




Paclobutrazol Summary

Document: Registration Review

March 2007

**Paclobutrazol Summary Document
Registration Review: Initial Docket
March 2007**

Case Number 7002

Approved by: 

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Director

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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 or sold in the United States generally must be registered by EPA, 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 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:

The Agency anticipates conducting a comprehensive ecological risk assessment, including an endangered species assessment for paclobutrazol. For human health assessments, the Agency anticipates that occupational and residential risk assessments may be needed for some uses.

Ecological Risk:

- While there are summaries of available effects and environmental data, there are no risk assessments available for paclobutrazol. Please refer to the Ecological Risk Assessment Problem Formulation, for a detailed discussion of the anticipated risk assessment needs.
- Based on preliminary screening-level risk estimates using Structure Activity Relationship parameters for structurally similar compounds, extrapolated toxicity endpoints indicate that risk quotients may exceed the Agency's level of concern using conservative exposure assumptions for birds, amphibians, and fish. It should be noted that these risk quotients have a high uncertainty level.
- In order to complete a comprehensive risk assessment for paclobutrazol, the Agency anticipates requiring additional toxicity data for plants and chronic toxicity data for birds and fish, as listed below.
 - (GLN 850.1400) Fish early life stage.
 - (GLNs 850.4320, 850.4320) Seedling emergence and vegetative vigor.
 - (GLN 850.2300) Avian reproduction.

Human Health Risk:

- Paclobutrazol has no food use registrations; therefore, a dietary (food only) risk assessment is not required. Additionally, no toxicity endpoint was identified for an acute dietary assessment. However, paclobutrazol has a turf use which could lead to exposure through drinking water. The Agency anticipates needing a groundwater and surface water exposure assessment analysis and a chronic drinking water risk assessment. No additional data are needed to conduct the drinking water assessment.
- Occupational risk assessments may be needed for uses on turf, outdoor ornamentals, greenhouse ornamentals, bulb soak treatments, and seed treatments; however, no additional data are needed to complete these assessments. The scenarios for the occupational assessments would include short- and intermediate-term dermal and inhalation scenarios.
- Paclobutrazol can currently be used on residential turf which requires residential risk assessments for short- and intermediate-term dermal and inhalation and children's incidental oral exposures. No additional data are needed for this assessment. The only technical registrant with residential lawn uses has requested that the Agency cancel this residential use. The Agency intends to publish the receipt of this request in the Federal Register and to take public comment as required under FIFRA 6(f). If this use for residential turf is removed from all paclobutrazol labels, no children's assessment will be required.

Timeline:

EPA has created the following estimated timeline for the completion of the paclobutrazol registration review. The Agency may conduct the residential or occupational assessment for turf, outdoor ornamentals, greenhouse ornamentals, bulb soak treatments, and seed treatments and residential assessments for turf 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 Paclobutrazol Docket	March 2007
Close Public Comment Period	June 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	Aug. 2007
Issue DCI	June 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	Aug. 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 paclobutrazol 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. There are no U.S. tolerances for paclobutrazol, nor are there Codex MRLs; so trade irritants are not expected for paclobutrazol.

Stakeholders are also specifically asked to provide information and data that will assist the Agency in refining the ecological risk assessment, including any species-specific effects determinations. The Agency is interested in 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 in units related to mass per unit area of treatment zone

- 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
- 13. data on the residues of paclobutrazol in above ground portions of vegetation following tree injection, root zone injection of basal drench, and soil drench uses.

Additionally, paclobutrazol 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. However, the Agency invites submission of other existing water quality data for these chemicals. To the extent possible, data elements identified in Appendix A of the “OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP’s Registration Review Risk Assessment and Management Process” should be provided (reference: <http://www.epa.gov/oppfead1/cb/ppdc/2006/november06/session1-sop.pdf>), in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

Next Steps:

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

II. FACT SHEET

Background Information:

- Paclobutrazol registration review case number: 7002
- Paclobutrazol PC Code: 125601 CAS#:76738-62-0
- Technical registrants: Syngenta Crop Protection, Chemtura USA Corporation, Fine Agricultural Chemicals Limited, and Zhejiang Tide CropScience Co. Ltd.
- First registered in 1985; therefore it was not subject to reregistration.
- No food uses or tolerances.
- Special Review and Reregistration Division Chemical Review Manager (CRM): Nathan Mottl: mottl.nathan@epa.gov
- Registration Division Product Contacts:
Tony Kish: Kish.Tony@epa.gov
John Bazuin: Bazuin.John@epa.gov
- 28 total active products are registered; 5 manufacturing use products, 19 end-use products, and 4 experimental use permits.
- Paclobutrazol is sold in several different formulations including wettable powder, soluble concentrates, granular fertilizer, and emulsifiable concentrate formulations.
- Paclobutrazol can be applied through drop and push spreader and a variety of spray equipment on grass; chemigation, foliar spray, drench, bulb soak in greenhouses; basal drench, soil incorporation, and tree injection

Use & Usage Information: (For additional details on label rates and allowed uses, please refer to the BEAD Appendix A document in the paclobutrazol docket.)

- Paclobutrazol is a plant growth regulator that slows vegetative growth by inhibiting gibberilin biosynthesis creating more compact plants.
- Paclobutrazol can be used as a tree injection, soil incorporation, and basal drench to reduce above ground vegetative growth (reduces terminal growth and pruning volume) of deciduous trees and pine trees for power line and utility rights of way. It is most effective when applied to the soil near the base of the tree.
- Paclobutrazol can be used on ornamental plants (flowers, seedlings, etc.) grown in containers in nurseries, greenhouses, shade houses and interior landscapes.
- Paclobutrazol is used on turf (e.g., residential, commercial, ornamental, and golf course applications) and can be combined with fertilizers. It can act as a non-selective, post-emergent herbicide for control of annual grasses and broadleaf weeds. It is used to reduce lawn mowing and to increase turf density.
- California use data indicate approximately 11,000 pounds used annually in California with rights of way as the predominant use).
- National usage data is not available.

Ecological Risk Assessment Status:

In order to meet current standards, new ecological risk assessments are needed for all registered outdoor uses. However a preliminary screening level assessment indicates that

- Risks are unlikely to exceed the Agency's LOC for listed and non-listed species include: acute risks to birds, mammals, fish, amphibians, aquatic invertebrates and chronic risks to mammals, aquatic invertebrate.
- Risks are likely to exceed the Agency's LOC for listed and non-listed species include: chronic risk to birds, fish, and amphibians.
- Risks to listed and non-listed plants have not been assessed, but may be expected to exceed the Agency's level of concern based on the chemical's known mechanism of action.

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):

- No tolerances since it has no food uses.
- Current turf use requires a drinking water assessment which has not been previously completed.

Residential:

- No risk assessments have been conducted for paclobutrazol use on residential turf. However, the only known technical registrant with this use has recently requested voluntary cancellation of the residential turf use which would preclude the need for assessing risk from this use scenario.

Occupational:

- No occupational risk assessments have been conducted for paclobutrazol.
- Occupational assessments will be required during registration review for use on turf, outdoor ornamentals, greenhouse ornamentals and bulb soak treatments.
- The Agency anticipates needing to assess short- and intermediate-term dermal and inhalation scenarios.

Tolerances:

- No MRLs for paclobutrazol have been established or proposed by Codex for any agricultural commodities.
- There are no Canadian or Mexican MRLs for paclobutrazol.
- No U.S. tolerances are listed.

Data Call-In Status:

- A DCI has not been issued for paclobutrazol.

Labels:

A list of registration numbers may be found in the paclobutrazol docket and the labels can then be obtained from the Pesticide Product Label System (PPLS) website:

<http://oaspub.epa.gov/pestlabl/ppls.home>.

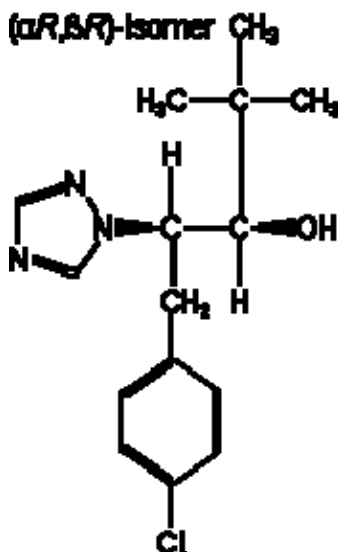
III. Ecological Risk Assessment Problem Formulation

REGISTRATION REVIEW

ECOLOGICAL RISK ASSESSMENT PROBLEM FORMULATION FOR:

PACLOBUTRAZOL

($\alpha R, \beta R$)-*rel*- β -[(4-chlorophenyl)methyl]- α -(1,1-dimethylethyl)-1*H*-
1,2,4-triazole-1-ethanol



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STRESSOR SOURCE AND DISTRIBUTION

The source of the stressor considered in this document is paclobutrazol. Paclobutrazol, ($\alpha R, \beta R$)-*rel*- β -[(4-chlorophenyl)methyl]- α -(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol, is a plant growth regulator used to modify the physical structure of vegetation. According to BEAD data for paclobutrazol use Updated Appendix A submitted to EFED on January 19, 2007, this compound is currently registered for use on golf course turf, ornamental potted plants, trees, shrubs, and vines.

Paclobutrazol is a cell elongation and internode extension inhibitor that retards plant growth by inhibition of gibberellin biosynthesis. The compound is expected to be systemically transported through the plant via the xylem. It is important to note that current screening risk assessment processes for wildlife exposure via treated vegetation do not address systemic pesticides. Additional risk assessment characterization is needed to discuss soil to plant transfer. The purpose of paclobutrazol use is to produce compact plants with denser vegetative growth. On turf, the material also reduces the frequency of required mowing.

INTEGRATION OF AVAILABLE INFORMATION

While there are summaries of available effects and environmental fate data, there are no risk assessments available in the docket. This document utilizes screening estimates of exposure and chemical analog data to investigate the significance of exposure and effects, data gaps on future risk assessment conclusions and to identify where there may be data generation opportunities that have important implications of confidence in risk assessment conclusions.

ECOLOGICAL EFFECTS

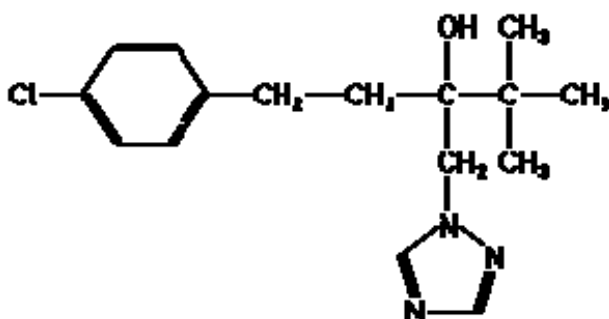
Available Toxicity Studies

The following table summarizes the available acute and chronic toxicity data available for paclobutrazol and includes data within OPP records as well as the web-based reported of public holdings of the ECOTOX database:

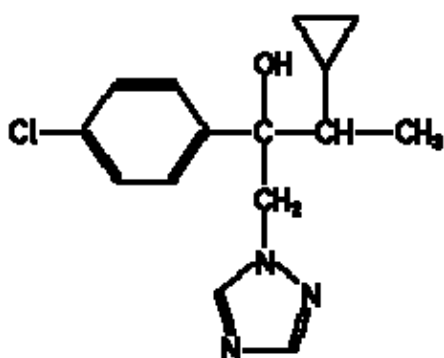
<u>Test Species</u>	<u>Effects Endpoint</u>	<u>Effects value</u>
Mallard duck	LD50	>7913 mg/kg-bw
Mallard duck	LC50	>5,000 mg.kg-diet
Bobwhite quail	LC50	>20,000 mg.kg-diet
Rat	LD50	1,336 mg/kg-bw
Rat	Reproduction	
	NOEL, NOEC	2.5 mg.kg-bw, 50 mg/kg-diet
Bluegill sunfish	LC50	23.6 mg/L

Rainbow trout	LC50	27.8 mg/L
<i>Daphnia magna</i>	LC50	33.2 mg/L
<i>Daphnia magna</i>	LC50	16 mg/L (a.i. based on tested formulation)
<i>Limnodrilus hoffmeisteri</i> (tubificid worm)	LC50	35.5 mg/L
<i>Pseudokirchneriella subcapitata</i> (green alga)	EC50	41.5 mg/L
<i>Bufo bofo</i> (toad)	LC50	11 mg/L
<i>Beauveria bassiana</i> (fungus)	LOEL	500 mg/L

There are no chronic toxicity data available for birds, fish, or aquatic invertebrates. To address the lack of data for chronic effects in these taxa, the Agency consulted the database for chemical analogs and identified tebuconazole and cyproconazole as having similar structures:



Tebuconazole 128997



Cyproconazole 128993

The Agency then consulted past risk assessments for these two analogs and compared within species acute and chronic endpoints for birds, fish, and aquatic invertebrates. The following table summarizes these findings. The acute to chronic ratios (ACRs) these data provide, while within species, are not likely always the product of endpoints derived within a single lab (i.e. paired studies) and so they include some increased variation from inter-laboratory sources. As a result, these ACRs do appear to be on the higher side of commonly encountered ratios.

Within Species Comparisons of Acute and Chronic Endpoints for Chemical Analogs

Chemical	Taxa	Acute Endpoint	Chronic Endpoint	Acute/chronic Ratio
tebuconazole	Rainbow trout	4400 ug/L	12 ug/L	367
	Sheepshead minnow	5900 ug/L	21.9 ug/L	269
	Daphnia	4000 ug/L	120 ug/L	33
	Bobwhite quail	>5000 mg/kg-diet	156 mg/kg-diet	>32
cyproconazole	Rainbow trout	19000 ug/L	150 ug/L	127
	Daphnia	26000 ug/L	290 ug/L	90
	Bobwhite quail	816 mg/kg-diet	50 mg/kg-diet	16
	Mallard duck	1197 mg/kg-diet	10 mg/kg-diet	120

There is little information to assess the mechanism of toxic action differences between these analogs and paclobutrazol. The analogs selected for the paclobutrazol problem formulation are triazole fungicides. They have a primary activity shared with all the De-Methylation Inhibitor (DMI) fungicides in that they act through modification of the CYP51 family of cytochromes. The CYP51 reference pertains to the lanosterol 14-alpha demethylase that is key in making cholesterol from lanosterol. In other words the triazole fungicides act on the sterol biosynthesis pathway, thereby disrupting cell membranes. This enzyme is evolutionarily conserved in plants, fungi and animals, and bacteria. This is the only P450 to be so highly conserved and it may have been the ancestor to all eukaryotic P450s. As such, chemical impact on sterol biosynthesis has potential implications for reproduction and development in higher organisms through possible effects on steroidal hormone synthesis in addition to cellular effects..

The question is whether paclobutrazol is biochemically similar. Paclobutrazol is a triazole which inhibits sterol as well as giberellin biosynthesis so it also has some fungicidal activity (against mildews and rusts). The inhibition of sterol synthesis is likely similar to the other triazoles. Therefore, effects on higher organisms (e.g., development and reproduction) as mediated by sterol products is likely similar to that of the fungicidal analogs used in the problem formulation.

The analogs are fungicides and while paclobutrazol is not labeled as a fungicide, available data summarized above shows that paclobutrazol can produce effects in at least one fungal species. Moreover, with aquatic organisms, the acute values for cyproconazole for trout and daphnids (19,000 and 26,000 ug/L) are on the order of those for paclobutrazol (27,000 and 33,000 ug/L). For terrestrial wildlife, the tebuconazole quail LD50 (>5000 mg/kg-diet as a limit test) cannot be said to be radically different from the paclobutrazol endpoint (>20,000 mg/kg-diet). With this limited information and assuming that structural analogs may exhibit similar, though not exact, toxicological properties, EFED selected the largest and smallest acute to chronic ratios (ACRs) for fish, aquatic invertebrates, and birds and then applied them to available paclobutrazol acute endpoints to conservatively estimate a chronic endpoint range for each un-tested taxa. The following table presents these results.

Taxa	Measured Acute Endpoint	Acute:Chronic Ratio	Estimated Chronic Endpoint
Fish	23.6 mg/L	127 to 367	0.06 to 0.19 mg/L
Aquatic phase amphibian	11 mg/L	127 to 367	0.03 to 0.09 mg/L*
Aquatic invertebrate	33.2 mg/L	33 to 90	0.37 to 1 mg/L
Bird	>5000 mg/kg-diet	16 to 120	>41.7 to > 312 mg/kg-diet

*high uncertainty concerning this extrapolation because it extends to another vertebrate taxonomic group

It should be noted that the measured effects values for the analogs are not used to directly predict a chronic endpoint for paclobutrazol. Rather, it is the relationships between the measured acute and chronic endpoints (ACRs) for these analogs that are used to estimate chronic endpoints from known acute paclobutrazol endpoints. Because these ACRs may be conservative (see above discussion), the resulting estimated chronic endpoints for paclobutrazol may also be conservative. However, the ACRs employed are not as great as an ACR for paclobutrazol in mammals, where the relationship between the rat LD50 and the rat reproduction NOEL is greater than 500.

The range of estimated toxicity values for paclobutrazol can be used to preliminarily determine the potential impact of reducing chronic effects endpoint uncertainty on conclusions generated by the ecological risk assessment. In addition, where available, information on toxicity to estuarine/marine organisms for analogs can be used to extrapolate values for paclobutrazol in future risk assessments.

In terms of direct effects to terrestrial plants, both dicots and monocots are known to be sensitive to paclobutrazol based on the target uses on turf (monocot) and ornamentals (dicot). The mechanism of action may be expected to product alterations in the growth characteristics of exposed non-plants. However, the lack of terrestrial plant effects data precluded a quantitative assessment of the magnitude of potential effects and the geographical extent of those effects, especially as they relate to analyses for effects on federally listed threatened or endangered species. Because some uses (e.g. turf) involve both spray and granular applications of paclobutrazol, exposures to non-target plants may occur via spray drift and surface runoff. These exposure routes suggest that both vegetative vigor and seedling emergence endpoints may be applicable to a risk assessment for paclobutrazol. Therefore, Tier 1 non-target plant toxicity testing with both monocot and dicot plants would provide an initial set of effects endpoints to quantify risk estimates relevant to expected paclobutrazol effects, patterns of use, and mechanisms of application.

Incident Reports

The Agency has no incident reports in the Ecological Incident Information System (EIIS) for adverse effects to fish or wildlife that were attributed to paclobutrazol use.

EXPOSURE CHARACTERISTICS

In general terms, paclobutrazol can be characterized as an environmentally stable compound with a moderate potential for mobility in soil and water environments.

Paclobutrazol is relatively stable in sterile aqueous solutions with 94.9- 95, 94.2-95.6, and 96.6-98.8 percent of triazole ring labeled compound present after 30 days in pH 4, 7 and 9 solutions, respectively (no MRID).

The compound did not undergo appreciable photolysis in water when exposed to 1.94-2.50 W/m² at 420 nm in pH7 buffer. By day 10 of the exposure, 96.6-98.8 percent of paclobutrazol was still present (no MRID). Similar results were observed for paclobutrazol photolysis on soil, with 87.4 percent of the compound still present on loam soil irradiated for 105.4 hours by xenon arc lamp (MRID 40685002).

Triazole- and methine-labeled paclobutrazol degraded with a half life of more than one year in loam soil incubated at 20°C with 40 percent moisture holding capacity. By the end of an entire incubation year, 54 percent of triazole-labeled and 50.4 percent of methine labeled parent were not degraded (MRID 40685003).

Both triazole- and methine-labeled paclobutrazol degraded with a half life of more than one year in flooded loam and silt loam soils incubated at 20°C. At 1 year post treatment 72.4 percent of triazole-labeled and 60.5 percent of methine-labeled parent were still present (MRID 40685003).

Batch equilibrium testing indicated that paclobutrazol has the capacity to be mobile on some conditions. Testing was conducted in nine soils ranging in texture from sand to silt loam. Values for K_{ads} ranged from 1.3 to 23.0 ml/g. Adsorption increased with an increase in soil organic matter content and a decrease in soil pH. Values for K_{des} ranged from 1.87 to 27.97 following the first desorption step and from 2.66 to 33.95 following the second desorption step (MRID 40685005).

Soil column leaching experiments involving aged (9 week) residues of methine-labeled paclobutrazol determined that the compound was relatively immobile in 30 cm columns of sand, sandy loam, loamy sand, and clay loam soils leached with 66 cm of calcium chloride solution over 9 weeks. In contrast, aged residues of triazole-labeled paclobutrazol determined that the compound to be of low mobility in 30 cm columns of sand and sandy loam soils, and mobile in loamy sand and clay loam soils. In all cases, the majority (58.6 – 90.7 percent of the applied) of the aged residue did not leach out of the upper 10 cm of the treated soil columns (MRID 40685004).

Further analysis of the underlying data is warranted to determine the soil factors influencing paclobutrazol sorption and mobility in soils. In particular, additional analysis of the existing dataset used to establish the role of organic carbon on adsorption in soils and sediment would have implications for surface water exposure modeling as well as determining whether sediment biota impacts need to be evaluated.

Paclobutrazol is unlikely to volatilize to any significant extent owing to a low estimated vapor pressure on the order of 10^{-6} mm Hg at 20°C. However, the log K_{ow} of 3.2 indicates a potential for this chemical to bioaccumulate in fish. A bioaccumulation in fish study, which was only conducted for 14 days, showed BCF factors of 20x for edible tissues (day 3), 248x for non edible tissues (day 3), and 44x for whole fish (day 10).

The only degradate of paclobutrazol is its ketone analog, (2RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-pentan-3-one, detected in the aerobic soil metabolism study at approximately 18% of total applied and at less than 10% in other soil studies.

Paclobutrazol residues were persistent and mobile in terrestrial field dissipation studies in California, West Virginia, Florida, North Carolina, Illinois, and Mississippi (Supplemental MRID 00155854, 40685007, 40685009, 40685010, 40685011, 4068512, and 40685006; and Pearson, 1985 no MRID). Paclobutrazol residues include paclobutrazol and its ketone metabolite. Half-lives of paclobutrazol residues ranged from 450-950 days for orchard soils in California, West Virginia, Florida and 25 weeks to 36 weeks in agricultural soils in Mississippi, North Carolina, and Illinois. Although, it was characterized as moderately mobile by laboratory studies, no significant movement of paclobutrazol was detected in the agricultural soils. In the orchard studies, paclobutrazol residues (parent plus degradate) were detected at 10% or less of total applied, in soil depth of 48 inches in the California study, 24 inches in West Virginia study, and 48 inches in the Florida study. Note that these depths are the maximum depths sampled at each study. The paclobutrazol ketone metabolite was predominately detected in the subsurface soil layers, also at insignificant levels.

Based on laboratory and field studies, paclobutrazol has the potential to contaminate ground water via leaching and surface water through mainly runoff. Using the highest rates from the current registered uses (4 ground applications of 0.75 lb ai/A per application), SCI-GROW modeling estimated 4 ppb of parent residues in ground water, while PRZM/EXAMS estimated acute and chronic concentrations of 40 and 20 ppb, respectively, in surface water.

CHARACTERISTICS OF ECOSYSTEMS POTENTIALLY AT RISK

For paclobutrazol and pesticides in general, the ecosystems at greatest risk are those in close proximity to the use areas. For existing registrations of this pesticide, these areas of potential concern for non-target organism effects would include golf courses, plant nurseries, urban landscape areas, residential landscapes, road rights of way, and water bodies directly adjacent to treated areas that may receive chemical residues via drift and/or runoff.

For golf course turf uses paclobutrazol is applied either as a spray or in granular form from a drop spreader at rates ranging from 0.1 to 0.75 pounds of active ingredient per acre. Mapping the locations of all golf courses is beyond the scope of this document. However, based on proprietary usage data, the spatial extent of potential treatment sites

could extend to tens of thousands of acres for this use alone. There is insufficient information available to establish locations of use but it is expected that potential candidate sites for paclobutrazol use extend to most areas of the United States. Additional information on the amount and geographical distribution of paclobutrazol used on golf courses would assist the Agency in defining the geographical scope of this use.

Tree applications involve urban environments, utility rights of way, residential areas, and other non-crop areas. The compound may be applied as a basal drench in a trench surrounding the tree trunk-soil intersection, soil injection to a depth of 3 to 6 inches around the base of the tree, or direct injection into the tree trunk. Application rates for basal and soil injection range from 1 to 4 g of active ingredient per inch of tree basal area and is tree species dependant. It is presumed that trunk injection is similar. As is the case for golf courses, mapping the locations of urban environments, rights of way, residential areas, and other non-crop areas is beyond the scope of this document. The Agency's Biological Evaluation and Assessment Division cannot, with available information, assess the mass of use per acre for this use scenario; therefore the spatial extent of the use site cannot be defined at this time. However it is expected that potential candidate sites for paclobutrazol use extends to most areas of the United States. Additional information on the amount and geographical distribution of paclobutrazol applied to these use sites would assist the Agency in defining the geographical scope of this use.

For potted ornamental uses the pesticide is applied as an indoor or outdoor foliar spray, bulb soak, and indoor soil drench. Labeling does not present application in terms of rates per unit area for these uses. Drenches to pots (EPA registration no. 10182266) range from 0.063 mg active ingredient for 4 inch pots to 5 mg active ingredient for 12 inch pots. All other applications to potted plants by drench or foliar application are as ppm in application water. The Agency's existing exposure models, both for terrestrial and aquatic organisms rely on application rates expressed in terms of mass per unit area of treatment. The labels for the foliar spray and soil drench methods are not expressed in these terms. Additional information on the application practices employed for these uses, specifically information that would allow for a conversion of labeled applications rates to units employed in Agency exposure models would all for a quantitative assessment of exposure to non target aquatic and terrestrial organisms.

The water column is expected to be the predominant compartment for exposure to paclobutrazol in aquatic systems. Owing to the use patterns described, it is possible that both freshwater and estuarine/marine systems may be exposed. Depending on additional analysis of sediment adsorption potential through reevaluation of organic carbon influences on available soil adsorption, exposure to sediment organisms for a persistent compound like paclobutrazol may also be considered in future risk assessments.

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 paclobutrazol.

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.

In terms of direct effects to terrestrial plants, both dicots and monocots are assumed sensitive to paclobutrazol, based on the turf (monocot) and tree (dicot) target uses. The mechanism of action may be expected to alter the growth characteristics of exposed plants. Because there are spray and granular applications possible under some use scenarios, exposures for non-target plants may involve exposure to both runoff and spray drift. The Agency commonly uses different effects endpoints (vegetative vigor and seedling emergence) for assessing risks to non-target plants from these different exposure routes.

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,

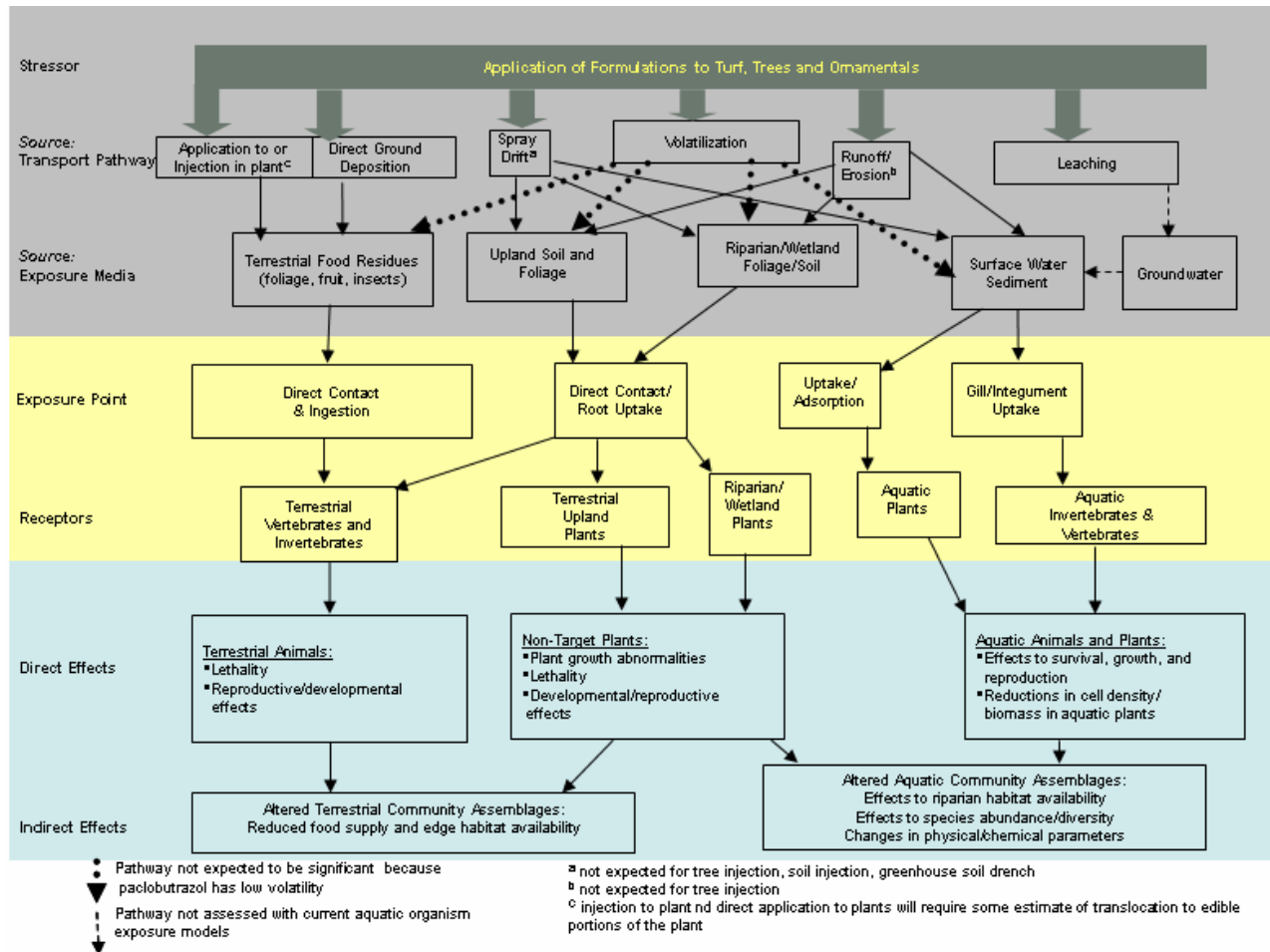
an environmental transport medium, a point of exposure for ecological receptors, and a feasible route of exposure.

The conceptual model (**Figure 1**) depicts the potential pathways for ecological risk associated with paclobutrazol use. The conceptual model provides an overview of the expected exposure routes for organisms within the paclobutrazol 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 paclobutrazol residues as a result of spraying, drift, and translocation from soil or plant injection through xylem flow. It is important to note that since current screening risk assessment processes for wildlife exposure via treated vegetation do not address systemic pesticides, additional risk assessment characterization is needed to discuss interplant, and soil to plant transfer. Simplifying first approximations of paclobutrazol exposure to wildlife from tree injection, soil drench, root area injection, etc. could explore pesticide residues either as a uniform translocation to all above ground biomass, or translocation concentrating the material in fruits, seeds, leaves of vegetation could be employed to establish coexposure to herbivorous wildlife. The Agency would be interested in any available residue monitoring in above ground portions of treated vegetation (particular trees and shrubs. This information would be important to refinement of first approximations of residues in browse for wildlife.

For aquatic animal species, the major routes of exposure are considered to be via the respiratory surface (gills) or the integument.

Direct contact and/or root uptake is the major route of exposure for terrestrial and wetland (riparian) plants, while aquatic plants may be exposed via direct uptake and adsorption. Estimated exposure concentrations for all organisms are obtained through the use of several Agency exposure models.

FIGURE 1. ECOLOGICAL CONCEPTUAL DIAGRAM FOR PACLOBUTRAZOL



RISK HYPOTHESIS

Based on an examination of the physical/chemical properties of paclobutrazol, 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.

The hypotheses for testing by risk assessment methods for each existing and proposed paclobutrazol use is *“paclobutrazol, used in accordance with the label, produces adverse effects on individual survival, growth, or reproduction in terrestrial vertebrates, terrestrial invertebrates, terrestrial plants, aquatic vertebrates, aquatic invertebrates, or aquatic plants.”*

ANALYSIS PLAN OPTIONS

In Registration Review, pesticide ecological risk assessments will follow the Agency’s Guidelines for Ecological Risk Assessment, will be in compliance with the paper titled “Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency” (“Overview Document”) (January 2004), and will be done in accordance with Section 7 of the Endangered Species Act.

Most paclobutrazol exposure scenarios associated with terrestrial wildlife and aquatic organisms are covered by existing Agency risk assessment methods. However, as indicated earlier in this document, direct injection of paclobutrazol to trees, soil injection in the root zone of vegetation, soil drench applications of the pesticide involve xylem translocation of the pesticide throughout the plant. For these uses, the Agency will incorporate in the risk characterization and exploration of different assumptions of the mass of pesticide in edible portions of treated plants. Any available information on above ground plant residues of paclobutrazol following these uses would allow the Agency an opportunity to consider refinement to these exposure assumptions.

There are no ecological risk assessments available for current and proposed uses of paclobutrazol. Therefore, to evaluate the adequacy of existing data sets, EFED conducted some comparisons of upper-bound exposure estimates with available and estimated effects endpoints.

To look at first approximations of upper bound aquatic exposure EFED conducted PRZM/EXAMS modeling for the turf use. Turf was selected for upper bound estimates of exposure because it likely represents the highest and most frequent applications of the pesticide. The following were results for this modeling (all in units of mg/L), assuming 4 applications per year of 0.75 lb ai/A per application and 28 day interval between application:

	Peak	96 hr	21day	60day	90day
PA Turf:	0.113	0.113	0.113	0.113	0.113
FL Turf:	0.176	0.176	0.176	0.176	0.176

A comparison of exposure estimates with fish, aquatic phase amphibian, and aquatic invertebrate effects was made to determine the possible ranges of aquatic risk concerns and to evaluate how the range of potential effects extrapolations could influence risk assessment conclusions. The following table summarizes these preliminary risk assessment results and shows that uncertainties surrounding chronic effects extrapolations do influence the risk conclusions for fish and aquatic phase amphibians.

Preliminary Risk Quotients for Turf Use Site and Measured and Estimated Aquatic Organism Effects Endpoints

Use Site	Taxa (endpoints mg/L)*	Peak EEC (mg/l)	Chronic EEC (mg/L)	Acute RQ	Chronic RQ
PA turf	Fish (acute:23.6) (chronic:0.06 to 0.19)	0.113	0.113	0.004	0.59 to 1.88*
	Amphibian (acute: 11) (chronic 0.03 to 0.09)	0.113	0.113	0.010	1.26** to 3.77**
	Invert (acute:33.2) (chronic: 0.37 to 1)	0.113	0.113	0.003	0.113 to 0.31
FL turf	Fish (acute:23.6) (chronic:0.06 to 0.19)	0.176	0.176	0.007	0.92 to 2.93**
	Amphibian (acute: 11) (chronic 0.03 to 0.09)	0.176	0.176	0.016	1.96** to 5.87**
	Invert (acute:33.2) (chronic: 0.37 to 1)	0.176	0.176	0.005	0.18 to 0.48

* chronic endpoint reflects the range in estimates from the range of available ACR values

**RQ exceeds the Agency chronic LOC

Preliminary risk estimates can also be made using measured and extrapolated avian effects values to determine if endpoint extrapolation uncertainties can potentially affect risk conclusions. Using a turf application rate of 0.75 lb ai/acre, the acute and extrapolated effects endpoint discussed in this document, and the Agency's T-TEX terrestrial wildlife risk assessment model the following preliminary risk results are possible. The reader should note that this set of calculations involves only a single application of paclobutrazol. The available labels suggest that multiple applications are possible, and depending on the application interval and residue dissipation rates, paclobutrazol exposures may be higher for multiple applications than depicted in the table. Therefore risk quotients may also be higher. The results show that two sources of uncertainty in effects endpoint extrapolation may influence the risk conclusions. First extrapolation from a non-definitive acute effects endpoint (i.e., a "greater than" LD50)

results in non-definitive chronic endpoints, which result in risk quotients with upper bounds but no lower bounds. Second, the range of possible ACR values results in a range in chronic endpoints that when used in the risk assessment model, result in risk conclusions that range above and below Agency concern levels. Therefore, uncertainties associated with chronic endpoint extrapolations can influence in ultimate avian risk conclusions. In addition information relative to the dissipation of paclobutrazol from turf may also influence exposure modeling for multiple application scenarios for the pesticide.

Preliminary Avian Risk Quotients for Turf Use Site and Measured and Estimated Effects Endpoints

Wildlife food item	EEC (mg/kg-diet)	Acute Endpoint (mg/kg-diet)	Chronic Endpoint (mg/kg-diet)*	Acute RQ***	Chronic RQ***
Short Grass	180.00	>5000	>41.7 to >312	<0.1	<0.58 to <4.32**
Tall Grass	82.50			<0.1	<0.26 to <1.98**
Broadleaf plants/small Insects	101.25			<0.1	<0.32 to <2.43**
Fruits/pods/seeds/large insects	11.25			<0.1	<0.04 to <0.27

* chronic endpoint reflects the range in estimates from the range of available ACR values

**RQ exceeds the Agency chronic LOC

*** The RQ values presented in this table refer to exposures from a single application of paclobutrazol. Multiple applications are possible under the label and, depending upon the dissipation of the compound from wildlife dietary items, residues may reach levels higher than depicted here and RQ values may be higher.

The Agency wishes to better understand 1) which environmental and product specific the results of the comparison between upper bound exposure estimates and measured and estimated aquatic organism effects endpoints suggest a potential for chronic effects concerns. Because all the aquatic organism chronic effects endpoints are estimated values, there is considerable uncertainty associated with risk estimates based on these endpoints. The ranges of the preliminary risk quotients for chronic either bracket or are very close to the screening level chronic level of concern ($RQ \geq 1$). The generation and incorporation of actual measured endpoint for chronic effects in future aquatic organism risk assessments could have substantial influence in the risk assessment conclusions.

If future ecological risk assessments continue to indicate that paclobutrazol may potentially impact, either directly or indirectly, listed species or critical habitat, and therefore does not support a “not likely to adversely affect” determination, further refinements to both assessment of exposure and evaluation of more taxonomically specific effects endpoints will likely be conducted. This will involve determining whether use of paclobutrazol “may affect” a particular listed species, and if so, whether it is “likely to adversely affect” the species, or in the case of critical habitat, whether use of the pesticide may destroy or adversely modify any principle constituent elements for the critical habitat, and if so, whether the expected impacts are “likely to adversely affect” the critical habitat. The first step in the process is to improve the exposure estimates based on refining the geographic proximity of paclobutrazol use and the listed species

and/or critical habitat. If there is no geographic proximity, this information would support a determination that paclobutrazol use will have no effect on the species or critical habitat. If after conducting the first step of this analysis the Agency determines that geographic proximity exists, both potential direct effects and any potential indirect effects of the pesticide use will be examined. This process is consistent with the Agency's Overview Document. The Agency will consult as necessary with the U.S. Fish and Wildlife Service and National Marine Fisheries Service (Services), consistent with the Services' regulations.

If the screening level risk assessment identifies potential concerns for indirect effects on listed species for those organisms dependent upon terrestrial plants, the next step for EPA and the Services would be to identify which listed species and critical habitat are potentially implicated. Analytically, the identification of such species and critical habitat can occur in either of two ways. First, the agencies could determine whether the action area overlaps critical habitat or the occupied range of any listed species. If so, EPA would examine whether paclobutrazol potential impacts on non-endangered species would affect the listed species indirectly or directly affect a constituent element of the critical habitat. Alternatively, the agencies could determine which listed species depend on biological resources, or have constituent elements that fall into, the taxa that may be directly or indirectly impacted by paclobutrazol. Then EPA would determine whether the use of paclobutrazol overlaps the critical habitat or the occupied range of those listed species.

ANTICIPATED DATA NEEDS

The Agency does not foresee requiring any additional environmental fate studies listed in 40 *CFR* Part 158 prior to conducting the planned assessments.

In contrast the Agency notes the absence of available data for terrestrial plants. In light of the complete absence of definitive terrestrial plant effects endpoints, Tier 1 terrestrial plant toxicity testing (guideline 122-1) with dicots and monocots and for emergence and vigor endpoints would allow the Agency to determine if non-target plant effects are possible. However, the mechanism of action of paclobutrazol suggests that Tier 1 plant testing would likely show at least a 25% effect in one or more plant species which would trigger Tier 2 testing to establish more definitive effects endpoints. Therefore, a move directly to Tier 2 (guideline 123-1), bypassing Tier 1 testing, would reduce resource expenditures and plant tests would supply effects endpoints necessary for quantitative assessment of plants risks for those uses (e.g. turf) where paclobutrazol may run off or drift to areas with non-target plant cover. The Tier 2 plant testing would be of potentially high value for assessing risks to non-target plants for over the top applications of paclobutrazol and would have important utility for assessing the potential for indirect effects to federally listed threatened and endangered species.

In addition, preliminary risk estimates for aquatic organisms indicate that extrapolation efforts to populate missing chronic endpoints for fish are very uncertain and that these uncertainties can influence the risk conclusions. Fish early life stage testing would be of

potentially high value in addressing the effects uncertainties that limit the potential confidence of assessment chronic risks to fish. Reproduction effects endpoints in terrestrial vertebrates have lead to risk concerns in terrestrial wildlife for chemical analogs, and the uncertainties surrounding avian reproduction endpoint extrapolations for paclobutrazol are large and play an important role in uncertainties associated with preliminary risk conclusions. Again, avian reproduction testing would be of potentially high value in addressing the effects uncertainties that limit the potential confidence of assessment chronic risks to birds. Considering the uncertainties surrounding risk conclusions associated with the use of extrapolated chronic effects endpoints in fish and birds, performance of fish early life stage (guideline 72-4) and avian reproduction (guideline 71-4) studies would be of potentially high value because endpoints established from this testing would allow for less uncertain effects endpoints than achievable with current analog extrapolations. These more definitive endpoints would, in turn, allow for a clearer set of risk conclusions for paclobutrazol for these taxonomic groups.

While the Agency will conduct a search of the open literature to ensure that all best available science is utilized, it is anticipated that such a search, based on a preliminary review of the on-line holdings of ECOTOX, will not produce additional effects data for terrestrial plants, aquatic organisms, or birds. Agency uses the ECOTOX database as its mechanism for searching the open literature for ecological effects information. 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.

ANTICIPATED RISK ASSESSMENT NEEDS

As stated previously, there are no drinking water and ecological risk assessments available in the docket for the current uses of this chemical. These assessments are needed for the Registration Review process and will be performed in accordance with the Agency's Guidelines for Ecological Risk Assessment ("Overview of the Ecological Risk Assessment Process in the Office of Pesticides Programs, U.S. Environmental Protection Agency", January 2004) and with the Section 7 of the Endangered Species Act.

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 in units related to mass per unit area of treatment zone

- 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)
 - g. maximum reported use rate (lbs ai/acre) from usage data – county
 - h. percent crop treated – county
 - i. median and 90th percentile number of applications – county
 - j. total pounds per year – county
 - k. the year the pesticide was last used in the county/sub-county area
 - l. 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
- 13. data on the residues of paclobutrazol in above ground portions of vegetation following tree injection, root zone injection of basal drench, and soil drench uses.

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.

IV. Human Health Effects Scoping Document

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460



OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 13 March 2007

SUBJECT: **Paclobutrazol:** Registration Review Scoping Document for Human Health Assessments; PC Code: 125601; DP Number: DP335538

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

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

TO: Nathan Mottl/Susan Lewis
Reregistration Branch 1
Special Review and Reregistration Division (7508P)

Attached is the human health scoping document to support the registration review of the plant growth regulator paclobutrazol.

HED Preliminary Work Plan for the Registration Review of Paclobutrazol
(PC Code 125601)

Introduction

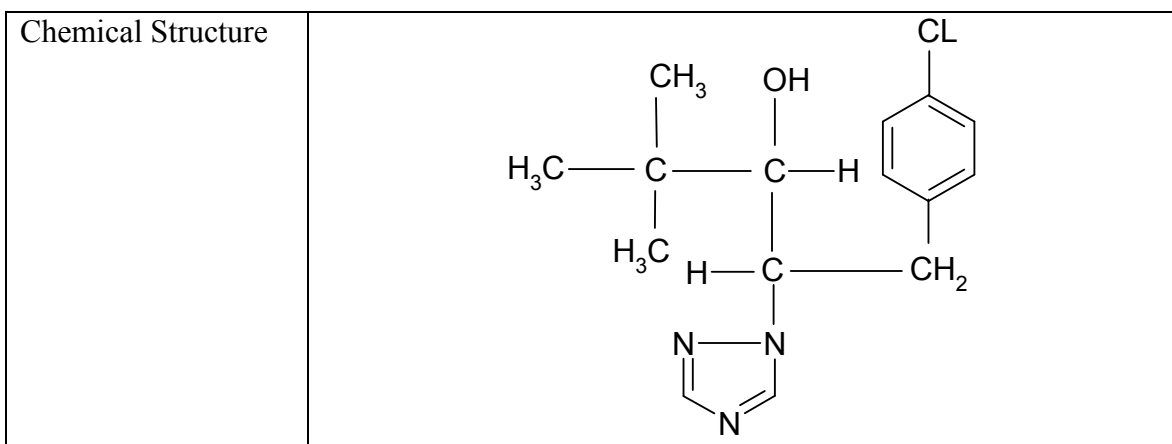
The HED Paclobutrazol Registration Review Team has evaluated the status of the human health assessments for the plant growth regulator paclobutrazol to determine the scope of work necessary to support registration review. The team looked at the hazard and exposure databases for paclobutrazol and attempted to determine whether changes in science policy or deficiencies in the databases *materially* affected the overall risk picture. The current supported uses for paclobutrazol include turf, outdoor ornamentals, greenhouse ornamentals and bulb soaks. Residential uses include use on turf. Paclobutrazol was first registered in 1985; therefore a Reregistration Eligibility Decision (RED) has never been performed. Although a dietary point of departure was identified previously, there are currently no food uses for paclobutrazol and therefore a dietary assessment is not required. In addition, the occupational and residential uses of paclobutrazol have never been assessed.

The primary sources for the status update were the most recent RfD/Peer Review reports (September, 1986; March, 1994) and an OPPIN bibliography search for any newly submitted data. No new toxicity data have been submitted to the Agency since the RfD/Peer Report of June 1994. Route specific inhalation data are currently not available 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 unavailable toxicity data (inhalation, cancer) for paclobutrazol. 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.

Paclobutrazol is currently registered for use on turf. Therefore, there are no tolerances for paclobutrazol on any commodities.

Section 1. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Paclobutrazol
IUPAC name	(2 <i>RS</i> ,3 <i>RS</i>)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1 <i>H</i> -1,2,4-triazol-1-yl)pentan-3-ol
CAS name	(a <i>R</i> ,β <i>R</i>)- <i>rel</i> -β-[(4-chlorophenyl)methyl]-a-(1,1-dimethylethyl)-1 <i>H</i> -1,2,4-triazole-1-ethanol
PC Code	125601
CAS registry number	76738-62-0
Registration Review Case No.	7002



Section 2. Toxicology

A human health assessment has not been performed for paclobutrazol. However, the RfD/Peer Review Committee evaluated the existing toxicology data in 1994 (Memo, G. Ghali, 6/21/94). The RfD Committee concluded there was no evidence, based on the available data, to suggest that paclobutrazol was associated with developmental or reproductive effects. Pesticidal uses of paclobutrazol do not involve use on food and, therefore, are not subject to the Food Quality Protection Act (FQPA) (1996). The risk assessment team has reevaluated the toxicity endpoints for the occupational and residential scenarios and current policies on selecting endpoints and uncertainty factors. The HED team believes that there are reliable data to assess occupational and residential risk of paclobutrazol for the process of registration review.

The toxicity database for paclobutrazol is adequate for the purpose of registration review. A short-term inhalation study is not available to assess occupational and residential risk. As such, an oral guideline toxicity study and endpoint will likely be used to estimate risk from inhalation exposure. In addition, an acceptable/guideline cancer study is not available. The current cancer studies are not acceptable since the highest dose was insufficient to adequately evaluate carcinogenicity. However, these cancer studies are considered adequate for the purposes of registration review. No toxicity studies have been received by the Agency since the RfD/Peer Review Committee Report of June 1994.

Table 2.1 includes the toxicity endpoints established from the 1994 RfD Peer Review Committee Report.

Table 2.1 Summary of Toxicological Point of Departures and Endpoints for Paclobutrazol from the RfD/Peer Review Committee Report (1994)				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <i>All populations</i>	No endpoints identified from the available developmental toxicity studies (rat and rabbit) appropriate for an acute dietary assessment for paclobutrazol.			

Table 2.1 Summary of Toxicological Point of Departures and Endpoints for Paclobutrazol from the RfD/Peer Review Committee Report (1994)				
Chronic Dietary <i>All Populations</i>	A chronic dietary assessment is not required due to the lack of food uses with paclobutrazol.			
Dermal Short-Term (<i>1-30 days</i>)	NOAEL = 10 mg/kg/day 24.5% absorption	UF _A =10x UF _H =10x	Occupational LOC for MOE = 100	21-Day Dermal- Rabbit Irritation LOAEL = 100 mg/kg/day, irritation appeared 2 nd week, dose-related effects included hyperkeratosis, acanthosis, inflammation of superficial dermal.
Dermal Intermediate-Term (<i>1-6 months</i>)				
Dermal Long-Term (<i>>6 months</i>)	Long-term dermal exposure is not expected based on the use pattern for paclobutrazol.			
Inhalation Short-Term (<i>1-30 days</i>)	Oral NOAEL = 2.5 mg/kg/day 100% absorption	UF _A =10x UF _H =10x	Occupational LOC for MOE = 100	2-Gen Reproduction-Rat LOAEL= 12.5 mg/kg/day, based on ↑ liver weights and fatty changes in parental females; ↑ incidence of chromodacryorrhea and thickened eyelids, dental malocclusion, liver mottling or accentuation of lobular structure, liver enlargement, pallor and discoloration in male and female pups.
Inhalation Intermediate-term (<i>1-6 months</i>)				
Inhalation Long-term (<i>>6 months</i>)	Long-term inhalation exposure is not expected based on the use pattern for paclobutrazol.			
Cancer (oral, dermal, inhalation)	Classification: Group D The RfD Committee noted that new carcinogenicity studies may be required if the current use pattern changes (i.e. food uses or uses which are in the high exposure category and require carcinogenicity data) (RfD Report, 1994).			

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). MOE = margin of exposure. LOC = level of concern.

Section 3. Current Dietary Assessments

In 1994 the RfD Committee considered critical endpoints appropriate for the acute and chronic dietary assessments of paclobutrazol. There were no pertinent effects from the available developmental toxicity studies to establish an acute RfD. The 2-generation reproductive rat study was appropriate for use in the chronic RfD. However, due to the lack of a tolerance and status as a non-food use, a dietary assessment is currently not required. A dietary assessment will be required if tolerances are requested at a later date.

Drinking water risks have never been assessed. The current turf use necessitates a screening level groundwater and surface water analysis. The HED paclobutrazol team believes that drinking water risks should be evaluated to ensure the turf use is acceptable

at current use rates. Available developmental studies indicate no appropriate endpoint for use in the acute dietary assessment. The 2-generation reproduction rat study, however, would provide a chronic endpoint for a screening water analysis.

Section 4. Aggregate and Cumulative Exposure

Paclobutrazol has no food registrations and is therefore not subject to FQPA which requires the Agency to consider aggregate and cumulative exposures. However, there is the potential for dietary exposures from drinking water as a result of its use on turf as well as non-occupational (i.e., residential) exposures from this use. These assessments should be conducted and the aggregate exposures considered. In addition, EPA has not yet determined whether paclobutrazol has a common mechanism with other compounds, consequently a cumulative assessment will not be performed.

Section 5. Occupational/Residential Exposure

Neither an occupational nor a residential assessment has been performed for paclobutrazol. For both a residential and occupational assessment, a 21-day dermal toxicity study is available; however, a 28-day inhalation study is not. An oral endpoint from the 2-generation reproduction study with 100% absorption factor may be used in lieu of inhalation data. For a residential assessment, there are sufficient toxicity data to evaluate incidental oral exposures. Occupational assessments will be required during registration review for use on turf, outdoor ornamentals, greenhouse ornamentals and bulb soak treatments. Based on currently supported uses, short- and intermediate-term dermal and inhalation scenarios will be required for registration review. A residential assessment will be required for the turf use for short- and intermediate-term dermal and inhalation and children's incidental oral exposures.

Section 6. Incident Reports

Based upon a review available data bases (OPP Incident Data System, Poison Control Centers, and NIOSH SENSOR) from 1992-2005, there were almost no reports of ill effects from exposure to paclobutrazol (M. Hawkins, D335541, 02/27/2007).

Section 7. Anticipated Data Needs

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

Section 8. Tolerances

There are no tolerances for paclobutrazol.

Section 9. Overall Conclusions

HED does not believe that new data are required for registration review. There is currently adequate information to support occupational and residential assessments of paclobutrazol. A screening level drinking water assessment will be conducted.

Section 10. 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
Pam Hurley	TXR 013485	4/11/94	Toxicology Endpoint Selection Document
George Ghali	TXR 011081	6/23/94	RfD/Peer Report of Paclobutrazol

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