an endangered species assessment, for all uses. A summary of potential risks, based on a preliminary analysis, is provided in section III of this document.

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Human Health Risk Assessment Status:

Please refer to Section IV of this document, Human Health Effects Scoping Document, for a detailed discussion of the anticipated risk assessment needs for human health. A summary follows:

Dietary (Food and Water):

- The most recent chronic and cancer dietary assessments were conducted in association with the new uses on grapes and persimmons in 2005. An acute dietary risk assessment was not performed because an endpoint of concern attributable to a single oral dose was not selected for any population subgroup (including infants and children). No risks of concern were identified.
- A currently labeled use of clofentezine on ornamentals was not included in previous drinking water assessments. It is unlikely that the addition of the ornamental use scenarios in future drinking water assessments would result in aggregate risks that exceed HED's level of concern; however a risk assessment will be performed to confirm this.

Residential:

- There are no residential uses for Clofentezine

Occupational:

- Dermal Occupational exposure assessments for clofentezine have been conducted for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears persimmons and walnuts. No risks of concern were identified; however, additional assessments are needed for several additional occupational scenarios.

Tolerances:

- US tolerances are listed under 40 CFR 180.446. A table listing the differences between current US tolerances as compared to Codex, Canada, and Mexico appears in the docket.

Data Call-In Status:

- There are no current data call-ins.

Labels:

- A list of registration numbers may be found in the clofentezine docket and the labels can then be obtained from the Pesticide Product Label System (PPLS) website: http://oaspub.epa.gov/pestlabl/ppls.home.

III. ECOLOGICAL RISK ASSESSMENT PROBLEM FORMULATION

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PC Code: 125501
DP Barcode:

MEMORANDUM

Subject: EFED Problem Formulation for Clofentezine Registration Review

To: Joy Schnackenbeck
Robert McNally
Registration Division
U.S. EPA, Office of Pesticide Programs

From: Stephen Carey, Biologist
Silvia Termes, Chemist
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Thru: Daniel Rieder, Branch Chief
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Date: February 2 2007

Attached is EFED's problem formulation document in support of the clofentezine registration review docket opening. This memorandum outlines (1) the methods that will likely be used in the ecological risk assessment of clofentezine, (2) anticipated LOC exceedances, (3) data gaps, and (4) additional data needs.

1. Problem Formulation

1.1. Nature of the Chemical Stressor, Chemical Family, and Pesticide Mode of Action (MOA)

Clofentezine (3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine; CAS Registry Number 74115-24-5 is the primary chemical stressor to be considered for registration review docket opening. Clofentezine belongs to the tetrazine chemical family of pesticides. The only other member of this family is diflovidazin (3-(2,6-clorophenyl)-6-(2,6-diflurophenyl)-1,2,4,5-tetrazine; CAS Registry Number 162320-67-4). Diflovidazin is not a registered pesticide in the United States.

Clofentezine is used as a selective mite growth regulator by acting as an ovicide. Its mode of action is not known or not specific as per the Insecticide Resistance Action Committee (IRAC), it appears not to be disruptive to beneficial insects and mites even though it has good residual activity on European red mites, McDaniel mites, Pacific spider mites, two-spotted spider mites, Eriophyes and Yellow spider mites. Hexythiazox is another example of mite growth regulator whose mode of action is unknown or not specific, but this chemical does not belong to the same chemical family as clofentezine.

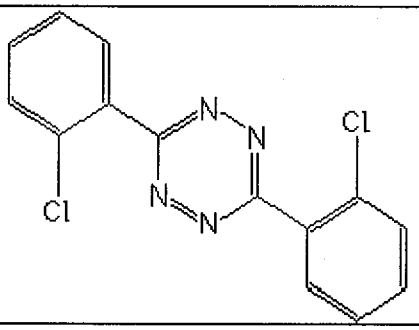
In addition, 2-chlorobenzonitrile, is released to the environment by clofentezine degradation via photolysis in both soil and water. Therefore, it is also considered as a potential stressor.

1. Chemical Identification of Clofentezine

Table IIA-1 presents the necessary chemical information to identify clofentezine as a chemical substance.

Table IIA-1 Chemical Identification of Clofentezine

Type pf Information	Clofentezine
IUPAC and CAS Name	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
CAS Registry Number	74115-24-5
Empirical Formula	$C_{14}H_8C_{12}N_4$
Smiles String	Clc1ccccc1c2nnc(c3ccccc3Cl)nn2

Chemical Structure	
U.S EPA Chemical Code	125501

2. Physical and Chemical Properties of Clofentezine

Physical and chemical properties are intrinsic properties of a chemical. Some of these properties can be use to identify *a priori* the potential behavior of a chemical in the environment. The physical and chemical properties of clofentezine are shown in Table IIA-2

Table IIA-3 Physical and Chemical Properties of Clofentezine

Physical and Chemical Properties	Value
Molecular Weight, Daltons	303.15
Physical State	Crystalline Solid (magenta crystals)
Melting Point, °C	179-182
Boiling Point, , °C	Not applicable
Solubility in Water, mgL^{-1}, 25, °C Solubility in Non-aqueous Solvents, 20, °C	< 1 (Uncertain) Acetone, 0.5 g/100mL Chloroform, 5 g/100mL Benzene, 0.25 g/100mL Ethanol, 0.1 g/100mL Hexane, 0.1 g/100mL
Dissociation Constant	Not applicable
Vapor Pressure, 25, °C	9.75×10^{-10}, mm Hg 1.31×10^{-7}, Pa
Henry's Law Constant	3.9×10^{-10}, atm-m^3mole^{-1} 9.9×10^{-5}, Pa-m^3mole^{-1}
Log *n*-octanol/water Partition Coefficient (Log Kow)	3.1

Based on its vapor pressure and Henry's Law Constant, clofentezine has low potential to volatilize from soil or water. The value of the Log K_{ow} of 3.1 would suggest some low potential to bioaccumulate in fish. However, a valid bioaccumulation in fish study indicated that it did not accumulate. The solubility of clofentezine in water, reported as "<1 mgL^{-1}" is uncertain. Solubility in water is an important input parameter in exposure (aquatic; terrestrial) estimation. The use of "<1 mgL^{-1}" is inappropriate for modeling, therefore additional data are needed.

1.2. Stressor Source and Distribution

Environmental stressors include the active ingredient, clofentezine (PC Code 125501), and a primary degradate, 2-chlorobenzonitrile.

The source of environmental exposures to clofentezine is from its labeled uses as an insecticide (see Section 1.3.). Clofentezine is applied at first sign of mite activity, early in the season through petal fall or first cover, or as a later season application. It can be applied by ground using either dilute or concentrate spray equipment. Aerial applications, application through any type of irrigation system, or grazing livestock in treated areas or harvesting cover crop for livestock feed are not permitted. The release rates for a single application are as high as 0.25 lbs a.i./acre (D301576); however, repeated use of miticides with a similar mode of action may lead to buildup of resistant strains of mites; it is recommended clofenezine is applied once per season. The extent of acreage treated is unknown, but the crops on which it is registered are, collectively, grown throughout the United States.

The abiotic hydrolysis product 2-chlorobenzoic acid (2-chlorobenzylidine) hydrazide and the photolytic product 2-chlorobenzonitrile (direct photolysis in water; photolysis on soil), can form in the environment. Therefore, these degradation products could be potentially considered as secondary chemical stressors whose fate in the environment is to be considered.

1.3. Overview of Pesticide Usage

Clofentezine is currently registered nationally on apples, pears, apricots, cherries, peaches, nectarines, almonds, walnuts, grapes and persimmons.

The currently approved clofentezine application rates range from 0.06 to 0.25 lb a.i./acre for a single ground application with a seasonal maximum label rate of 0.25 lb ai/acre. Repeated use of miticides with a similar mode of action may lead to a buildup of resistant strains of mites. The label states that the product be applied only once per season.

1.4. Environmental Fate Summary

1.4.1. Clofentezine

Abiotic hydrolysis and direct photolysis in water (clear shallow water) are the major routes of transformation for clofentezine in the environment. Abiotic hydrolysis is pH and temperature dependent. At 25°C, the hydrolytic half-lives of clofentezine are 10.4 days (pH 5), 1.4 days (pH 7) and 0.18 days (pH 9). The direct photolysis half-life is less than 7 days. Although clofentezine under laboratory conditions appears to be more persistent in aerobic soil ($t_{1/2}$ = 4 weeks in clay, 6 weeks in loamy sand and 8 weeks in clay loam), abiotic hydrolysis and/or direct photolysis are likely to control the degradation of clofentezine in the environment. However, extensive

mineralization (i.e., CO_2 formation, up to 56% in aerobic soil after one year) was found in the aerobic soil metabolism studies. Thus, mineralization can also be included as a route of transformation in the environment.

Clofentezine mobility in soils is uncertain because of the experimental methodology used to assess its mobility (soil-TLC as opposed to batch-equilibrium adsorption/desorption studies, the currently accepted methodology to determine sorption coefficients). However, the soil-TLC data suggests that clofentezine may have low-to-moderate mobility in soils. Clofentezine has low potential to volatilize from soil or water. There are no data on the behavior of clofentezine in water-sediment systems (anaerobic/aerobic conditions). Even though mobility in soil data suggest the potential of clofentezine to partition into the sediment phase, hydrolytic and photolytic processes in the water column are likely to decrease the amount of clofentezine available for sorption onto the sediment phase. The major degradates of clofentezine are 2-chlorobenzonitrile (direct aqueous photolysis) and/or 2-chlorobenzoic acid (2-chlorobenzylidine)hydrazide (abiotic hydrolysis). Except for CO_2, only traces of other degradates were identified in aerobic soils.

Clofentezine may move off-site as dissolved residues or on suspended solids in runoff, as well as by spray drift. Once in the water body, relatively rapid abiotic hydrolysis and direct photolysis (clear, shallow water) are likely to decrease the concentration of clofentezine in the water column.

In an acceptable bioconcentration in fish, the reported bioconcentration factor (BCF) was 230X after 14 days for the whole fish. The majority (~95%) of the BCF was present in the non-edible (carcass) and viscera fractions and only about 5% in edible tissues. Approximately 50% of the radioactivity extracted from the edible tissue was identified as the parent compound, clofentezine. During the depuration phase, 93% of this accumulated radioactivity was eliminated from the whole body of the fish and virtually completely eliminated during the first 3 days. Small quantities of clofentezine metabolites, 2-chlorobenzoic (2-chlorobenzylidine) hydrazide and 2-chlorobenzamide were identified in the fish tissue.

1.4.2 Degradation Products of clofentezine

There are no direct data on the degradates of clofentezine (i.e, data from studies conducted with degradates as the test substance, as required under FIFRA conducted accordingly to established guidelines). However, it is likely that the 2-chlorobenzonitrile might be an important degradation intermediate. Reactions of nitrile (cyano) groups are known yield amides, aldehyde, and carboxylic acid, functional groups. All of these functional groups have been identified in clofentezine degradation products. However, environmental fate data for these chemical species may be obtained by searching the open literature (e.g., ECOTOX database, TOXNET). In addition, Quantitative Structure-Activity Relationship (QSAR) methodology could be used to estimate their physical and chemical properties and potential behavior in the environment.

The product 2-chlorobenzoic acid (2-chlorobenzylidine)hydrazide) has been identified as an abiotic hydrolysis product. The rate of abiotic hydrolysis is pH and temperature dependent.. At 25° C, t he half-lives of clofentezine decrease with increasing pH (10.4 day at pH 5, 1.4 day at pH 7, and 0.18 day at pH 9). The percentage, as percent of the applied radioactivity, of the hydrolysis product increases with increasing pH. At the conclusion of 30 days, it accounted 14-23% at pH 5, 38% at pH 7, and 45% at pH 9. The direct photolysis of clofentezine may involve the hydrolytic product as an intermediate. However, direct photolysis would only be significant in clear, shallow water but not in deep, turbid water. Given that the role of indirect photolysis is not known, aquatic organisms may be potentially exposed to the hydrolysis product rather than the photolytic product 2-chlorobenzonitrile.

1.5. Ecological Effects Summary

A summary of the available ecotoxicity data on clofentezine is below. No data is available on 2-chlorobenzonitrile. Additional information is presented in Section 1.9.

1.5.1. Clofentezine

The toxicity of clofentezine varies across taxa. The acute toxicity of clofentezine for fish (LC_{50} >14.6 µg ai/L, MRID 105918), freshwater invertebrates (EC_{50} >1.15 µg ai/L, MRID 40568203) are greater than the maximum solubility limit. Because of problems with solubility with clofentezine, results from acute testing with APOLLO SC will be used as surrogate for the technical grade tests toxicity tests. The acute toxicity of APOLLO SC for fish (LC_{50} >24000 µg APOLLO SC/L, MRID 40912101), freshwater invertebrates (EC_{50} >51000 µg APOLLO SC/L, MRID 40568202) are greater than the maximum solubility concentration.

Clofentezine does not cause reproductive or growth effects for freshwater fish and invertebrates at the maximum solubility limit. The fish Early Life-Stage NOAEC and LOAEC were 6 and >6 µg ai/L, respectively (MRID 42735201). The daphnia Life Cycle NOAEC and LOAEC were 26.2 and >26.2 µg ai/L, respectively (MRID 42523901); however, immobility was 11.5% in the solvent control and was 16.3% in the limit dose of 26.2 µg ai/L. Without negative controls, it was not possible to calculate if 16.3% immobility was significant or not.

Clofentezine is classified as practically non-toxic to birds and mammals on an acute oral basis. Reproduction studies in birds indicated an NOAEC of 30 mg ai/kg-diet based on reduction of embryo viability at 90 and 270 mg ai/kg-diet, and reductions of hatchling rate and hatchling body weight at 270 mg ai/kg-diet. In mammals, a reproduction NOAEC of ≥20 mg ai/kg/day was reported based on no treatment-related effects at the highest concentration tested.

The toxicity of clofentezine to terrestrial and aquatic plants, including estuarine/marine fish and invertebrates are unknown.

1.5.2 Degradates of Clofentezine

There are no ecological toxicity studies on the abiotic hydrolysis product 2-chlorobenzoic acid (2-chlorobenzylidine) hydrazide and the direct photolysis product 2-chlorobenzonitile. That is, ecological toxicity data on the secondary stressors are not available.

1.6. Ecosystems at Risk

The terrestrial ecosystems potentially at risk include the treated area and areas immediately adjacent to the treated area that might receive drift or runoff, and might include other cultivated fields, fencerows and hedgerows, meadows, fallow fields or grasslands, woodlands, riparian habitats and other uncultivated areas. The ecosystems and communities at risk will tend to be those in close proximity to and downwind/downstream/down gradient from these and other registered use sites.

For Tier 1 assessment purposes, risk will be assessed to terrestrial animals that are assumed to feed on and otherwise occupy the treated area. Exposure to animals off the treated site is also possible, but exposure and risk estimates are not likely to be higher than on the treated site.

Aquatic ecosystems potentially at risk include water bodies adjacent to, or down stream from the treated field and might include impounded bodies such as ponds, lakes and reservoirs, or flowing waterways such as streams or rivers. For uses in coastal areas, aquatic habitat also includes marine ecosystems including estuaries. For tier 1 assessment purposes, risk will be assessed to organisms in small ponds receiving runoff and drift from treated areas.

1.6.1 Receptors

The aquatic receptors likely to be exposed include fish, invertebrates, aquatic stages of amphibians and plants living in waterways adjacent to or downstream from treated areas.

Terrestrial receptors likely to be exposed to clofentezine include birds, mammals, reptiles and terrestrial stages of amphibians that may occur in treated fields and terrestrial plants adjacent to, or down slope from treated areas.

1.6.2. Assessment Endpoints

Assessment endpoints include reduced survival of individuals or reproduction within populations and/or adverse effects to communities. Organisms potentially exposed include terrestrial and aquatic plants and animals. Potential effects are determined through testing of surrogate

representatives within those taxonomic groups, or from other related taxonomic groups. Assessment endpoints and toxicity data used to evaluate the assessment endpoints are identified in Table 1.

Table 1. Summary of assessment endpoints and proposed measures of effects for screening level risk assessment of clofentezine

Assessment Endpoint	Measurement Endpoint
1. Survival, reproduction, and growth of **birds** (Birds also serve as surrogates for reptiles and terrestrial phase amphibians in that birds are generally more sensitive than species from these other taxonomic groups.)	•Acute oral LD_{50} values, subacute 5-d dietary LC_{50} values •Avian reproduction study NOAEC
2. Survival, reproduction, and growth of **mammals**	•Acute oral mammalian LD_{50} values •Mammal 2-generation reproduction study NOAEC or NOAEL
3. Survival and reproduction of **freshwater fish** and **invertebrates** (Fish also serve as surrogates for aquatic phase amphibians because fish are generally more sensitive than amphibians)	•Freshwater fish 96-h LC_{50} and early life-stage NOAEC •Freshwater invertebrate 48-h EC_{50} and life cycle NOAEC
4. Survival and reproduction of **estuarine/marine fish** and **invertebrates**	•Estuarine/marine fish 96-h LC_{50} and early life-stage NOAEC* •Estuarine/marine invertebrate 96-h LC_{50} (clofentezine) and life cycle NOAEC* *Currently, no acute or reproduction study using clofentezine has been submitted. Without these data, freshwater data could be used as surrogate for these tests.
5. Perpetuation of non-target **terrestrial plants** (crops and non-crop species)	•Monocot and dicot seedling emergence EC_{25} and NOAEC, or EC_{05} (clofentezine TEP) * •Monocot and dicot vegetative vigor EC_{25} and NOAEC, or EC_{05} (clofentezine TEP) * * Currently, no terrestrial plant study using clofentezine TEP has been submitted. Without terrestrial plant data, assumptions of sensitivity would be made based on mode of action and other available information.
6. Survival of beneficial insect populations (Terrestrial invertebrates are represented by the honey bee)	•Honey bee acute contact LD_{50}
7. Maintenance and growth of **aquatic plants** from standing crop or biomass	•Aquatic plant growth and biomass 96-h EC_{50} * •Aquatic plant growth and biomass 96-h NOAEC or EC_{05} * *Currently, no aquatic plant study using clofentezine has been submitted. Without aquatic plant data, assumptions of sensitivity would be made based on mode of action and other available information.

LD_{50} : Lethal dose to 50% of test population
LC_{50} : Lethal concentration to 50% of the test population
EC_{50} : median effect concentration is the concentration that results in a specific effect (e.g., immobility, emergence) to 50% of the exposed test population
EC_{05} and EC_{25} : the concentration that results in a specific effect to 5% and 25%, respectively, of the exposed test population.
NOAEC = No observed adverse effect concentration

1.7. Conceptual Model

The conceptual model is generally that once released from agricultural sprayers, most clofentezine will settle on the target site and some will drift off site. That which settles on the target site will either remain there, percolate into the soil, or runoff with surface water. Some may also volatilize. The conceptual model includes the transformation of clofentezine to 2-chlorobenzoic acid (2-chlorobenzylidine) hydrazide or by direct photolysis in water (clear shallow water) to 2-chlorobenzonitrile, however, ecological data are not available to assess risk. Without further information, structural activity relationship will be used to determine potential hazarad.

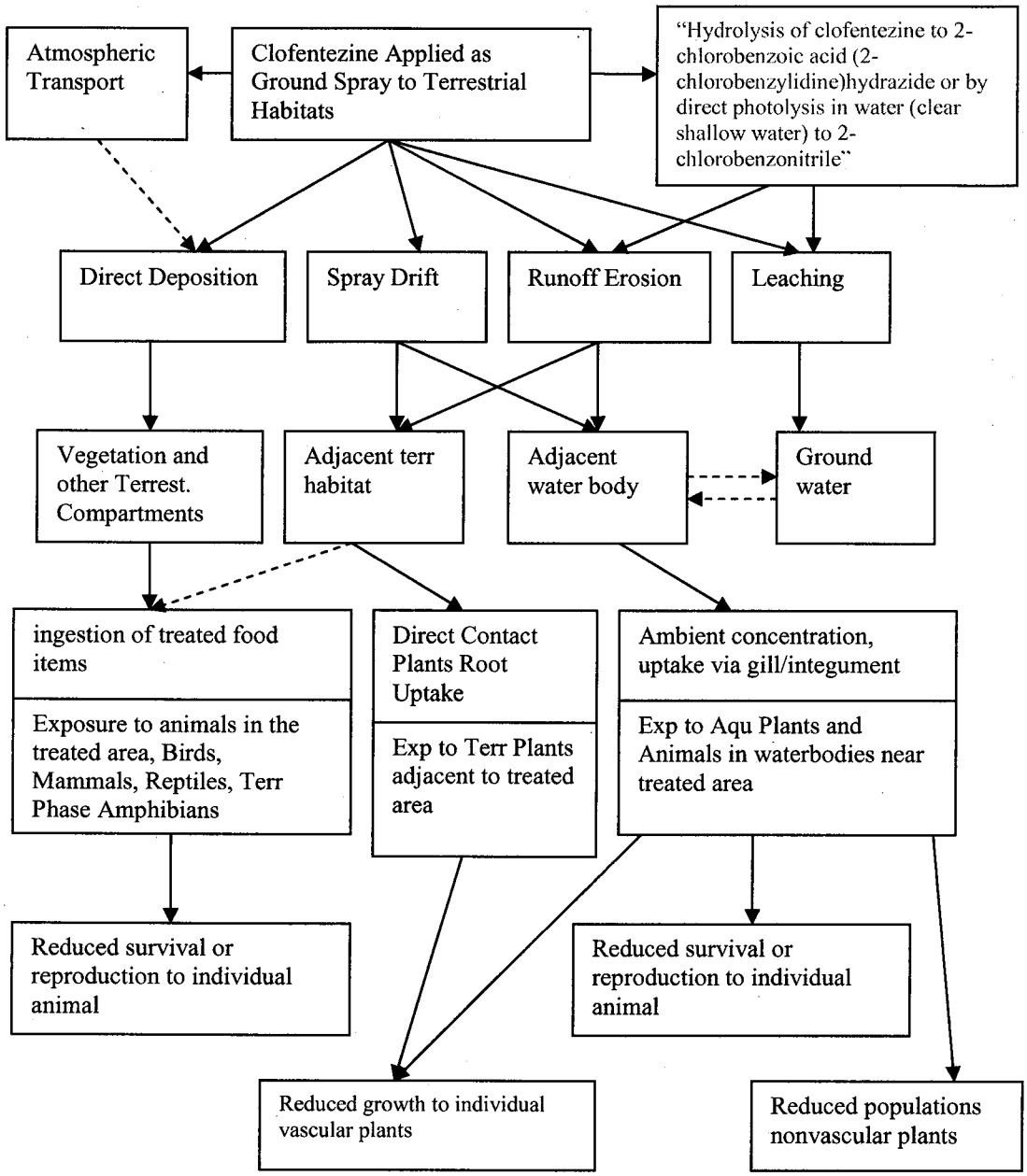


Figure 3. Conceptual Model Diagram: Ground Spray to Terrestrial Habitats

1.8. Risk Hypotheses

Hypothesis: *Nontarget terrestrial and aquatic plants and animals are at risk of direct and indirect effects resulting from labeled uses of clofentezine.* The purpose of the assessment would be to determine if this hypothesis is correct or not.

1.9. Analysis Plan

The analysis plan is the final step in Problem Formulation. During this step, measurements of effect and exposure used to evaluate the risk hypotheses are delineated, and initial data gaps and assumptions required to address them are identified. The Analysis Plan provides a synopsis of measures that will be used to evaluate risk hypotheses. There are three categories of measures: exposure, effects, and risk.

1.9.1. Measures of Exposure

The measures of exposure will be estimated using models. Aquatic exposure will consist of aquatic EECs derived using a waterbody that is vulnerable and representative of static ponds and first order waterways. Terrestrial exposure will be estimated using a model that assumes direct application to a variety of avian, mammalian and reptilian food items. Exposure to terrestrial plants would be estimated using a model that assumes clofentezine drifts or moves with runoff to adjacent habitats, if data are available.

Based on preliminary modeling (Tier I GENEEC, review dated January 13, 2005 under DP Barcodes D298392 and D301576), an application rate of 0.25 lb ai/acre once per season may produce aquatic clofentezine EECs of 6.5 µg ai/L (peak), 0.8 µg a.i./L (21-day) and 0.3 µg a.i./L (60-day). However, some of the input parameters used to run GENEEC carry a high degree of uncertainty (solubility in water, sorption coefficients, aerobic soil metabolism half-lives).

Use Site	Scenario Modeled	Application Method	GENEEC Concentrations (µg/L)		
			Peak	21-day Average	60-day Average
Grapes / Persimmons	GENEEC	ground	6.5	0.8	0.3
			SCIGROW Concentrations (µg/L)		
	SCIGROW			0.04	

Preliminary terrestrial EECs are presented in Section 1.12 for clofentezine.

1.9.2. Measures of Effect

Aquatic Animals and Plants

The technical grade (TG) of clofentezine is practically insoluble (1 mg/L), and studies with the TGAI on aquatic animals yielded questionable results because of solubility problems. The typical end-use product (TEP) is formulated to increase its dispersion in water to maximize solubility. Formulated testing indicates clofentezine is slightly toxic to *Daphnia magna*, rainbow trout and bluegill sunfish. A preliminary aquatic EEC was estimated to be 6.5 µg ai/L. Based on the formulated product toxicity data, the EEC is well below the estimated endangered species concern levels for fish and aquatic phase amphibians, as represented by rainbow trout toxicity (1/20 the rainbow trout LC_{50} = >0.5 mg/L) and Daphnia (1/20 LC_{50} = >2.55 mg/L). The EEC is also below the acute concern levels for nonendangered fish and aquatic phase amphibians, as represented by rainbow trout (1/10 LC_{50} = >1 mg/L) and invertebrates as represented by daphnia (1/10 LC_{50} = >5.1 mg/L).

The acute toxicity of APOLLO SC to freshwater fish and invertebrates are greater than the solubility limit of clofentezine in aquatic environments, however, exposure is presumed less than the Level of Concern (LOC) indicating adverse effect to survival of those taxonomic groups are not expected from ground spraying.

Clofentezine does not cause reproductive and growth effects to freshwater fish and invertebrates at the maximum solubility concentration in chronic tests. However, immobilitization of freshwater invertebrates was recorded in the invertebrate life-cycle test; without negative controls, it was not possible to calculate if 16.3% immobility is a significant effect.

Aquatic plant data on clofentezine are not available. However, hazard will be based on mode of action and other available information.

Terrestrial Animals and Plants

Clofentezine is practically nontoxic to birds on an acute oral and subacute dietary basis (LD_{50} >3000 mg ai/kg-bw (MRID 105914), LC_{50} >19860 mg ai/kg-diet (MRID 105915)). An avian NOAEC of 30 mg ai/kg-diet was observed in bobwhite quail (MRID 42776101) and 270 mg ai/kg-diet (MRID 42776102) in mallard ducks for clofentezine.

Clofentezine is practically non-toxic to mammals (LD_{50} >3200 mg ai/kg-bw) on an acute oral basis. The rat 2-generation LOAEL and NOAEL was > 20.0 mg ai/kg/day and ≥ 20.0 mg ai/kg/day, respectively, for clofentezine based on no effects observed at the highest level tested.

Clofentezine is practically non-toxic to honey bees with an LD_{50} of >192 µg a.i./bee (MRID 159121).

Terrestrial plant data on clofentezine are not available. However, hazard will be based on mode of action and other available information.

The measures of effects will either be the results of actual tests or will be derived or assumed based on other data. Where data are lacking and extrapolated effects endpoints cannot be reliably estimated, risk will be presumed unless data are submitted. In cases where risk is presumed, but cannot be quantified based on lack of data, conservative assumptions will be made, and some analyses will not be able to be conducted. For example, effectiveness of risk mitigation measures cannot be evaluated without quantification of RQs.

The following table lists the specific toxicity values that will be used to assess risk to receptors.

Table 2. Summary of assessment endpoints and proposed measures of effects for screening level risk assessment of clofentezine

Assessment Endpoint	Measurement Endpoint	
1. Survival, reproduction, and growth of **birds**	Acute oral LD_{50}	Clofentezine LD_{50}>3000 mg ai/kg bw
	5-day dietary LC_{50}:	Clofentezine LC_{50}>19860 mg ai/kg diet
	Avian reproduction:	Clofentezine NOAEC: 30 mg ai/kg diet
2. Survival, reproduction, and growth of **mammals**	Acute oral LD_{50}:	Clofentezine LD_{50}: >3200 mg ai/kg bw
	Mammal Reproduction:	Clofentezine NOAEC: >20 mg ai/kg/day
3. Survival and reproduction of **freshwater fish** and **invertebrates**	Fish, Acute:	Clofentezine 96-h LC_{50}: >14.6 µg ai/L APOLLO SC 96-h LC_{50}: >24000 µg APOLLO SC/L [1]
	Fish, Chronic:	Clofentezine Early life stage NOAEC: 6 µg ai/L
	Invertebrate, Acute:	Clofentezine 48-hr EC_{50}: >80 µg ai/L APOLLO SC 48-hr EC_{50}: >51000 µg APOLLO SC/L[1]
	Invertebrate, Chronic:	Clofentezine NOAEC: 26.2 µg/L
4. Survival and reproduction of **estuarine/marine fish** and **invertebrates**	Fish, Acute:	Clofentezine 96-h LC_{50}: None available
	Fish, Chronic:	Clofentezine NOAEC: None available
	Invertebrate, Acute:	Clofentezine 96-hr LC_{50}: None available
	Invertebrate, Chronic:	Clofentezine NOAEC: None available
5. Perpetuation of non-target **terrestrial plants** (crops and non-crop species)	Seedling Emergence:	Clofentezine: None available *
	Vegetative Vigor:	Clofentezine: None available *
	*The mode of action does not suggest hazard to plants, and no label statements or incidents suggest terrestrial plants are sensitive to clofentezine	
6. Survival of beneficial insect populations	Honey bee acute contact:	Clofentezine LD_{50} >192 µg/bee
7. Maintenance and growth of **aquatic plants** from standing crop or biomass	Vascular plants:	Clofentezine: None available *
	Non-vascular Plants:	Clofentezine: None available *
	*The mode of action does not suggest hazard to plants, and no label statements or incidents suggest terrestrial plants are sensitive to clofentezine	

1.9.3. Preliminary Identification of Data Gaps

The following table identifies the studies that are missing or unacceptable, but that are normally available to derive toxicity results used to assess risk to the environment. An evaluation of the

[1] Test results from testing with formulated products will be used as surrogate for the technical grade tests because of solubility problems.

uncertainty that each of these data gaps introduces to ecological risk assessment is discussed below.

Table 3. Preliminary Identification of Data Gaps		
Taxa	**Acute study**	**Chronic/Reproduction study**
Saltwater Invertebrates	No data	No data
Aquatic Plants	No data	
Terrestrial Plants, Vegetative Vigor	No data	
Terrestrial Plants, Seedling Emergence	No data	

1.9.4. Status of Data Requirements

Environmental Fate

Submitted Studies

The following data requirements have been satisfied:

161-1 [Abiotic] Hydrolysis; 105943 & 159135
161-2 [Direct] Photolysis is Water; 159136 & 159152
161-3 Photolysis on Soil; 159136 & 159152
162-1 Aerobic Soil Metabolism; 105939; 114271; 159134; 159138; 40048101; 40048102 ; 41203701
164-5 Bioaccumulation in Fish 403635-01, 404679-12, 405522-01

The following data requirements are not satisfied:

162-3 Anaerobic Aquatic Metabolism (Partly satisfied)

162-4 Aerobic Aquatic Metabolism (No study submitted)
163-1 Mobility in Soil (Partially satisfied)

The following studies were waived:

163-2; 163-3 (Volatilization from Soil (Laboratory; Field)

The quality or lack of the following data were identified as major sources of uncertainties:

The following data will assist the Agency in refining the environmental fate and exposure assessment of clofentezine and its degradate 2-chlorobenzonitrile. The data from theses studies are used as crucial input parameters in simulation models. These data will reduce the uncertainty in estimating environmental exposure concentrations (EECs) and help reduce the uncertainties in the ecological risk assessment. The Agency is very much interested in obtaining the following data:

1. Solubility in water study

The available solubility of clofentezine is uncertain, as it is reported as < 1 mg/L (at 25° C.). Solubility in water is a crucial important input parameter for FIRST, GENEEC, PRZM-EXAMS simulation models used in aquatic exposure or drinking water assessments. It is also crucial information needed to evaluate environmental fate and ecological toxicity studies. A major uncertainty in all of the environmental fate studies, as well as in the ecological toxicity studies, is the actual solubility in water. Thus, the actual concentrations in stock, test solutions, and test media may significantly deviate from "nominal" concentrations reported in the studies.

2, Mobility in Soil Data (163-1)

A Batch-equilibrium adsorption/desorption study conducted with clofentezine and its photoproduct "2-chlorobenzonitrile" (CAS Reg. No. 873-32-5) as test substances. 163-1 is needed. This photoproduct forms by direct photolysis in water. The available mobility in soil data was obtained by soil-thin layer chromatography (Soil-TLC), which is a experimental methodology no longer accepted. Sorption coefficients (Kd; Koc) are crucial important input parameters used in FIRST, GENEEC, PRZM-EXAMS. Sorption data obtained from batch-equilibrium adsorption/desorption are less uncertain than those derived from soil-TLC studies.

2. Anaerobic and Aerobic Aquatic Metabolism Studies (162-3 and 162-4)

The behavior of clofentezine in water-sediment systems (aerobic and anaerobic) is unknown (i.e. persistence, transformation, and partitioning). Even though it does

mineralize in soils, it may not do so or to the same extent in water-sediment systems. In addition, the extent of partitioning into the sediment phase is not known.

Metabolism studies are conducted in the dark and, therefore, the photoproduct will not be observed. If used as the test substance, the behavior of clofentezine in water-sediment systems will not be observed. To account for both parent and photoproduct, a deviation from the guidelines may be necessary.

The following approach is proposed

Conduct parallel aquatic metabolism (anaerobic; aerobic). One conducted under dark conditions and another under irradiated conditions (Xe-arc lamp; within the wavelength range of natural sunlight). Submission of protocols is recommended.

The data from these aquatic metabolism studies would be used as input parameters instead of a default value based on the aerobic soil metabolism half-life, thus reducing the uncertainty in the aquatic exposure assessment.

Ecological Effects

A number of toxicity data gaps have been identified for clofentezine. The following table presents an evaluation of the uncertainty resulting from the data gap. In some cases, strategies were used to make use of existing data. There is inherent uncertainty associated with not receiving data to fulfill data gaps. However, submission of some studies is unlikely to affect conclusions in the risk assessment, whereas some data gaps are more critical. This determination is made on a case-by-case basis.

Table 4. Evaluation of the need for additional effects data on clofentezine

Assessment endpoint with data gap	Chemical	Value of data gap	Basis for decision
Perpetuation of non-target terrestrial plants, crops and non-crop species (122-1, vegetative vigor and seedling emergence) and maintenance and growth of aquatic plants (123-1).	Clofentezine	Low value	Scientifically justifiable alternative assumptions to be made concerning potential risk to terrestrial plants in the absence of terrestrial plant toxicity data for insecticides were not derived; conservative assumptions of potential sensitivity based o nmode of action or other information would be made. Clofetenzine products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility. There are no reported incidents in the incident database. Risks to plants are unlikely.

Survival, estuarine/marine fish (72-1c)	Clofentezine	Low value	No data available to determine the potential risks to estuarine/marine fish in coastal counties. If clofentezine is anticipated to be used in coastal counties where apples and cherry are grown and contaminate the estuarine/marine environment; the potential risk to estuarine/marine fish could not be determined without a study and an indirect effects assessment would be highly uncertain for listed species that depend on estuarine/marine fish for sustenance, e.g. shorebirds. Without estuarine studies, freshwater species data would be used as surrogate.
Survival, estuarine/marine invertebrates (72-3)	Clofentezine	Medium value	No data available to determine the potential risks to estuarine/marine invertebrates in coastal counties. If clofentezine is anticipated to be used in coastal counties where apples and cherry are grown and contaminate the estuarine/marine environment; the potential risk to estuarine/marine invertebrates could not be determined without a study and an indirect effects assessment would be highly uncertain for listed species that depend on estuarine/marine invertebrates for sustenance, e.g. shorebirds. Without estuarine studies, freshwater species data would be used as surrogate.
Reproduction, estuarine/marine Invertebrates (72-4, 850.1350)	Clofentezine	Medium value	Clofentezine is effective against mite eggs and young motile stages; therefore, it may also effect the eggs or young stages of estuarine/marine invertebrates. Also, clofentezine is persistent in water by having a half-life longer than 4 days and may be used in coastal counties. RQ dervied from daphnid chronic is close to the LOC. However, the magnitude of potential risks could not be determined without a study, and an indirect effects assessment would be highly uncertain for listed species that depend on estuarine/marine invertebrates for sustenence, e.g. shorebirds. Without estuarine studies, freshwater species data would be used as surrogate.
Reproduction, estuarine/marine fish (72-4)	Clofentezine	Low value	Clofentezine is effective against mite eggs and young motile stages; therefore, it may also effect the eggs or young stages of estuarine/marine fish. Also, clofentezine is persistent in water by having a half-life longer than 4 days and may be used in coastal counties. However, the magnitude of potential risks could not be determined without a study, and an indirect effects assessment would be highly uncertain for listed species that depend on estuarine/marine fish for sustenence, e.g. shorebirds. Without estuarine studies, freshwater species data would be used as surrogate.

Reproduction, freshwater invertebrates (72-4)	Clofentezine	Low value	In the 21-day chronic toxicity of clofentezine to daphnids was studied under a limit test to determine the effects of clofentezine on daphnids. Only one treatment level and a solvent group was used. It is uncertain because without blank controls or a dose response pattern, a statistical analysis could not be performed. At 21-day, immobilitity was 11.5% and 16.3% in the solvent control and 26.2 ppb group, respectively. It is possible that the NOAEC could be lower in a 5 treatment level test and might result in exceedances of the chronic LOC.

As noted in the above table, some data gaps do not result in significant added uncertainty, whereas other data gaps are expected to contribute considerable uncertainty to the risk assessment. In summary, request of the following guideline studies is proposed:

Estuarine/marine Invertebrate Acute, 72-3
Estuarine/marine Invertebrate Life-Cycle, 72-4, or a better quality freshwater Invertebrate Life-Cycle 72-4

Without these data, ecological risk assessment would be highly uncertain. Submission of other studies to fulfill data gaps identified in Table 4 would reduce uncertainty; however, supportable conclusions can be made without submission of studies outside of those proposed for testing identified in Table 4 (assuming the requested studies will be submitted).

1.10 Open Literature

Before requesting that new ecological effects studies be conducted by the registrant to fulfill these potential data gaps, the Agency will conduct a search of the open literature to determine if the data are indeed already available. If so, an evaluation will be made as to whether or not the data are adequate for use in a risk assessment. The Agency uses the ECOTOX database as its mechanism for searching the open literature. ECOTOX integrates three previously independent databases - AQUIRE, PHYTOTOX, and TERRETOX - into a system which includes toxicity data derived predominately from the peer-reviewed literature, for aquatic life, terrestrial plants, and terrestrial wildlife, respectively. At this point in time, a full and complete ECOTOX search has not been performed, but will be done prior to issuance of any Data Call-In.

A scan of the on-line ECOTOX database shows that the only applicable data in that system are those that are in the EFED files. So far, no open literature studies have been found that might provide useful information in the areas of these data gaps.

1.11. BINNING DECISION

EFED needs additional data (or will apply alternative effects assumptions) and would need to conduct new assessments for all registered outdoor uses. Therefore, clofentezine is recommended to be assigned to Bin 1. The new assessments are needed because:

a) Previous assessments did not include risk to terrestrial or aquatic plants, nor estuarine/marine risk estimations.
b) Previous assessments were not done with current models and risk assessment calculations
c) Previous environmental and exposure assessments used inadequate data
d) Previous assessments did not include open literature as identified by ORD, MED ECOTOX literature search program

Drinking water is not expected to be a risk issue to humans based on modeling at rates slightly higher than currently registered uses.

1.12. SUMMARY OF RISKS

1.12.1. Summary of Risks identified from Preliminary Analysis for This Problem Formulation

Expected LOC exceedances for clofentezine are summarized in Table 5 below. Additional discussion if the LOC exceedances are in Sections 1.13.2, 1.13.3, and 1.13.4. All conclusions are preliminary and may change during the risk assessment process.

Table 5. Preliminary identification of LOC exceedances for clofentezine *

Chemical Stressor	Endpoint	Birds	Mammals	Terr. Plants	Insects	Fish	FW Inverts	SW Inverts	Aquatic Plants
Clofentezine	Acute			unlikely				N/A	unlikely
	Reproduction	✓					uncertain	N/A	

* All risk conclusions are preliminary and may change over the course of the risk assessment process
✓ Risk is anticipated to be > any of the Agency's LOC
P Risk may or may not be above the Agency's LOC
Blank cells indicate no LOC exceedances
N/A No data to assess risk

1.12.2. Clofentezine

Aquatic Organisms and Plants

A summary of anticipated LOC exceedances for clofentezine is presented below. Additional detail is provided in Table 6 below. Based on preliminary modeling for this problem

formulation, an application rate of 0.25 lb ai/acre once per season may produce aquatic clofentezine EECs of 6.5 µg ai/L (peak), 0.8 µg a.i./L (21-day) and 0.3 µg a.i./L (60-day). Based on a fish LC_{50} of >14.6 µg a.i./L, the RQ is not calculated since there were no mortality at the maximum solubility limit. Based on a fish NOAEC of 6 µg a.i./L and 60-day EEC, the chronic RQ is less than the chronic LOC of 1. This modeling indicates minimal risk to aquatic animals for endpoints where data are available. However, preliminary risk to marine/estuarine invertebrates is presumed lower than the chronic LOC of 1 based on the assumption is made that estuarine/marine invertebrates would be of similar sensitivity as freshwater invertebrates. Although a chronic NOAEC is not available, chronic risk to marine/estuarine invertebrates is presumed to be minimal because of the assumption is made that estuarine/marine and freshwater invertebrates are of similar sensitivity. Even though an assumption of similar sensitivity is made, risks to estuarine/marine organisms are uncertain because no data were submitted. In addition, risks to aquatic plant are assumed to be minimal since clofentezine is registered on numerous crop species/taxa, including monocots and dicots, with no label restrictions based on plant susceptibility.

Table 6. Aquatic EECs and RQs for clofentezine based on one application of 0.25 lb ai/acre per season

Taxa	Toxicity	EEC	RQ
Fish	Acute LC_{50}: 24000 µg a.i./L	6.5 µg/L (peak EEC)	RQ<LOC
	Chronic NOAEC: 6 µg a.i./L	0.3 µg/L (60-day EEC)	RQ<LOC
Aquatic Invertebrate	Acute EC_{50}: 51000 µg a.i./L	6.5 µg/L	RQ<LOC
	Chronic NOAEC: 26.2 µg a.i./L	0.8 µg/L (21-day EEC)	RQ<LOC
Aquatic plants	Lemna gibba, NOAEC: unknown	6.5 µg/L	*
Estuarine/marine invertebrates	Mysid shrimp, EC_{50}: unknown	6.5 µg/L	**
	Mysid shrimp NOAEC: unknown	0.8 µg/L	++

1 There were no mortality at the maximum solubility limit resulting in a greater than toxicity value, RQs are not calculated and are presumed to be below the LOC.

* Data is not available. However, risks to endangered aquatic plants are unlikely at this time; conservative assumptions of potential sensitivity would be made. However, clofentezine products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility. There are no reported incidents in the incident database.

** Acute EC_{50} is not available in marine/estuarine invertebrates. Risk is uncertain anticipated to be below the LOC of 0.05 based on the assumption that estuarine/marine invertebrates and freshwater invertebrates are of similar sensitivity and no mortality was seen in freshwater invertebrates acute study at the maximum solubility limit.

++ Chronic NOAEC is not available in marine/estuarine invertebrates. Risk is uncertain but anticipated to be below the LOC of 1.0 based on the assumption that estuarine/marine invertebrates and freshwater invertebrates are of similar sensitivity.

Terrestrial Animals and Plants

Clofentezine is practically non-toxic to terrestrial animals from an acute standpoint. Analysis with the Agency's (Terrestrial Residue EXposure) T-REX model produced acute RQs for birds and mammals of <0.1 which is the acute endangered species LOC (Tables 7 - 9). This indicates that clofentezine is expected to pose minimal acute risk to avian and mammalian non-target and endangered species. However, reproduction risk quotients for birds were as high as 2 (Table 8) for clofentezine, which is well above the LOC of 1.0. Clofentezine reproduction data are available for mammals; however, risk is presumably negligible for mammals based on a rat NOAEC of ≥20 mg/kg/day.

Table 7. Estimated acute dose-based risk quotients (RQs) for birds assuming one application at 0.25 lb ai/acre

Food Material	Avian Acute RQs for birds of various weights		
	20 g	100 g	1000 g
Short Grass	<0.1*	<0.1	<0.1
Tall Grass	<0.1	<0.1	<0.1
Broadleaf plants/sm insects	<0.1	<0.1	<0.1
Fruits/pods/seeds/lg insects	<0.1	<0.1	<0.1

*This RQ was calculated using a "greater than" toxicity value to represent the LD_{50}. A definitive LD_{50} was not derived for birds, and there was no mortality at that level, so this RQ of <0.1 is not interpreted as representing a risk of acute effects to birds.

Table 8. Acute and chronic risks to birds, 1 application at 0.25 lb ai/A

Dietary-based RQs (Dietary-based EEC/LC_{50} or NOAEL)	RQs	
	Acute	Chronic
Short Grass	<0.1	**2.00****
Tall Grass	<0.1	0.92
Broadleaf plants/sm insects	<0.1	**1.13**
Fruits/pods/lg insects/seeds	<0.1	0.13

** Bold indicates LOC exceedance

Table 9. Acute and Chronic risk to Mammals, 1 application at 0.25 lb ai/acre						
Dose-based RQs (Dose-based EEC/LD50 or NOAEL)	**15 g mammal**		**35 g mammal**		**1000 g mammal**	
	Acute	**Chronic**	**Acute**	**Chronic**	**Acute**	**Chronic**
Short Grass	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Tall Grass	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Broadleaf plants/sm insects	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Fruits/pods/lg insects	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Seeds (granivore)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1

No terrestrial plant toxicity information has been received for clofentezine or APOLLO SC. Exposure to non-target terrestrial plants is unlikely from application of clofentezine from spray drift or runoff. Terrestrial plants, including endangered species are unlikely to be at risk because clofentezine products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility. There are no reported incidents in the incident database.

1.12.3 Summary of Expected Risks from Clofentezine and APOLLO SC (formulated product)

Table 10. Summary discussion of LOC exceedances for clofentezine and Apollo SC		
Taxa	**Anticipated Risk**	**Basis for Risk Conclusion**
Birds, Acute	Clofentezine: RQ < LOC	**Clofentezine**: Acute avian RQs does not exceed the endangered species LOC of 0.1 based on a foliar dissipation rate of 35 days and an LD_{50} of >3000 mg/kg-bw.
	APOLLO SC: No data	**APOLLO SC:** No data are available; however, acute RQs for birds exposed to clofentezine <LOC.
Birds, reproduction	**Clofentezine: RQ >LOC**	**Clofentezine**: Chronic avian RQs exceeds the chronic and endangered species LOC of 1 based on dietary-based exposure for short and tall grasses.
	APOLLO SC: Uncertain	**APOLLO SC**: No data are available; however, reproductive risk to birds is presumed because clofentezine exceeds the LOC.
Mammals, Acute	Clofentezine and APOLLO SC: RQ < LOC	Based on application rate of 0.25 lbs a.i./Acre (1 application) and LD_{50} of >3200 mg/kg-bw for clofentezine, RQs are expected to be less than the endangered species LOC of 0.1. No data were available for APOLLO SC; however, acute risks to mammals is not presumed since clofentezine does not exceed the LOC.
Mammals, Reproduction	Clofentezine: RQ < LOC	**Clofentezine**: Chronic mammalian RQs do not exceed the chronic and endangered species LOCs of 1.
	APOLLO SC: RQ <LOC	**APOLLO SC**: No data are available; however, all mammalian RQs are expected to be <LOC of 1.0 because clofentezine does not exceed the LOC.
Terrestrial Plants	Clofentezine or APOLLO SC: RQ<LOC	Data do not allow for risk estimation; however, clofentezine products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility. There are no reported incidents in the incident database.

Table 10. Summary discussion of LOC exceedances for clofentezine and Apollo SC		
Taxa	**Anticipated Risk**	**Basis for Risk Conclusion**
Fish, Acute	Clofentezine and APOLLO SC: Not calculated	**Clofentezine and APOLLO SC**: Toxicity values of fish are greater than the maximum solubility concentration at which no mortality was seen; exposure is presumed to be lower than the LOC
Fish, reproduction	Clofentezine: RQ < LOC APOLLO SC: RQ < LOC	**Clofentezine:** Based on a 60-day EEC of 0.3 µg/L and a NOAEC of 6 µg/L, the reproduction RQ is expected to be < the LOC of 1.0. **APOLLO SC:** No data are available; however, chronic risks to fish is not presumed because clofentezine does not exceed the LOC.
Freshwater Invertebrates, Acute	Clofentezine and APOLLO SC: RQ<LOC	**Clofentezine and APOLLO SC**: Toxicity values of invertebrates are greater than the maximum solubility concentration at which no mortality was seen; exposure is presumed to be lower than the LOC
Freshwater Invertebrates, Chronic	Clofentezine: Uncertain APOLLO SC: Uncertain	**Clofentezine**: Based on the limit dose toxicity test at the maximum solubility concentration, chronic/reproductive RQs for invertebrates are <LOC. Similar conclusions for invertebrates are expected because freshwater invertebrates were slightly less sensitive than fish in acute studies. However, immobility of invertebrates was observed. A reliable NOAEC could not be estimated because a statistical analysis could not be performed in absence of blank (negative) control groups, in addition to the limit test which one treatment level is insufficient to do such an analysis. It is uncertain if a lower NOAEC will result in any LOC exceedances from conducting a statistical analysis with several treatment levels and a negative control group. Requested data in mysid shrimp will also provide additional support for risk conclusions for freshwater invertebrates. **APOLLO SC:** No data are available; however, chronic/reproductive risks are not presumed because clofenezine exposure does not exceed the LOC based on technical grade testing. However, it is uncertain if the clofentezine NOAEC is valid as discussed above.
Aquatic Plants	Clofentezine and APOLLO SC: RQ<LOC	**Clofentezine and APOLLO SC**: No data are available; however, clofentezine products are registered for use on numerous crop species/taxa, including both monocots and dicots, with no label restrictions based on specific plant susceptibility. There are no reported incidents in the incident database.

1.13. Additional Uncertainties

In addition to known data gaps for taxonomic groups for which the Agency normally has data, there is a possibility that through public comment and literature searches, additional data may be found that identifies different adverse effects, effects to other taxonomic groups or effects at lower exposure levels. The Agency also plans to search open literature to locate potentially useful data that may provide additional information on the potential effects of clofentezine. Previous assessments did not include a search of open literature for such information.

Previous assessments have not addressed indirect effects. Direct effects to plants and other taxonomic groups have the potential to indirectly affect other species even if those other species may not be affected directly by clofentezine. For example, if use of clofentezine results in direct effects to terrestrial plants, there is a possibility of indirect effects to terrestrial animals such as to birds, mammals and reptiles through loss of habitat or cover and reduced food supply. Aquatic animals might be at risk if riparian plant communities are impacted by reducing shading or resulting in increased erosion. Previous assessments have not taken into account indirect effects or effects to critical habitat of endangered species.

In addition to the need to assess risk to taxonomic groups for which data were not available, none of the currently registered uses has been assessed according to current tools and models that would be required to bring the Agency risk assessment on clofentezine into compliance with the Endangered Species Act and Agency guidance on ecological risk assessment. Some recent changes to the methods of ecological risk assessment include a revised mammalian exposure model that tends to result in higher tier 1 risk quotients. Aquatic modeling is more refined with additional regionally specific scenarios that take into account local runoff and meteorological conditions. Drift has not been assessed using AgDrift, which is a drift model that takes into account several relevant factors such as wind speed, release height and droplet size.

A critical aspect of risk assessments that comply with current policy is risk refinements. If screening level risk assessments indicate potential risk of direct or indirect effects to endangered species these assessments must be refined at a local level to determine if potential affects are likely to adversely affect or not likely to adversely affect the listed species. None of the potential risks identified for clofentezine have been refined. For example, the potential risk of reproductive effects to birds has not been refined to determine if endangered birds are likely to be exposed, and if that exposure might adversely affect the species. Likewise, the suspected risk to plants has not been refined to determine if endangered plants might be adversely affected or if direct effects to non-endangered plants might indirectly affect endangered animals.

1.14. Clofentezine Residues in Water

The extent and nature of residues of clofentezine and/or its degradation products is uncertain. Crucial environmental fate data used in simulation models are uncertain (solubility in water; sorption coefficients; persistence and partitioning in water-sediment systems). Thus, these uncertainties carry over to the aquatic and drinking water assessments. There are no monitoring data for clofentezine.

1.15 Other Information Needs

There is specific information that will assist the Agency in refining the ecological risk assessment, including any species-specific effects determinations. The Agency is very much interested in obtaining the following information:

13. confirmation on the following label information
    a. sites of application
    b. formulations
    c. application methods and equipment
    d. maximum application rates
    e. frequency of application, application intervals, and maximum number of applications per season
    f. geographic limitations on use
14. use or potential use distribution (e.g., acreage and geographical distribution of relevant crops)
15. use history
16. median and 90th percentile reported use rates (lbs ai/acre) from usage data – national, state, and county
17. application timing (date of first application and application intervals) by crop – national, state, and county
18. sub-county crop location data
19. usage/use information for non-agricultural uses (e.g., forestry, residential, rights-of-way)
20. directly acquired county-level usage data (not derived from state level data)
    a. maximum reported use rate (lbs ai/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
21. typical interval (days)
22. state or local use restrictions
23. ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
24. monitoring data

Docket Number: EPA-HQ-EPA- OPP-2006-0240-0003
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IV. HUMAN HEALTH EFFECTS SCOPING DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: January 31, 2007

SUBJECT: **Clofentezine:** Registration Review Scoping Document for Human Health Assessments; PC Code: 125501; DP Number: D336110

REVIEWER: Charles Smith, Risk Assessor/Environmental Scientist
Elissa Reaves, Ph.D., Toxicologist
Reregistration Branch 2
Health Effects Division (7509P)

THROUGH: William Hazel, Ph.D., Chief
Reregistration Branch 2
Health Effects Division (7509P)

TO: Joy Schnackenbeck, Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division (7508P)

Attached is the human health scoping document to support the registration review of the insecticide clofentezine.

Docket Number: EPA-HQ-EPA- OPP-2006-0240-0003
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HED Preliminary Work Plan for the Registration Review of Clofentezine
(PC Code 125501)

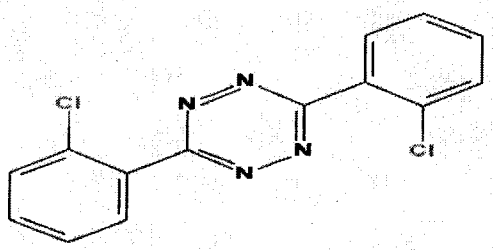
Introduction

The HED Clofentezine Registration Review Team has evaluated the status of the human health assessments for the acaricide clofentezine to determine the scope of work necessary to support registration review. The team looked at the hazard and exposure databases for clofentezine and attempted to determine whether changes in science policy or deficiencies in the databases *materially* affected the overall risk picture. The current supported uses for clofentezine include uses on almonds, apples, apricots, cherries, Christmas trees, grapes, nectarines, ornamentals (greenhouse and outdoor), peaches, pears, persimmons, and walnuts. Clofentezine currently has no residential uses.

Clofentezine is currently registered for use on almonds, apples, apricots, cherries, Christmas trees, grapes, nectarines, ornamentals (greenhouse and outdoor), peaches, pears, persimmons, and walnuts. The Christmas tree and ornamental uses of clofentezine have not been assessed by HED. The primary sources for the status update are the risk assessment developed for the proposed uses of clofentezine on grapes and persimmons (Memo, J. Tyler, 2005; D283816), a risk assessment that examined all stone fruit and nut tree uses (Memo, D. Vogel, 1999; D 252864), and an OPPIN bibliography search for any newly submitted data. Clofentezine was first registered in 1989 and therefore not subject to reregistration; however, tolerances were reassessed when additional food uses were registered in 2005.

No new toxicity data have been submitted to the Agency since the RfD/Peer Report of June 1994. Route specific inhalation data are missing for the occupational inhalation scenarios. A comprehensive search of the open literature was not done primarily because a screening Google search and a Science Direct search indicated very little information was available that pertained to missing toxicity data (inhalation) for clofentezine. A comprehensive listing of the documents considered is presented in Section 9 of this document. The purpose of this screen is to determine whether sufficient data are available to support registration review. The HED Risk Assessment team includes Elissa Reaves and Charles Smith.

Section 1. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Clofentezine
IUPAC name	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
CAS name	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
PC Code	125501
CAS registry number	74115-24-5
Registration Review Case No.	7602
Chemical Structure	

Section 2. Toxicology

The toxicity database for clofentezine is adequate for registration review purposes. The clofentezine database has been reviewed by several HED committees over the past 20 years. Endpoints for clofentezine were reviewed by the Agency RfD Committee in September 1987 and by the Hazard Identification Review Committee (HIARC) in 1999. FQPA considerations were made by the FQPA Safety Factor Committee (SFC) in 1998. The FQPA safety factor was reevaluated again in accordance with the February 2002 OPP 10X guidance document and determined that the previous decision should remain unchanged (1X) (Memo, J. Tyler, 2005; D283816).

Subchronic inhalation and dermal toxicity studies are not available to assess occupational risk. The lack of these route specific studies will require the Agency to consider oral toxicity studies for estimating inhalation and dermal risk. A dermal absorption study was evaluated in 1999 to determine the appropriate absorption factor: however, it was found to be unacceptable. The dermal absorption factor will be reconsidered at the time of the dermal assessment for purposes of registration review. For the inhalation assessment, a default factor of 100% absorption will be used along with an oral endpoint.

The classification of clofentezine as a possible human carcinogen (classification of C, possible human carcinogen) was reviewed by the HED Cancer Peer Review Committee (CARC) in June of 1988, July of 1988, and April of 1990. In December 1998, a Q_1* was generated based on male rat thyroid follicular cell adenoma and/or carcinoma combined tumor rates (Memo, A. Kocialski, 1998; TXR013002). Subchronic and chronic studies indicate the liver is the primary target organ with secondary effects on the thyroid thereby causing an imbalance in homeostasis. Clofentezine does, however, cause thyroid tumors in male rats after long-term high exposure resulting in progressive effects on the thyroid that leads to hyperplasia and eventual tumor formation. No mechanism or mode of action has been accepted formally by the CARC at this time. The current Q^*1 value for clofentezine using the ¾ inter species scaling factor is 3.76×10^{-2} $(mg/kg/day)^{-1}$.

The risk assessment team has re-evaluated the toxicity database and endpoints for the occupational scenarios and current policies on selecting endpoints and uncertainty factors. In addition, clofentezine is subject to the Food Quality Protection Act (1996) and an aggregate assessment of food and water is required. Table 2.1 outlines the toxicity endpoints which are updated from the last HIARC in 1999. The toxicity database, therefore, is adequate to support the registration review of clofentezine.

Table 2.1: Summary of Clofentezine Toxicological Endpoints for Use in Human Risk Assessment[1]

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	No appropriate endpoint was identified in oral toxicity studies including the developmental studies in rats and rabbits for risk assessment because no adverse effects were associated with a single clofentezine dose.			
Chronic Dietary	NOAEL = 1.25	UF_A=10x UF_H=10x FQPA SF=1x	Chronic RfD= 0.013 cPAD= 0.013	1-year chronic dog study- LOAEL = 25 mg/kg, based on increased liver weights, hepatocellular enlargement, and increased serum cholesterol, triglycerides and alkaline phosphatase levels
Dermal Short-Term (1-30 days) Dermal Intermediate- (1-6 mos)	NOAEL = 2.0 MOE = 100 100% absorption	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	13-week rat study- Increased cholesterol, increased liver weights, thyroid colloid depletion and thyroid follicular cell hypertrophy
Dermal Long-Term (>6 mos)	Long-term dermal exposure is not expected based on maximum of one application per year as prescribed by the label.			
Inhalation Short-Term (1-30 days) Inhalation Intermediate-	NOAEL = 2.0 MOE = 100 100% absorption	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	13-week rat study- Increased cholesterol, increased liver weights, thyroid colloid depletion and thyroid follicular cell hypertrophy

(1-6 mos)				
Inhalation Long-Term (>6 mos)	Long-term dermal exposure is not expected based on maximum of one application per year as prescribed by the label.			
Cancer (oral, dermal, inhalation)	Classification: possible human carcinogen (classification of C), Q* using the ¾ interspecies scaling factor is 3.76×10^{-2} $(mg/kg/day)^{-1}$			

[1] **Explanation of Abbreviations:** 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 SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Section 3. Current Dietary Assessments

Chronic and cancer dietary assessments were conducted in association with the proposed new uses on grapes and persimmons in 2005 (Memo, J. Tyler, 2005; D283816). An acute dietary risk assessment was not performed because an endpoint of concern attributable to a single oral dose was not selected for any population subgroup (including infants and children). For the chronic and cancer dietary assessments for food alone and food plus water (the Environmental Fate and Effects Division provided Tier 1 ground water and surface water concentrations) all exposures did not exceed HED's level of concern. It should be noted that clofentezine is currently labeled for use on ornamentals but it does not appear that these scenarios were included in previous drinking water assessments. It is unlikely that the addition of the ornamental use scenarios in future drinking water assessments would result in dietary risks that exceed HED's level of concern. However, an assessment will need to be completed to verify this belief.

Section 4. Aggregate and Cumulative Exposure

There are no residential uses of clofentezine so the aggregate assessments in the most recent assessment include only food and water. An acute aggregate risk assessment was not performed because an endpoint of concern attributable to a single oral dose was not selected for any population subgroup (including infants and children). For the chronic and cancer dietary assessments for food alone and food plus water (EFED provided Tier 1 ground water and surface water concentrations) all exposures did not exceed HED's level of concern.

Chronic dietary exposure estimates are below HED's level of concern for the general U.S. population and all population subgroups (less than 1% of the risk cup). The Tier 1 clofentezine water concentrations generated by EFED indicate that clofentezine residues in drinking water occupy only a fraction of the risk cup. Therefore, the chronic aggregate risk (food + water) associated with the proposed uses of clofentezine does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Similar to the chronic dietary assessment, food occupies very little of the risk cup for cancer. Considering the contribution from water, cancer risks are below the Agency's level of concern (i.e., 1 x 10-6).

Section 5. Occupational Exposure

A summary of the available occupational exposure assessments for clofentezine is presented in Table 5.1. Occupational handler dermal assessments have been conducted for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons, and walnuts. All of these assessments were below HED's level of concern; some scenarios required a single layer of dermal protection (e.g. chemical-resistant gloves). Post-application assessments have been conducted for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons, and walnuts. No risks of concern were identified for clofentezine residues on the day of application. Consequently, the Agency has applied a 12 hour re-entry interval on the labels for clofentezine. Occupational handler and postapplication assessments have not been conducted for Christmas trees and ornamentals (greenhouse and outdoor).

The following occupational assessments will be required in registration review: handler dermal and inhalation assessments for Christmas trees and ornamentals (greenhouse and outdoor) which were not previously assessed; handler inhalation assessments for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons, and walnuts based on use patterns (airblast equipment); and a post-application assessment for ornamentals.

Section 6. Anticipated Data Needs

HED does not believe additional data are needed for registration review.

Section 7. Tolerances

Tolerances are currently established under 40 CFR §180.446(a)(1) for the residues of clofentezine *per se* in or on the following RACs: almond hulls (5.0 ppm), almonds (0.5 ppm), apple pomace (3.0 ppm), apple (0.5 ppm), apricot (1.0 ppm), cherry (1.0 ppm), grape (1.0 ppm), nectarine (1.0 ppm), peach (1.0 ppm), pear (0.5 ppm), persimmon (0.05 ppm), and walnut (0.02 ppm). Tolerances are also established under 40 CFR §180.446(a)(2) for the combined residues of clofentezine and the 3-(2-chloro-4-hydroxyphenyl)-6-(2-chlorophenyl)-1,2,4,5-tetrazine metabolite in or on the food commodities of cattle, goat, hog, horse, and sheep. The tolerance level established in the fat, meat, and meat byproducts (except liver) of these livestock animals is 0.05 ppm, the tolerance established in liver is 0.4 ppm, and the tolerance in milk is 0.01 ppm).

Section 8. Overall Conclusions

HED does not believe that new data are needed for registration review and that existing dietary risk assessments will support registration review, but new occupational assessments will be required. The recent risk assessment in support of the new uses includes a comprehensive assessment of aggregate exposure and no risks of concern were identified. Occupational assessments have never been conducted for several scenarios including: handler dermal and inhalation assessments for Christmas trees and ornamentals (greenhouse and outdoor) which were not previously assessed; handler inhalation assessments for almonds, apples, apricots, cherries, grapes, nectarines, peaches, pears, persimmons, and walnuts based on use patterns (airblast equipment); and a postapplication assessment for ornamentals. These assessments should be conducted during registration review.

Section 9. Reference Memoranda

The memoranda listed in Table 9.1 were considered in the development of this document.

Table 9.1. HED Memoranda Relevant to Registration Review

Author	Barcode	Date	Title
Jen Tyler	283816	1/04/05	Clofentezine in/on Grapes, Persimmons, Almonds (Label Amendment), and Stone Fruit (Label Amendment).
Dana Vogel	252864	2/18/99	Occupational and Residential Exposure and Risk Assessment/Characterization for Clofentezine.
FQPA Safety Factor Committee	TXR 013226	2/18/99	Clofentezine [Apollo]: Report of the FQPA Safety Factor Committee
HIARC	TXR 013084	1/8/99	Clofentezine [Apollo]: Report of the Hazard Identification Assessment Review Committee
Albin Kocialski	TXR 013002	12/3/98	Clofentezine (Apollo) Qualitative Risk Assessment (Q_1*) based on Crl:CD Sprague-Dawley BR Rat Chronic Dietary Study w/ ¾'s Interspecies Scaling Factor

V. GLOSSARY of TERMS and ABBREVIATIONS

ai	Active Ingredient
AR	Anticipated Residue
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.

MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24©) of FIFRA)
TGAI	Technical Grade Active Ingredient
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard

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