Hexythiazox Summary Document: Registration Review

January 2007

Docket Number: EPA-HQ-OPP-2006-0114
www.regulations.gov

Hexythiazox Summary Document
Registration Review Docket
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I. Preliminary Work Plan

Introduction:

The Food Quality Protection Act of 1996 mandated a new program: registration review. All pesticides distributed and sold in the United States must first be registered by EPA, based on scientific data showing that they do not pose 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 registration review program, the Agency will periodically reevaluate 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 will review each registered pesticide approximately every 15 years to determine whether it continues to meet the 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, data, or information it believes are needed to make a registration review decision. Hexythiazox is one of the first chemicals going through the registration review process.

Anticipated Risk Assessment and Data Needs:

The Agency anticipates conducting a comprehensive ecological risk assessment, including an endangered species assessment for all uses, and that additional ecological data will be needed for registration review. However, the Agency does not anticipate that any additional human health risk assessments or related data will be needed.

Ecological Risk:

- Although ecological risk assessments for most hexythiazox uses were completed in 2005, the Agency has not conducted a risk assessment which 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:
    - Estuarine/Marine Invertebrate, Acute (72-3c)
    - Estuarine/Marine Invertebrate Life-cycle (72-4b)

Human Health Risk:

- The Agency believes that previously completed dietary assessments are adequate and that there is no dietary risk that exceeds the Agency's level of concern (LOC); thus, no additional data are needed. Please refer to Section IV of this document, Human Health Effects Scoping Document, for a detailed discussion of the human health risk assessments.

Timeline:
EPA has created the following estimated timeline for the completion of the hexythiazox registration review.

Activities	Estimated Month/Year
Phase 1: Opening the docket	
Open Public Comment Period for Hexythiazox Docket	January 2007
Close Public Comment Period	May 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	July 2007
Issue DCI	March 2008
Data Submission	March 2010
Open Public Comment Period for Preliminary Risk Assessments	July 2011
Close Public Comment Period	September 2011
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	December 2011
Close Public Comment Period	February 2012
Final Decision and Begin Post-Decision Follow-up	June 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 hexythiazox 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 levels (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.

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

1. What is the frequency of application, application intervals, and maximum number of applications per season for use sites for which you have experience or knowledge?
2. What is the application timing, such as season and time of day for use sites?
3. Do you know of any emerging equipment or cultural practices that could reduce hexythiazox exposure to workers or the environment?
4. Hexythiazox is not identified as causes of impairment for any water bodies 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 water quality data for this chemical. To the extent possible, data should conform to the quality standards in Appendix A of the "OPP Standard Operating Procedure: Inclusion of Water Quality & Impaired Water Body Data in OPP's Registration Review Risk Assessment & Management Process", included in the hexythiazox docket, in order to insure that they can be used quantitatively or qualitatively in pesticide risk assessments.

Growers and other stakeholders with more detailed hexythiazox use information are asked to provide information addressing the "Other Information Needs" in Section III—Ecological Risk Assessment Problem Formulation, p.27.

Next Steps:

After the comment period closes in early May of 2007, the Agency will issue a Final Work Plan for this pesticide.

II. FACT SHEET

Background Information:

- Hexythiazox Registration Review case number: 7404
- Hexythiazox PC Code: 128849/ CAS#: 78587-05-0
- Technical registrant: Gowan Company
- First approved for use in a registered product in 1989
- There are seven FIFRA Section 3 active registrations for hexythiazox
- Not subject to reregistration; thus, no Reregistration Eligibility Decision (RED) was prepared
- Chemical Review Manager: Molly Clayton: clayton.molly@epa.gov
- Product Manager: George LaRocca: larocca.george@epa.gov

Use and Usage Information:

- Hexythiazox is an ovacide (kills mite eggs) used on a variety of crops, such as citrus, grapes, pome fruit, hops, strawberries, and dates.
- Hexythiazox is formulated as a wettable powder, emulsifiable concentrate, and dry flowable.
- Pests controlled include tetranychid mites.
- The crops with the highest average percent crop treated are hops at 60%, strawberries at 25%, and dates at 10%. For all other crops, percent crop treated is less than 5%.
- Less than 12,500 pounds of hexythiazox are used annually.
- Use information, such as application rates and number of applications, is found in Appendix A in the docket.

Recent Regulatory Actions:

- A final rule for hexythiazox was issued on 3/22/06 (71 FR 14409) which established tolerances on *grapes; fruit, citrus group 10; apple, wet pomace; citrus, dried pulp; citrus, oil; fruit, pome, group 11;* and animal byproducts (e.g. *sheep, meat byproducts*, etc.)
- A final rule for hexythiazox was issued on 11/10/04 (69 FR 65073) which established time-limited FIFRA Section 18 tolerances on *corn, field, grain; corn, field, stover;* and *corn, field, fodder*.
- A final rule for hexythiazox was issued on 3/5/03 (68 FR 10370) which established a tolerance on *date, dried fruit.*
- A final rule for hexythiazox was issued on 4/18/01 (66 FR 19879) which established tolerances on *plum; plum, prune, dried; plum, prune, fresh; peppermint, tops; spearmint, tops; caneberry crop subgroup; nut, tree, group;* and *pistachio*.
- Tolerances established prior to August 1998 were reassessed on 10/16/98 (63FR 55547) as part of the consideration for establishing a tolerance on *hops.*
- Pending actions include:
    - Pending new use on turf, both commercial and residential (commercial applicators only).

  - Pending new residential uses (commercial applicators only) on caneberries, pome fruit, stone fruit, and nut trees (these uses are currently registered in commercial plantings only).
  - Petition to establish regional tolerances and FIFRA Section 3 registration for use on field corn. (EPA Registration No. 10163-277)
- There is an emergency exemption approved for hexythiazox use on field corn in Texas for mite treatments, which expires 12/31/2007.

Ecological and Environmental Fate Risk Assessment Status:

- The most recent environmental fate and ecological risk assessments were conducted on 10/6/05 for FIFRA Section 3 registrations for use on corn, and 8/2/05 for FIFRA Section 3 registrations for use on grapes, citrus, indoor greenhouse use on tomatoes, and apples. The 8/2/05 assessment considered the risks from all existing hexythiazox uses at the time.
- Based on all available data and the expected exposures, hexythiazox poses little acute risk to freshwater fish, freshwater invertebrates, birds and mammals, and does not pose a chronic risk to freshwater invertebrates and mammals.
- The following have not been assessed by the Agency due to a lack of data: potential acute and chronic risk to estuarine organisms, risk to aquatic and terrestrial plants, chronic risks to freshwater fish, and chronic risk to birds.

Human Health Risk Assessment Status:

- The most recent acute and chronic dietary assessments, conducted on 7/06/05, was an unrefined aggregate assessment, which considered exposure to hexythiazox from both food and drinking water. The risk assessments evaluated exposures from hexythiazox use on pome fruit, citrus, and grapes. The concentrations of both hexythiazox and its major degradate forms were modeled assuming the highest registered/proposed application rate.
- Risk assessments were completed on 11/18/02 for use on dates and 2/22/01 for use on caneberries, mint, tree nuts, pistachios, and stone fruit.
- There are no dietary risks that exceed the Agency's LOC.

Tolerances:

- There are 29 U.S. tolerances listed under 40 CFR 180.448.
- MRLs for hexythiazox have been established by Codex for apple, strawberry, cherry, peach, and plum.
- Please refer to Section IV of this document, HED Scoping Document, for a listing of tolerance levels and MRLs.

Data Call-In Status:

- There have been no previous data call-ins issued for hexythiazox.

Labels:

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

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

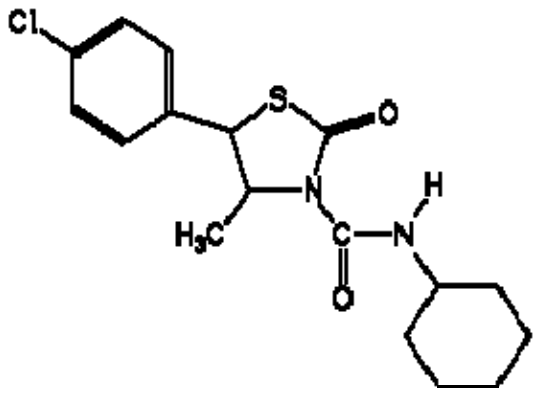
REGISTRATION REVIEW

ECOLOGICAL RISK ASSESSMENT PROBLEM FORMULATION FOR:

HEXYTHIAZOX

PC Code: 128849

(5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-3-thiazolidenecarboxamide)



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STRESSOR SOURCE AND DISTRIBUTION

Hexythiazox (5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-3-thiazolidenecarboxamide) (DPX-Y5893) is an acaricide used for control of mites on plants (CAS No.: 78587-05-0). Specifically, hexythiazox is an ovicide whose mode of action is unknown but is used for the control of mite growth through activity on eggs or early stages of development. Hexythiazox is used on major crops such as pear, apple, citrus, tree nuts, stone fruits, caneberries, pome fruits, non-bearing trees & vines, strawberries, cotton, hops, mint, ornamental landscape plantings, orchids, and alfalfa. Hexythiazox is typically applied to bare roots, to containerized stock, used on dormant stock, to foliar stock, to nonbearing stock and to nursery stock. Hexythiazox is formulated as a wettable powder (WP) and an emulsifiable concentrate (EC). Hexythiazox is typically applied by ground equipment and aerial applications. Most crop applications are 0.1875 lbs ai/A once per season. The current registrant is Gowan Company.

INTEGRATION OF AVAILABLE INFORMATION

The last risk assessment available in the docket and which serves as the basis for this problem formulation is:

- 2005 assessments of newly proposed uses:
  Grapes, Citrus, Corn and Indoor Greenhouse Use on Tomatoes (DP Barcode D313192 et al., document dated 8/2/2005)

ECOLOGICAL EFFECTS

TOXICITY STUDIES

Hexythiazox is practically nontoxic on an acute basis. The bobwhite acute LD50 is >2,5100mg/Kg while the mallard and bobwhite LC50's were >5,620 ppm. However, no avian reproduction studies were reviewed. Hexythiazox is also practically nontoxic to small mammals (LD50 >5000 mg/kg, reproductive NOAEL ≥ 2400 ppm laboratory rat, acute and two generation), and beneficial insects (honey bee topical LD50 >200 µg/bee; LC50 >1000 ppm for honey bees exposed to treated filter paper).

Hexythiazox is acutely highly toxic to freshwater species. The LC50 for bluegill is 0.53 ppm and the EC50 for Daphnia is 0.74 ppm. In a supplemental chronic life-cycle test, exposure to technical hexythiazox adversely affected survival in daphnia (NOAEC = 6.1 ppb and LOAEC = 12.7 ppb). No terrestrial or aquatic chronic or plant toxicity data were submitted.

INCIDENT REPORTS

The Agency's Ecological Incident Information System (EIIS) does not contain any reports of damage or adverse effects to non-target organisms attributed to the use of Hexythiazox. No incidents of contamination of surface, ground and drinking water have been reported to the Agency. A lack of reported incidents does not necessarily mean that such incidents have not

occurred. In addition, incident reports for non-target plants and animals typically provide information on mortality events only. Reports for other adverse effects, such as reduced growth or impaired reproduction, are rarely received.

EXPOSURE CHARACTERISTICS

Environmental Fate

Hexythiazox has six major metabolites that are of environmental significance (see Figure 1 for chemical names and structures). Each of these major metabolites is structurally very similar to parent hexythiazox with only minor alterations. Since most of the degradates were very similar to the parent, total toxic residue half lives were estimated for each pathway. All degradates were identified in aerobic soil metabolism, anaerobic aquatic, and aqueous photolysis studies.

In aqueous solutions hexythiazox is hydrolytically stable at pH 5 to 9 and is moderately persistent when exposed to light. The predicted environmental photolytic half-life was calculated to be 24.6 days for the total toxic residues (16.6 days for parent only). Photolytic degradation on soil surfaces does not significantly contribute to the dissipation of hexythiazox in the environment (parent half-life of 116 days). In aerobic soil metabolism studies parent hexythiazox half-lives ranged from 8 to 25 days depending on soil type. A total toxic residue half-life was estimated to be about 41 days in aerobic soil. Under laboratory anaerobic aquatic conditions (no aerobic aquatic data were available), a whole system half life for parent hexythiazox was reported to be 120 days; a total toxic residue half-life could not be calculated. Under field conditions, hexythiazox dissipated with reported parent compound half lives of 5 to 26 days (total toxic residue half-lives are not available). In summary, degradation is most rapid (half-lives of a few weeks or less) in aerobic soil and in water when the presence of sunlight enables photolysis.

Hexythiazox is a relatively non-volatile compound with a vapor pressure of 2.54×10^{-8} mmHg at 20 C. Hexythiazox has low solubility in water (reported as 0.5 or 1.2 ug/L).

Batch equilibrium studies for hexythiazox resulted in K_d values of 15.8, 30.0, 31.9, and 63.3 and with corresponding K_{oc} values of 2589, 3234, 5747, and 13621. No measurements of adsorption / desorption are available for hexythiazox degradates; however, there is no reason to believe, based on structural similarities, that soil sorption behavior would be dramatically different from parent hexythiazox for any of the degradates of concern.

Hexythiazox has moderate bioaccumulation potential. Hexythiazox has peak bioconcentration factors (BCF) of 300-510x in muscle, 550-750x in remaining carcass, 1000-1600 in whole fish, and 12900-17500 in viscera. The BCF factor, if stable, would suggest potential for impacts on higher trophic level species which rely on fish for food. Hexythiazox was metabolized to compounds not of concern in the fish (only 6 to 12% and 7 to 38% remained as residues of concern in the viscera and muscle, respectively after 28 days of continuous exposure). Furthermore, depuration was nearly complete within 14 days of withdrawal of exposure to

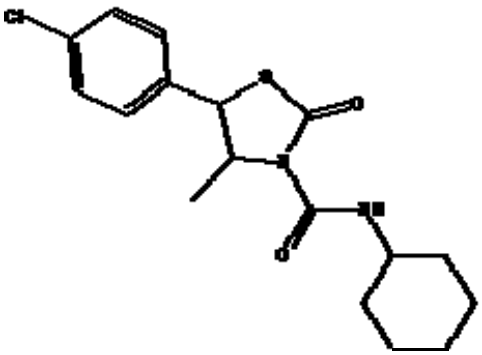
hexythiazox (42 days total after the exposure was initiated) – 92 to 97% of accumulated radioactivity was removed from the whole fish. Taking into account the results of the laboratory fate and field dissipation studies, it does not appear hexythiazox will leach in the environment, though it could be transported to surface water through erosion of soil particles containing bound hexythiazox and via spray drift.

The Agency and international community (LRTAP and POPs) generally consider a chemical persistent and bioaccumulative if its half-life is >2 months to >6 months in soil/sediment, >2 months in water, and its bioconcentration / bioaccumulation factor (BCF/BAF) is >1000 to >5000 mL/g. Hexythiazox and each of its degradates of concern do not clearly meet either of these criteria:

- Hexythiazox bioaccumulation peaks (but is not sustained) barely above the minimum threshold
- Persistence criteria are not met in all media, and only when considering the total residues as one compound (instead of 7 different ones) are the persistence criteria even met for some water (anaerobic) systems.

Furthermore, the rapid depuration observed indicates long-term exposure to fish would be minimal.

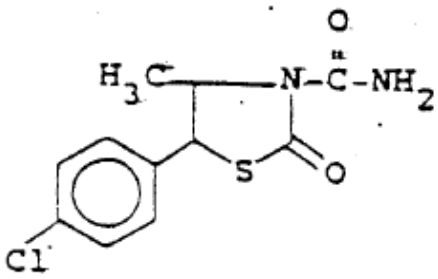
Figure 1. Chemical structures of hexythiazox and its major metabolites.



Parent Hexythiazox
5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-3-thiazolidenecarboxamide (DPX-Y5893)

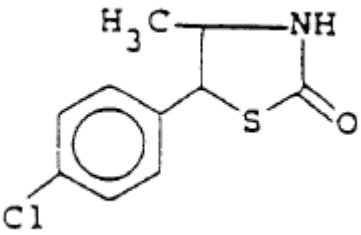
Degradates of concern:

1



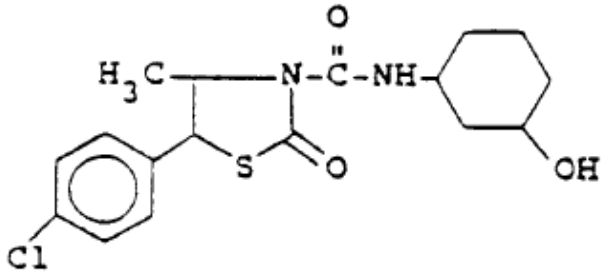
5-(4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-2**)

2



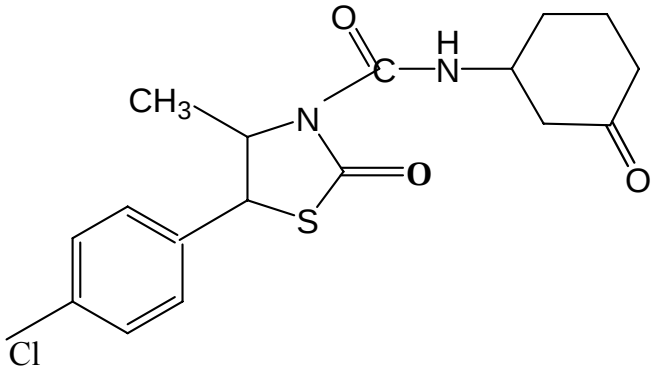
5-(4-chlorophenyl)-4-methyl-2-thiazolidenone (**PT-1-3**)

3



5-(4-chlorophenyl)-N-(3-hydroxycylohexyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-4**) Cis- and trans- forms.

4



5-(4-chlorophenyl)-4-methyl-2-oxo-N-(3-oxocyclohexyl)-3-thiazolidenecarboxamide (**PT-1-5**)

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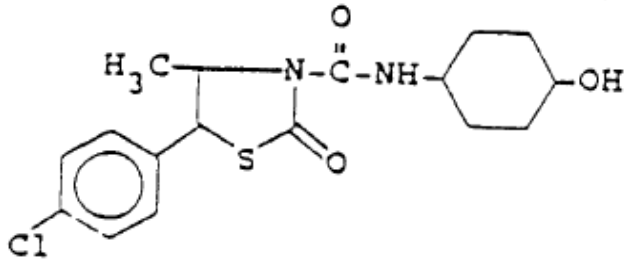
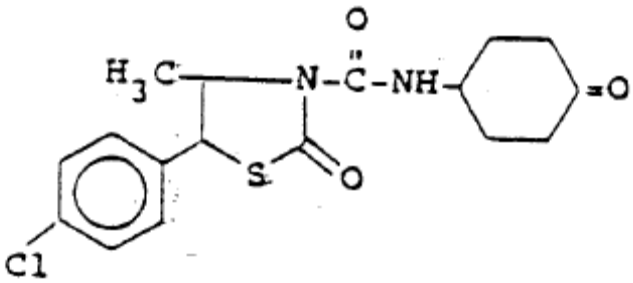
	
5-(4-chlorophenyl)-N-(4-hydroxycyclohexyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-8**) Cis- and trans- forms	5-(4-chlorophenyl)-N-(4-hydroxycyclohexyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-8**) Cis- and trans- forms

Modeling: Exposure Estimates

Since environmental fate data has not been submitted which would allow specific modeling for any of the degradates, EFED has completed a total residue exposure assessment covering currently registered uses. This total residue approach entails revisiting each relevant environmental fate study (hydrolysis, aqueous photolysis, aerobic soil metabolism, etc.) and summing the parent and degradates identified above which are present in each study at each time interval. The summed parent plus degradates concentration (or percent applied) is used to recalculate the rate constant and half life for each study. The total residue half lives are then used within PRZM/EXAMS in accordance with EFED's current guidance for establishing model inputs and generating aquatic EECS. Based on modeling results, the estimated environmental concentrations for aquatic exposure to hexythiazox plus all degradates of toxicological concern are:

4.1 ug/L for the 1 in 10 year annual peak concentration
3.3 ug/L for the 21-day average concentration, and
2.7 ug/L for the 60-day average concentration

The maximum 1 in 10 year annual peak aggregate, 1 in 10 year 21-day mean, and 1 in 10 year 60-day mean aggregate concentrations result from modeling hexythiazox plus all degradates of toxicological concern are used on corn in Texas.

CHARACTERISTICS OF ECOSYSTEMS POTENTIALLY AT RISK

For hexythiazox and pesticides in general, the ecosystems at greatest risk are those in close proximity to the use areas. These would include agricultural fields (surrounding non-agricultural terrestrial habitats) and water bodies directly adjacent to treated fields that may receive chemical residues via drift, volatilization, and/or runoff. Within water bodies, the water column, sediments, and pore water are all compartments of concern. Table 1 summarizes the agricultural use sites that hexythiazox is reported to be used on, the annual percent of crop treated (average and maximum) for each crop, and average annual pounds of hexythiazox applied for each crop. Based on these estimates, the sites where the majority of hexythiazox is currently used include

strawberries, hops, apples, pears and peaches. These crops cover a large portion of the U.S. and a wide diversity of terrestrial and aquatic environments.

There are no organisms of concern where data were available to assess risk.

Table 1. Screening level estimates of agricultural uses of hexythiazox

(Sorted Alphabetically)

	Crop	Lbs. A. I.	Percent Crop Ttd.	
			Avg.	Max.
1	Almonds *	<500	<1	<2.5
2	Apples	1,000	<1	5
3	Apricots	<500	5	5
4	Cherries	<500	<1	<2.5
5	Dates	<500	10	10
6	Hops (NCFAP '97)	2,000	60	--
7	Nectarines *	<500	5	5
8	Peaches	1,000	5	5
9	Pears	1,000	5	15
10	Prunes & Plums *	<500	<1	<2.5
11	Strawberries	4,000	25	30
12	Walnuts	<500	<1	<2.5

All numbers rounded.
<500 indicates less than 500 pounds of active ingredient.
<2.5 indicates less than 2.5 percent of crop is treated.
<1 indicates less than 1 percent of crop is treated.
* CA data only, but 95% or more of U.S. acres are in California

ASSESSMENT ENDPOINTS

Assessment endpoints are defined as "explicit expressions of the actual environmental value that is to be protected." Defining an assessment endpoint involves two steps: 1) identifying the valued attributes of the environment that are considered to be at risk; and 2) operationally defining the assessment endpoint in terms of an ecological entity (i.e., a community of fish and aquatic invertebrates) and its attributes (i.e., survival and reproduction). Therefore, selection of the assessment endpoints is based on valued entities (i.e., ecological receptors), the ecosystems potentially at risk, the migration pathways of pesticides, and the routes by which ecological receptors are exposed to pesticide-related contamination. The selection of clearly defined assessment endpoints is important because they provide direction and boundaries in the risk assessment for addressing risk management issues of concern. Changes to assessment endpoints are typically estimated from the available toxicity studies, which are used as the measures of effects to characterize potential ecological risks associated with exposure to a pesticide, such as hexythiazox.

To estimate exposure concentrations, the ecological risk assessment considers a single application at the maximum application rate to fields that have vulnerable soils. The most

sensitive toxicity endpoints are used from surrogate test species to estimate treatment-related direct effects on acute mortality and chronic reproductive, growth and survival assessment endpoints. Toxicity tests are intended to determine effects of pesticide exposure on birds, mammals, fish, terrestrial and aquatic invertebrates, and plants. These tests include short-term acute, sub-acute, and reproduction studies and are typically arranged in a hierarchical or tiered system that progresses from basic laboratory tests to applied field studies. The toxicity studies are used to evaluate the potential of a pesticide to cause adverse effects, to determine whether further testing is required, and to determine the need for precautionary label statements to minimize the potential adverse effects to non-target animals and plants.

CONCEPTUAL MODEL

In order for a chemical to pose an ecological risk, it must reach ecological receptors in biologically significant concentrations. An exposure pathway is the means by which a pesticide moves in the environment from a source to an ecological receptor. For an ecological exposure pathway to be complete, it must have a source, a release mechanism, an environmental transport medium, a point of exposure for ecological receptors, and a feasible route of exposure.

The conceptual model (Figure 2) depicts the potential ecological pathways for exposure associated with hexythiazox use. The conceptual model provides an overview of the expected exposure routes for organisms within the hexythiazox action area. For terrestrial organisms, the major route of exposure considered is the dietary route; consumption of food items such as plant leaves or insects that have hexythiazox residues as a result of spraying, drift, and volatilization. For aquatic animal species, the major routes of exposure are considered to be via the respiratory surface (gills) or the integument. For plants, direct exposure to foliage and root uptake are the main routes of exposure. Estimated exposure concentrations for all organisms are obtained through the use of several Agency exposure models.

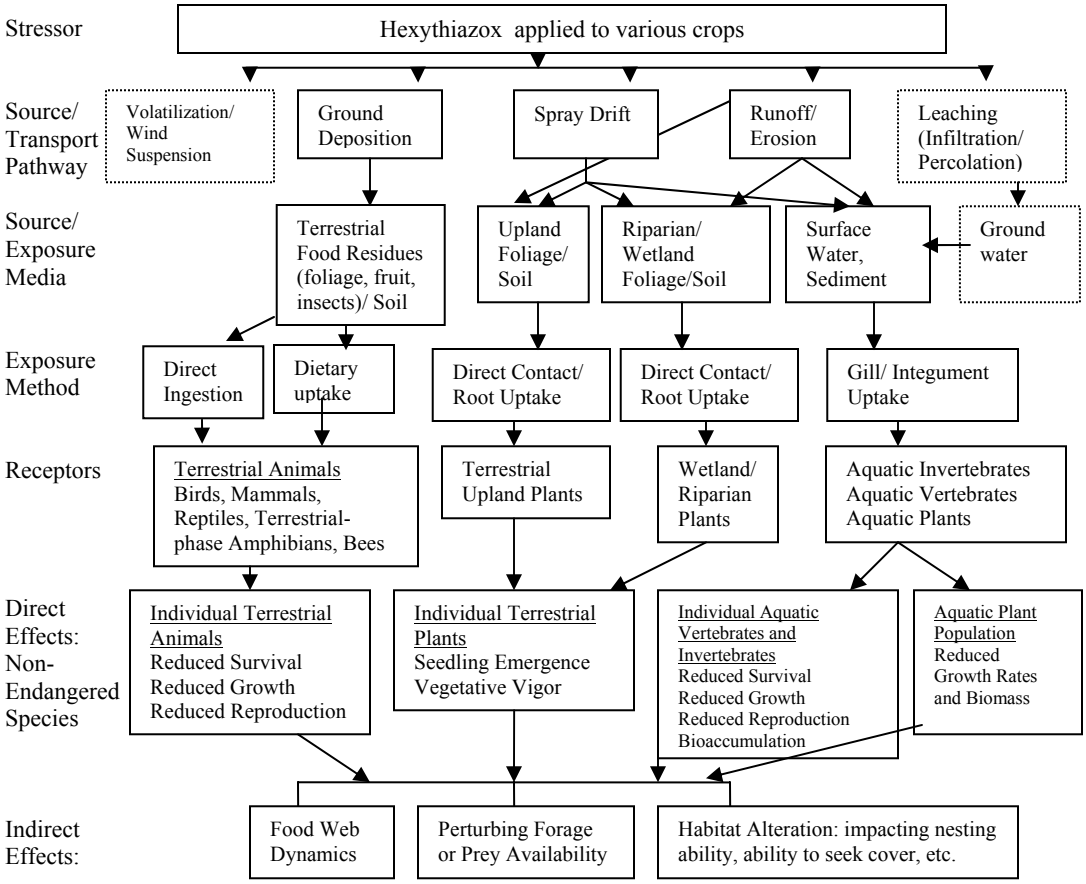


Figure 2. Conceptual Model depicting possible ecological pathways.

RISK HYPOTHESIS

Based on an examination of the physical/chemical properties of hexythiazox, the fate and disposition in the environment, and mode of application, a conceptual model was developed that represents the possible relationships between the stressor, ecological receptors, and the assessment endpoints. A major transport pathway for hexythiazox is spray drift and erosion, resulting in possible exposure to various aquatic receptors.

ANALYSIS PLAN OPTIONS

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.

Measures of Exposure

The measures of exposure will be estimated using models. Aquatic exposure will consist of aquatic EECs based on a total residue approach and 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 will be estimated using a model that assumes hexythiazox drifts or moves with runoff to adjacent habitats.

Measures of Effect

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.

Preliminary Identification of Information Needs

Table 2 identifies: 1) studies that are missing or unacceptable, but that are normally available to derive toxicity results used to assess risk to the environment, and 2) anticipated LOC exceedances based on previous risk assessments. An evaluation of the uncertainty that each of these data gaps introduces to ecological risk assessment is discussed below.

Table 2. Preliminary Identification of Data Gaps/Anticipated LOC Exceedances.

Taxa	Acute Risk	Chronic Risk
Freshwater Fish	No Exceedance	No data
Saltwater Fish	No data	No data
Freshwater Invertebrates	No Exceedance	No Exceedance
Saltwater Invertebrates	No data	No data
Terrestrial (bees) Invertebrates	No Exceedance	N/A
Birds	No Exceedance	No data
Terrestrial and Aquatic Plants	No data	N/A

N/A = Not applicable.

Additionally, a battery of fate and effects studies for Hexythiazox major degradates of environmental significance had been preliminarily identified as data gaps, see below.

Status of Data Requirements

Fate

Data is available for Hexythiazox; however, Hexythiazox has six major metabolites that are of environmental significance for which there is no data (other than secondary formation and decline data from some studies with hexythiazox). Each of theses major metabolite is structurally very similar to parent hexythiazox. In the previous ecological risk assessment EECs were estimated using the total residue method and no LOCs were exceeded. Therefore, additional fate studies are not required at this time to complete a screening-level ecological risk assessment.

Effects

A number of toxicity data gaps have been identified for Hexythiazox. Table 3 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 based on current application rate and number of applications and is made on a case-by-case basis.

Table 3. Evaluation of the need for additional effects data on hexythiazox

Assessment endpoint with data gap	Chemical	Projected status of data gap	Basis for decision
Survival, estuarine/marine invertebrate acute study (72-3c) with mysid	Hexythiazox	**Proposed to request study**	Currently there is no data available on any estuarine/marine species. The use area may be in proximity to estuarine/marine habitats. Hexythiazox is highly toxic to freshwater aquatic invertebrates (daphnid EC 50 = 0.74 ppm; chronic NOAEC = 6.1 ppb). If there is a 10 fold difference in species sensitivity (which is possible) the LOCs would be exceeded. Additionally, the values from this study will be needed to determine test concentrations for a Mysid chronic study.
Reproduction, estuarine/marine invertebrate life-cycle study (72-4b)	Hexythiazox	**Proposed to request study**	Currently there is no data available on any estuarine/marine species. The use area may be in proximity to estuarine/marine habitats. Hexythiazox is highly toxic to freshwater aquatic invertebrates (daphnid EC 50 = 0.74 ppm; chronic NOAEC = 6.1 ppb). RQ derived from daphnid chronic is close to chronic level of concern.
Survival, estuarine/marine mollusk LC 50 study (72-3b)	Hexythiazox	Study **not** requested at this time	Although Hexythiazox is highly toxic to freshwater invertebrates (daphnid EC 50 = 0.74ppm) the mysid shrimp study is being requested and there is no evidence to suggest that a mollusk specific mechanism of action (effect on calcium uptake) is present; additionally, it is seldom that the mollusk is a more sensitive species than the mysid shrimp.
Survival, estuarine/marine fish LC 50 study (72-3a)	Hexythiazox	Study **not** requested at this time	Although Hexythiazox is acutely highly toxic to freshwater fish (bluegill sunfish LC 50 0.53ppm), because of the low use rates, the fish acute RQ is less than 0.01.

Reproduction, fish early life stage and full life-cycle studies (72-4 and 72-5)	Hexythiazox	Study **not** requested at this time	Comparison of the lowest LC 50 (530 ppb) to the 21-day EEC (4.1ppb) suggests that hexythiazox would need to be more than 160 times more toxic on a chronic basis compared with its acute toxicity to result in chronic LOC exceedances. Additionally, there is no indication of adverse reproductive effects in other vertebrate reproduction studies (rat 2-generational study).
Reproduction and growth, avian reproduction study (71-4)	Hexythiazox	Study **not** requested at this time	No indication of adverse reproductive effects in other vertebrate reproduction studies (rat 2-generation reproduction study). All avian (avian acute > 2510 mg/kg, avian dietary > 5260 ppm) and mammalian (rat acute oral > 5000 mg/kg) acute data show no effects even at high dose levels. Because of the low use rate the maximum residues on food/feed items is very low (45 ppm). Comparison of the LC 50 >5260 ppm to the estimated exposure (maximum residues on food/feed items 45 ppm) suggests that hexythiazox would need to be more than 117 times more toxic on a chronic basis relative to its acute toxicity to result in LOC exceedances
Maintenance and growth of aquatic plants (aquatic non-vascular plant study 122-3) and perpetuation of non-target terrestrial plants (vegetative vigor and seedling emergence 122-1a and 122-1b)	Hexithiazox	Study **not** requested at this time	Hexythiazox 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.

Battery of ecological studies	5-(4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-2**), 5-(4-chlorophenyl)-4-methyl-2-thiazolidenone (**PT-1-3**), 5-(4-chlorophenyl)-4-methyl-2-oxo-N-(4-oxocyclohexyl)-3-thiazolidenecarboxamide (**PT-1-9**), 5-(4-chlorophenyl)-4-methyl-2-oxo-N-(3-oxocyclohexyl)-3-thiazolidenecarboxamide (**PT-1-5**), 5-(4-chlorophenyl)-N-(4-hydroxycyclohexyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-8**) Cis- and trans- forms, 5-(4-chlorophenyl)-N-(4-hydroxycyclohexyl)-4-methyl-2-oxo-3-thiazolidenecarboxamide (**PT-1-8**) Cis- and trans- forms	Study **not** requested at this time	EECs were estimated using the total residue method. Total residue method was used because of the structural similarities of the degradates to the parent. Degradates were included in the ecological risk assessment using a total residue exposure approach and no LOCs were exceeded.

As noted in Table 3, 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 to support the current uses:

Estuarine/Marine Invertebrate, Acute (72-3c)
Estuarine/Marine Invertebrate Life-cycle (72-4b)

Without the data we are proposing be requested, ecological risk assessment would be highly uncertain. Submission of other studies to fulfill data gaps identified in Table 3 as not being essential to support current uses would reduce uncertainty, however, analysis of available results from already conducted studies indicates a low probability of identifying concerns if these studies were to be conducted to support the current uses.

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. Also, results of a search from the open literature could potentially provide more sensitive endpoints or data for which there are currently no endpoints available. 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.

Endangered Species Considerations

In Registration Review, pesticide ecological risk assessments will follow the Agency's Guidelines for Ecological Risk Assessment, will be in compliance with the Agency's Overview Document ("Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency" (January 2004)), and will address Endangered Species Act, Section 7 (a)(2) obligations.

Although the previously completed screening level risk assessments indicate that there are no acute endangered species LOC exceedences for birds, mammals, freshwater fish and invertebrate No Effect determinations can not be made at this time since the previous risk assessment was not conducted consistent with the methodology discussed in the Overview Document. The Overview Document issued in 2004 outlines a risk assessment methodology the US Fish and Wildlife Service (USFWS) and National Marine Fisheries Service (NMFS) believe will produce effect determinations consistent with the goals of the Endangered Species Act. The Overview Document describes, for example, how EPA will consider public literature, degradates, sublethal effects, etc.

Summary

- While no fate or ecological effects data are available for the degradates, they were assessed together with the parent as total toxic residues. This conservative approach did not result in endangered species LOCs being exceeded.
- Although the screening level assessment of chronic risk to birds had not been completed due to a lack of avian reproduction toxicity studies, EPA will conduct an assessment of this potential risk using other lines of evidence. In the absence of these data EPA will rely on other vertebrate species, avian acute studies and exposure considerations.

- The screening level assessment of acute and chronic risk to some aquatic organisms had not been completed due to a lack of toxicity data. EPA will conduct an assessment of this potential risk using other lines of evidence. In the absence of these data EPA will rely on acute fish toxicity data, acute and chronic freshwater invertebrate data, acute and chronic estuarine/marine invertebrate data which EPA is proposing to request, and exposure considerations.

- Although the screening level assessment of risk to terrestrial and aquatic plants had not been completed due to a lack of plant toxicity data; EPA will conduct an assessment of this potential risk using other lines of evidence. In the absence of these data EPA will rely on an evaluation of incident data, implications regarding the lack of toxicity to multiple crops with registered uses, and any available data the registrant has developed for labeling restrictions for plants.

Detailed Description

- Hexythiazox has six major metabolites that are of environmental significance. Each of these major metabolites is structurally very similar to parent hexythiazox with only minor alterations. These degradates are assessed with the parent as total toxic residues; therefore, EECs were estimated using the total residue method. When the degradates were included in the screening level ecological risk assessment using a total residue exposure approach (which in this case should provide a more conservative or higher estimate than separate evaluations of each compound) no endangered species LOCs were exceeded.

- An assessment of chronic risk to birds has not been completed. While the Agency lacks a chronic reproduction study in avian species, the Agency is not proposing to request this study based on the following information. There was no indication of adverse reproductive effects in other vertebrate reproduction studies (rat 2-generation reproduction study). All of the available avian (avian acute > 2510 mg/kg, avian dietary > 5260 ppm) and mammalian (rat acute oral > 5000 mg/kg) acute data show no effects even at high dose levels. Because of the low use rate the maximum residues on food/feed items is very low (45 ppm). Comparison of the LC 50 >5260 ppm to the estimated exposure (maximum residues on food/feed items 45 ppm) suggests that hexythiazox would need to be more than 117 times more toxic on a chronic basis relative to its acute toxicity to result in LOC exceedances. There is some uncertainty surrounding this estimated value; however, the Agency does not believe a new study would change the overall risk conclusions.

- An assessment of acute and chronic risks to estuarine/marine invertebrates has not been completed due to lack of data. Currently the Agency is proposing to request these data for the following reasons. The current use areas for Hexythiazox may be in proximity to estuarine/marine habitats and there are no data available on any estuarine/marine species. The available data indicate that Hexythiazoxis highly toxic to freshwater aquatic

invertebrates (daphnid EC 50 = 0.74 ppm; chronic NOAEC = 6.1 ppb). If there is a 10 fold difference in species sensitivity, which is possible, the LOCs would be exceeded. RQs derived from the daphnid chronic study results are close to the chronic level of concern.

- An assessment of the acute risks to estuarine/marine mollusks has not been completed. While the Agency lacks data on the acute risks to these mollusks, we are not proposing to request this study based on the following information. Although Hexythiazox is highly toxic to freshwater invertebrates (daphnid EC 50 = 0.74ppm) the mysid shrimp study is being requested and will be utilized in the assessment of risks to mollusks. There is no evidence to suggest that a mollusk specific mechanism of action (effect on calcium uptake) is present. Additionally, it is seldom that the mollusk is a more sensitive species than the mysid shrimp.

-An assessment of acute and chronic risks to estuarine/marine fish has not been completed. While the Agency lacks these data, we are not proposing to request these studies based on the following information. Although Hexythiazox is acutely highly toxic to freshwater fish (bluegill sunfish LC 50 = 0.53ppm), because of the low use rates, the fish acute RQ is less than 0.01. With regard to the chronic studies, a comparison of the lowest LC 50 (530 ppb) to the 21-day EEC (4.1ppb) suggests that hexythiazox would need to be more than 160 times more toxic on a chronic basis compared with its acute toxicity to result in chronic LOC exceedances. Additionally, there is no indication of adverse reproductive effects in other vertebrate reproduction studies (rat 2-generational reproduction study).

- A risk assessment for aquatic and terrestrial plants has not been completed. While these data are lacking, we do not propose to request these studies based on the following information. Hexythiazox 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.

Path Forward

The planned ecological risk assessment will evaluate the lines of evidence and make a determination of potential effects to endangered species. If the planned ecological risk assessment indicates that hexythiazox may affect, either directly or indirectly, listed species or affect critical habitat, the Agency will take steps to refine the assessment to determine whether this pesticide's uses are likely to adversely affect, or are not likely to adversely affect the species. In the case of critical habitat, the Agency will assess whether use of the pesticide may destroy or adversely modify any principle constituent elements for the critical habitat.

If the Agency's assessment results in a determination that the pesticide may affect but is not likely to adversely affect a listed species or designated critical habitat, the Agency will request concurrence by the USFWS and NMFS (Services) on that determination. If the Services do not concur, the Agency will enter into Formal Consultation with them under the Endangered Species

Act. If the Agency's assessment results in a determination that the pesticide is likely to adversely affect a listed species or designated critical habitat, the Agency will initiate Formal Consultation with the Services. Formal Consultation concludes with issuance of a Biological Opinion to the Agency. The Agency may seek to change the terms of registration to address unacceptable risks to a listed species should EPA determine such risks exist.

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:

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 not already reported to the Agency
12. monitoring data

The analysis plan will be revisited and may be revised depending upon the data available in the open literature and the information submitted by the public in response to the opening of the Registration Review docket.

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 Hexythiazox is recommended to be assigned to Bin 1. The new assessments are needed because:

a) Previous assessments did not include risk to birds and aquatic organisms
b) Previous assessments did not comply with the Overview Document
c) 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 on currently registered use rates.

IV. HUMAN HEALTH EFFECTS SCOPING DOCUMENT

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 19, 2006

MEMORANDUM

SUBJECT: Hexythiazox: HED Registration Review Scoping Document.
PC Code: 128849, DP Barcode: D335052.

FROM: Toiya Goodlow, Chemist
Whang Phang, Ph.D., Toxicologist
Reregistration Branch 1
Health Effects Division (7509P)

THROUGH: Michael S. Metzger, Branch Chief
Reregistration Branch 1
Health Effects Division (7509C)

TO: Molly Clayton, Chemical Review Manager
Special Review and Reregistration Division (7508C)

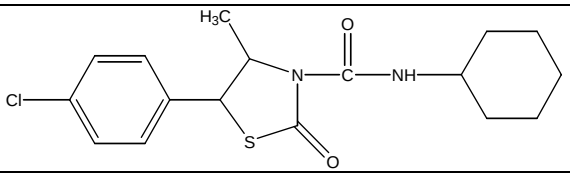
Attached is the Health Effects Division chapter of the hexythiazox scoping document. This document was written to support the registration review of hexythiazox.

Introduction

The HED Hexythiazox Registration Review Team has evaluated the human health assessments for the ovicide hexythiazox to determine the scope of work necessary to support the registration review. The team considered the current use profile and the toxicity and exposure databases for hexythiazox. The primary sources for the status update were the three most recent risk assessments (February 22, 2001; November 18, 2002 and July 6, 2005) and the HIARC report (December 16, 1999). A screening search of the open literature was performed using TOXNET and PubMed of the U.S. National Library of Medicine; however, no data was found related to the effects of hexythiazox on human health. The purpose of this screen is to determine whether sufficient data are available and whether a new human health risk assessment is needed to support registration review. A comprehensive listing of the documents considered is presented in Section 9 of this document. The HED Registration Review team includes Toiya Goodlow, Whang Phang and Michael Metzger.

Hexythiazox is currently registered for use on a variety of crops such as citrus, grapes, pome fruit, hops, strawberries and dates. Tolerances are established in 40 CFR 180.448 for these commodities. Time limited tolerances are established for field corn (grain, forage, and stover), which expire December 31, 2007. There are currently no residential uses of hexythiazox. However, the registrant is proposing new residential uses on caneberries, pome fruit, stone fruit and nut trees. There is also a pending action for the Section 3 registration of field corn.

Section 2. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Hexythiazox
IUPAC name	(4RS,5RS)-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-1,3-thiazolidine-3-carboxamide
CAS name	trans-5-(4-chlorophenyl)-N-cyclohexyl-4-methyl-2-oxo-3-thiazolidinecarboxamide
PC Code	128849
CAS registry number	78587-05-0
Registration Review Case No.	7404
Chemical Structure	

Section 3. Toxicology

The toxicity database for hexythiazox is complete. No toxicity studies have been received since the last human health risk assessment (July 2005). The risk assessment team has reevaluated the toxicity endpoints and doses considering current policies on selecting endpoints and uncertainty factors. These conclusions are summarized below.

Cancer classification: The HED Cancer Assessment Review Committee classified hexythiazox as a "possible human carcinogen" in 1988 and established a unit risk of 2.2×10^{-2} based on the increased incidence of liver tumors in female mice. Due to the changes in policy since this 1988 decision, HED plans to reevaluate the cancer classification in order to be consistent with current policy.

Dermal toxicity: In the 2001 HED risk assessment document, a 28-day dermal toxicity was considered as a data gap. After evaluating the entire toxicity database, it was decided that under the current use patterns, conducting another 28-day dermal toxicity study would not provide additional information needed for risk assessment purposes. Therefore, a 28-day dermal toxicity study is not required at this time. HED has sufficient data to access dermal risks. The following discussion supports this conclusion.

In a 90-day feeding study in rats, hexythiazox was found to cause liver, ovarian, and kidney weight increases at a lowest observed adverse effect level (LOAEL) of 38 mg/kg. The no observed adverse effect level (NOAEL) was established at 5.4 mg/kg. If one were to apply this NOAEL for risk assessment for intermediate-term dermal exposure, extrapolating the oral dose to dermal dose using the dermal absorption factor of 2% established from a dermal penetration study, the calculated dermal NOAEL would have been 270 mg/kg. In the unacceptable 28-day dermal toxicity study in rats, only one dose was tested (1000 mg/kg) and caused ovarian weight increase. This was consistent with the effects seen in the 90-day oral toxicity study. Appling a safety factor of 10 for extrapolating the LOAEL (1000 mg/kg from the 28-day dermal toxicity study) to a NOAEL would yield a NOAEL 100 mg/kg for short-term dermal risk assessment. With the current highest dermal exposure value (0.0079 mg/kg) for workers and an extrapolated dermal NOAEL of 100 mg/kg, the calculated MOE would have been 12,658, which was substantially greater than the target MOE (100). This crude analysis indicated there was no real risk concern from dermal exposure with these uses. This analysis was also supported by the finding that the dermal LD_{50} for hexythiazox was >5000 mg/kg.

Inhalation toxicity: The acute inhalation toxicity data indicated that hexythiazox has low acute inhalation toxicity (Tox. Category IV). Currently, the short- term and intermediate- term inhalation risk MOEs ranged from 19,000 to 242,000. Hexythiazox also has a low vapor pressure of 2.3×10^{-8} mm Hg.

FQPA safety factor: The toxicity database required to perform a FQPA assessment is complete. Hexythiazox exhibits no neurotoxicity in the toxicity studies of various durations; therefore, a developmental neurotoxicity study (DNT) is not required. The FQPA Safety factor to account for increased sensitivity of infants and children was reduced to 1x by the FQPA Safety Factor Committee in April 1998 based on the completeness of the data, no indications of susceptibility or sensitivity in developmental and repro studies, and no residual concerns for pre- or postnatal toxicity to infants and children. The Agency believes that, even though policies on determining an appropriate FQPA factor have changed since 1998, that the same conclusion would be reached today, i.e., that there are reliable data to remove the factor.

Tables 2.1 and 2.2 include the toxicity endpoints from the most recent risk assessment. There are no outstanding toxicity studies for hexythiazox, so it is not anticipated that further changes to this profile would be required in registration review for the existing uses.

Table 2.1 Toxicological Doses and Endpoints for Hexythiazox for Use in Dietary and Non-Occupational Human Health Risk Assessments [1]

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary *General Population*	A dose and endpoint attributable to a single exposure were not identified from the available oral toxicity studies, including maternal toxicity in the developmental toxicity studies.			
Acute Dietary *Females 13-49 years of age*	NOAEL = 240 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 2.4 mg/kg/day aPAD = 2.4 mg/kg/day	Developmental Toxicity Study – Rat Developmental LOAEL = 720 mg/kg/day based on delayed ossification.
Chronic Dietary *All Populations*	NOAEL=2.5 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Chronic RfD = 0.025 mg/kg/day cPAD = 0.025 mg/kg/day	One-Year Toxicity Feeding Study - Dog LOAEL = 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology.
Cancer (oral, dermal, inhalation)	Category C (possible human carcinogen)	Q_1* =2.22x10^{-2}		Increases in incidence of malignant and combined benign/malignant liver tumors in female mice.
Endpoints and doses have not been selected for the following scenarios as there are no residential exposures to Hexythiazox: Incidental Oral (Short- and Intermediate-Term), Dermal (Short- and Intermediate-Term), and Inhalation (Short- and Intermediate-Term).				

[1] 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 (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 2.2 Summary of Toxicological Doses and Endpoints for Hexythiazox for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days)[2]	Oral maternal NOAEL = 240 mg/kg/day (dermal absorption rate = 2%)	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Developmental Toxicity Study - Rat LOAEL = 720 mg/kg/day based on decreased maternal body weight gain during gestation days 7-17 and decreased food consumption on gestation days 9-12.
Inhalation Short-Term (1-30 days)[2]	Oral maternal NOAEL= 240 mg/kg/day (inhalation absorption rate = 100%	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Developmental Toxicity Study - Rat LOAEL = 720 mg/kg/day based on decreased maternal body weight gain during gestation days 7-17 and decreased food consumption on gestation days 9-12.
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans at doses that do not cause the biochemical and histopathological changes in the liver of rodents. The chronic endpoint is protective of the carcinogenic effects so a separate cancer assessment is not needed.			

[1] 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 (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[2] HED has revised the definitions used in its human- health risk assessments to describe occupational and residential exposure durations (Memo, M. Stasikowski, 04-JUN-2001, "Changes in the Definition of Exposure Durations for Occupational/Residential Risk Assessments Performed in the Health Effects Division"). The new exposure durations are as follows: 1) short-term, defined as lasting from 1-day to 1 month; 2) intermediate-term, defined as lasting from 1 to 6 months; 3) long-term, defined as lasting longer than 6 months. In this risk assessment, the toxicity endpoints originally selected for hexythiazox for the short-term (1-7 days) dermal and inhalation endpoints are also applicable for the new exposure duration definitions for these routes of exposure.

Section 3. Residue Chemistry

The residue chemistry database is complete, pending the review of the orange processing study submitted November 2006. This study was originally required in the July 2005 risk assessment as a condition of registration. The conclusions from this study were not included in this review. The Agency anticipates no additional human health risk assessment will be required after this data is reviewed, since conservative assumptions were made and default processing factors were incorporated into the previous risk assessment to account for the lack of data.

Section 4. Dietary Exposure

The dietary exposure database is complete. There are adequate residue data on all existing formulations to assess dietary risk. The most recent dietary assessment was performed June 29, 2005. The acute, chronic and cancer analyses incorporated modeled surface water estimates for total hexythiazox residues resulting from the parent compound plus its metabolites containing the (4-clorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety. The surface water estimates were

generated using PRZM/EXAMS. The acute assessment included tolerance level residues and 100% crop treated. The chronic and cancer assessments assumed average/projected percent crop treated estimates, average field trial residues, FDA monitoring data for stone fruit (excluding cherry) and pome fruit, experimentally determined processing factors when available, default processing factors and anticipated livestock residues based on refined dietary burden calculations. For both acute and chronic dietary risks, dietary exposures for food and water were $\leq$ 1% of the population adjusted dose (PAD). The resulting cancer dietary exposure yielded a cancer risk of 2.30×10^{-6} and 2.03×10^{-6} for the U.S. population using DEEM-FCID™ and Lifeline™ exposures models respectively, and are therefore below the Agency's level of concern. It is not expected that new dietary assessments would be required in registration review because the assessments incorporated conservative assumptions and the most recent toxicity information.

Section 5. Aggregate and Cumulative Exposure

There are currently no residential uses of hexythiazox, so the aggregate assessments in the most recent assessment include only food and water. All of the aggregate exposures are below the level of concern. Aggregate tables from the most recent risk assessment using DEEM-FCID™, since this exposure model produces the highest dietary estimates, are provided in Table 5.1 below.

Table 5.1 Summary of Dietary Exposure and Risk for Hexythiazox – Food and Drinking Water

Population Subgroup	Acute Dietary (95th Percentile)		Refined Chronic Dietary		Refined Cancer Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	NA[1]		0.000115	<1	0.000104	2.30×10^{-6}
All Infants (< 1 year old)			0.000217	<1	N/A	N/A
Children 1-2 years old			0.000267	1		
Children 3-5 years old			0.000235	<1		
Children 6-12 years old			0.000144	<1		
Youth 13-19 years old			0.000087	<1		
Adults 20-49 years old			0.000096	<1		
Adults 50+ years old			0.000100	<1		
Females 13-49 years old	0.010176	<1	0.000093	<1		

[1] N/A = Not applicable.

Section 6. Occupational Exposure

The occupational database is complete and all relevant occupational scenarios are assessed for all existing uses. The last risk assessment (July 2005) prior to this review was for use on pome fruit, citrus and grapes. Based on the proposed use (one application per year with ground equipment only), HED anticipates short-term dermal and inhalation exposures to non-commercial handlers. Risks are not anticipated for commercial handlers because this pesticide is typically applied by private pesticide handlers (i.e. grower, farmer). Combined inhalation and dermal MOEs for handlers performing mixing/loading with and without gloves ranged from 48,000-1,300,000 and 19,000-38,000 respectively, and are therefore below the Agency's level of concern. Workers entering treated fields are anticipated to have short-term dermal exposures; intermediate-term dermal exposures are not expected because only one application per year is permitted for hexythiazox. The MOEs for potential post-application exposures range from 25,000-50,000 and are therefore less than the Agency's level of concern. Cancer risk estimates for handlers (with gloves as specified on the label), applicators, and post application workers ranged from 8.8×10^{-6} to 5.4×10^{-8}. After the cancer reclassification of hexythiazox, the Agency may need to reevaluate worker cancer risks, since risks are within the range where refinements and/or mitigation may be required.

Section 7. Anticipated Data Needs

There has not been a data call in issued for hexythiazox. HED does not believe additional data are needed for registration review.

Section 8. Tolerances

There are 29 U.S. tolerances listed under 40 CFR 180.448 for hexythiazox. Based on residue data submitted in response to residue chemistry deficiencies reported in the July 2005 risk assessment, the Registration Action Branch 1 (RAB1) of HED has recommended the reduction of the current tolerances listed for the following commodities: pome fruit (crop group 11), apple, wet pomace, and the meat byproducts of cattle, sheep, goat and horse. Time limited tolerances are established for field corn (grain, forage, and stover), which expire December 31, 2007. Tolerances with regional registrations are established for cotton gin byproducts, cotton undelinted seed, and citrus fruits (crop group 10).

Maximum Residue Levels (MRLs)for hexythiazox have been established by Codex for apples, cherries, peaches, dry hops, pears, plums, fresh prunes, strawberries, citrus fruits, common ean (pods and immature seeds), cucumbers, currants (red and white), grapes and tomatoes. There are no Canadian MRLs established. One Mexican MRL is established for strawberries. The CODEX and Mexican MRLs are not compatible with the U.S. tolerances because the U.S. tolerance expression currently includes parent, hexythiazox, and its metabolites containing the (4-chlorophenyl)-4-methyl -2-oxo-3- thiazolidine moiety, while the MRLs are established for hexythiazox alone. See Tables 8.1, 8.2 and 8.3 for all U.S. tolerances and MRLs established for hexythiazox.

Table 8.1 Comparison of Residue Definitions for Hexythiazox			
U.S. (40 CFR 180.448)	**Codex**	**Canada**	**Mexico**
Hexythiazox and its metabolites containing the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety	Hexythiazox	None	Hexythiazox

Table 8.2 U.S. Tolerance Summary Table for Hexythiazox		
Commodity	**Current Tolerance (ppm)**	**Comment**
Tolerances listed under 40 CFR §180.448 (a):		
Almond, hulls	10	
Apple, wet pomace	2.5	RAB1 of HED has recommended the reduction of this tolerance.
Caneberry subgroup 13A	1.0	
Cattle, fat	0.02	
Cattle, meat byproducts	0.12	RAB1 of HED has recommended the reduction of this tolerance.
Citrus, dried pulp	1.5	
Citrus, oil	0.90	
Date, dried fruit	1.0	
Fruit, pome, group 11	1.7	RAB1 of HED has recommended the reduction of this tolerance.
Fruit, stone, group 12, except plum	1.0	
Goat, fat	0.02	
Goat, meat byproducts	0.12	RAB1 of HED has recommended the reduction of this tolerance.
Grape	0.75	
Hog, fat	0.02	
Hog, meat byproducts	0.02	
Hop	2.0	
Horse, fat	0.02	
Horse, meat byproducts	0.12	RAB1 of HED has recommended the reduction of this tolerance.
Milk	0.02	
Nut, tree, group 14	0.30	
Peppermint, tops	2.0	
Pistachio	0.30	
Plum	0.10	
Plum, prune, dried	0.40	
Plum, prune, fresh	0.10	

Sheep, fat	0.02	
Sheep, meat byproducts	0.12	RAB1 of HED has recommended the reduction of this tolerance.
Spearmint, tops	2.0	
Strawberry	3.0	
Tolerances listed under 40 CFR §180.448 (b):		
Corn, field, grain	0.05	Expiration/revocation date: 12/31/07
Corn, field, forage	2.0	Expiration/revocation date: 12/31/07
Corn, field, stover	2.0	Expiration/revocation date: 12/31/07
Tolerances listed under 40 CFR §180.448 (c):		
Cotton, gin byproducts, CA only	3.0	
Cotton, undelinted seed, CA only	0.20	
Fruit, citrus group 10 (CA, AZ, TX only)	0.35	
Tolerances needed under 40 CFR §180.448 (a):		
Apple, wet pomace	0.40	
Cattle, meat byproducts	0.02	
Fruit, pome, group 11	0.25	
Goat, meat byproducts	0.02	
Horse, meat byproducts	0.02	
Sheep, meat byproducts	0.02	

Table 8.3 Comparison of MRLs for Hexythiazox

Commodity	U.S. (ppm)	Codex (mg/kg)	Canada (mg/kg)	Mexico (mg/kg)
Almond hulls	10		None	
Apple		0.5		
Apple, wet pomace	2.5			
Caneberry subgroup 13A	1.0			
Cattle, fat	0.02			
Cattle, meat byproducts	0.12			
Citrus, dried pulp	1.5			
Citrus, oil	0.90			
Date, dried fruit	1.0			
Fruit, pome, group 11	1.7			
Fruit, stone, group 12, except plum	1.0	1.0 (cherries, peach)		
Goat, fat	0.02			
Goat, meat byproducts	0.12			
Grape	0.75	1.0		
Hog, fat	0.02			
Hog, meat byproducts	0.02			

Hop	2.0	2.0 (dry)		
Horse, fat	0.02			
Horse, meat byproduct	0.12			
Milk	0.02			
Nut, tree, group 14	0.30			
Pear		0.5		
Peppermint, tops	2.0			
Pistachio	0.30			
Plum	0.10	0.2		
Plum, prune, dried	0.40			
Plum prune, fresh	0.10	0.2		
Sheep, fat	0.02			
Sheep, meat byproducts	0.12			
Spearmint, tops	2.0			
Strawberry	3.0	0.5		3.0
Cotton, gin byproducts, CA only	3.0			
Cotton, undelinted seed, CA only	0.20			
Fruit, citrus group 10 (CA,AZ, TX only)	0.35	0.5		
Common ean (pods and/immature seeds)		0.5		
Cucumber		0.1		
Currant, red and white		0.2		
Tomato		0.1		

Section 9. Overall Conclusions

HED does not believe that new data are needed for registration review (orange processing study still under review) and that existing risk assessments will support registration review. Dietary, occupational and aggregate assessments are available for all uses, and there are no dietary or aggregate exposure risks of concern. HED plans to reevaluate the cancer classification of hexythiazox. Upon completion, HED may need to reevaluate worker cancer risks, since risks are within the range where refinements and/or mitigation may be necessary. The Agency anticipates no additional human health risk assessments will be needed for the existing uses of hexythiazox. Pending new uses may require additional risk assessments.

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
T. Bloem	D327763	07/03/2006	Hexythiazox. Pome Fruit, Citrus, Grape and Alfalfa and Clover Grown for Seed. Review of Amendment Dated 23-February-2006 Submitted in Response to Residue Chemistry Deficiencies.
T. Bloem	D319090	07/03/2006	Hexythiazox in/on Field Corn. Summary of Analytical and Residue Chemistry Data.

Table 9.1. HED Memoranda Relevant to Registration Review			
Author	**Barcode**	**Date**	**Title**
M. Dow	D321219	01/03/2006	Hexythiazox- Exposure/Risk Assessment for the Use of Hexythiazox on Turf, Residential Caneberries, Pome Fruit, Stone Fruit and Nut Trees.
T. Bloem	D310292, D315433	07/06/2005	Hexythiazox in/on Pome Fruit, Citrus and Grapes. HED Risk Assessment.
T. Bloem	D317359, D317361	06/29/2005	Hexythiazox- Application of Hexythiazox to Pome Fruit, Citrus and Grape. Acute, Chronic and Cancer Dietary Exposure Assessments.
G. Kramer	D286278	11/18/2002	Hexythiazox in./on Dates. HED Risk Assessment.
W. Dykstra	D279202	05/22/2002	Data Evaluation Record: 28-day Dermal Toxicity Study-Rat
G. Kramer	D269766, D269769	02/22/2001	Hexythiazox in/on Caneberries, Mint, Tree Nuts, Pistachios and Stone Fruit. HED Risk Assessment
J. Kidwell	HED Doc. No. 014022	03/01/2000	Hexythiazox- Report of the Hazard Identification Assessment Review Committee.
L. Brunsman	HED Doc. No. 012704	04/16/1998	Savey (NA-73) Quantitative Risk Assessment (Q_1*) Based on $B_6C_3F_1$ Mouse Dietary Study with ¾'s Interspecies Scaling Factor
E.T. Haeberer	NA	06/17/1988	Savey on Apples; Comparative Review of Cow and Goat Metabolism Studies Elucidating Species Differences; Review of Analytical Bridging Data
E. Rinde	NA	03/16/1988	Second Peer Review of Savey- Reevaluation Following the December 15, 1987 Science Advisory Panel Review.
E. Rinde	NA	02/02/1987	Peer Review of Savey
E.T. Haeberer	NA	01/13/1986	Savey on Apples; Lactating Goat Metabolism Study; Evaluation of Analytical Methodology and Residue Data

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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)
SOP	Standard Operating Procedure
TGAI	Technical Grade Active Ingredient
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard
WQ	Water Quality