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

5/2/1997

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of EFED's registration chapter for Isoxaflutole (Chemical # 123000; Case 286745; DP Barcodes D225503, D223678, D231444, D232445, and EFED's recommendations for Isoxaflutole for its use on corn

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Attached to this memo is the EFED chapter for the proposed registration of isoxaflutole (Case # 286745 - technical isoxaflutole). For this registration, isoxaflutole (Chemical # 123000) will be formulated as a 75 % water-dispersible granule (75 WDG), and will be applied preplant or preemergence to corn as a herbicide by ground equipment only at a maximum rate of 0.25 lb product/A (0.1875 lb ai/A).

The attached document contains the environmental fate assessment and the ecological risk assessment for isoxaflutole, as well as an integrated ecological risk characterization for the proposed use on corn. Also attached are two environmental fate DERs. The Method Validation study (MRID 43904841) has been sent to Bay St. Louis for review. EFED has estimated surface water and ground water concentrations using PRZM-EXAMS and PATRIOT, respectively for HED to consider for FQPA implementation. In surface water, the maximum, <u>initial</u> estimated PRZM-EXAMS (1-in-10-years) concentration for parent isoxaflutole is 0.4. PRZM-EXAMS also predicts 36-year maximum concentrations in surface water of 0.1, 2.9, and 5.8 ppb for parent isoxaflutole, RPA 202248, and RPA 203328, respectively (pp. 8 to 9 of attached Science Chapter). For acute toxicity, EFED uses the 1-in-10-year maximum concentration of parent isoxaflutole and/or the 36-year maximum concentration of RPA 202248 in the risk assessment. PATRIOT does not provide specific values, but only gives general estimates. Parent isoxaflutole was not predicted to leach to shallow ground water in each of the representative hydrologic soil groups. However the predicted concentrations of RPA 202248 and RPA 203328 were estimated to be in the **<u>hundreds of ppb</u>** at the top of the water table (pp. 14 to 15 of attached Science Chapter). If HED needs additional exposure estimates, HED should inform EFED. Tables indicating the status of the data requirements are included in this memo.

A. Executive Summary Risk Characterization

EFED has serious concerns for risk to water resources and non-target plants, including other crops, from the proposed use of isoxaflutole on corn. However, at this time, EFED cannot perform a realistic environmental fate and effects assessment for isoxaflutole because of data gaps for both the fate and effects of the transformation products. These data gaps have forced EFED to make the following assumptions for a worst case assessment: (1) phytotoxicity of the transformation products is the same as parent isoxaflutole, (2) isoxaflutole residues are stable in aerobic aquatic environments, and (3) isoxaflutole's apparent terminal residue, RPA 203328 does not bind to soil (K_{oc}=0.0). Using the available data and worst case presumptions, an assessment was made. **<u>Based on this assessment, we recommend against registration at this time.</u>**

If RD decides to pursue registration, then EFED recommends that RD incorporate the terms and conditions that are currently being used in RD for ground and surface water mitigation criteria. The justification for our recommendation follows: The transformation products of isoxaflutole have properties and characteristics associated with chemicals detected in ground and surface water. The terms and conditions should address the assumed phytotoxic trigger (22 ppt) in shallow ground and surface water. Levels of isoxaflutole above 22 ppt in water used for irrigation may adversely affect sensitive crops. If the phytotoxicity of the transformation products is not as sensitive to non-target plants as parent isoxaflutole after we review phytotoxicity data requested of the registrant, then the trigger will need to be adjusted. The drinking water trigger will also depend upon HED's assessment, and the adopted trigger should be the lower of the two. The registrant should discuss their water monitoring program (i.e. sites, study design, methods, etc.) with the Agency. If levels in water exceed the phytotoxic level of concern (22 ppt), then the Agency should take some action under the Conditional Registration.

1. General Risk Characterization

Parent isoxaflutole degrades rapidly and sequentially in the environment to the primary transformation product, RPA 202248, and what appears to be the terminal transformation product, RPA 203328. The transformation products are expected to reach surface water and shallow ground water where they will persist and accumulate. There is evidence to show that RPA 202248 is biologically active. Since parent isoxaflutole is not expected to persist long enough in the environment for animals to be chronically exposed, the EEC's to animals in the environment are based on the transformation products. There are no data available to assess chronic risk to animals from the tranformation products. Therefore, EFED is not able to provide a complete chronic risk assessment at this time. Acute risk to birds, mammals, aquatic organisms, and beneficial insects is expected to be minimal from parent isoxaflutole and its transformation products. Terrestrial plants are expected to be highly vulnerable to runoff and spray drift from ground application.

A brief summary of the risk from the proposed use of isoxaflutole is provided below. However, there are uncertainties associated with these risks. These uncertainties include the lack of data for the transformation products on phytotoxicity, persistence and mobility, chronic toxicity to birds and mammals, and acute toxicity to shrimp and estuarine fish. Parent isoxaflutole is very non-persistent, and yet is expected to have season-long control. Therefore, the transformation products are expected to have some phytotoxicity. Because of the lack of phytotoxicity data for the transformation products, the phytotoxicity values of parent isoxaflutole will be used for the transformation products.

- There is phytotoxicity risk to non-target terrestrial plants from ground spray drift of parent isoxaflutole. Compared to sulfonylureas (which have similar phytotoxicity) and picloram (the only herbicide to have restricted use based on phytotoxicity) this chemical poses more risk to non-target plants because the application rate is higher. However, minimal adverse affects to non-target <u>aquatic</u> plants are expected from spray drift.

- There is phytotoxicity risk to non-target aquatic and terrestrial plants from runoff of parent isoxaflutole and it's transformation products.

- Endangered plant species may be affected from the proposed use of isoxaflutole.

- Chronic risk to birds, mammals, shrimp and estuarine fish cannot be determined because data on the transformation products have not been submitted.

- EFED expects that the transformation products will persist and accumulate in surface water and shallow ground water surrounding treated areas.

3

A Reference Dose (RfD) for isoxaflutole has not been established at this time. Therefore, it is not possible to estimate a Lifetime Health Advisory (HA) for isoxaflutole residues in drinking water.

- There is a potential risk to other crops from the presence of potentially phytotoxic transformation products in irrigation water. However, the major areas of corn production that use irrigation (Western U. S. corn belt) have deep aquifers with slow recharge rates that are not likely to have sufficient concentrations of the transformation products to adversely affect other crops. In other parts of the U.S. where corn is also grown and where shallow ground water is used for irrigation, sporadic irrigation is used for other crops. Crops such as soybeans, which are rotated with corn and are sensitive to irrigation waters containing isoxaflutole residues, could be adversely affected.

- Estimated maximum concentrations of isoxaflutole residues in ground water exceed the phytotoxic triggers to non-target plants (e.g. other crops) up to 4,500 times, presuming that the transformation products are as toxic as parent isoxaflutole.

2. Spray Drift Phytotoxicity Concerns

In the Risk Characterization Section of the attached EFED Science Chapter, the Comparative Analysis of Phytotoxicity table shows that the risk quotients (RQ's) for 1% (ground application) and 5 % (aerial application) spray drift exceed the LOC by 187 and 938 times, respectively. For spray drift, these RQs are greater than the most toxic of the sulfonylureas (Oust™), as well as picloram. Non-target terrestrial plants are expected to be adversely affected from the proposed use of isoxaflutole. Although EFED understands that this registration action is limited to ground application to corn, the registrant has indicated that aerial application will be requested in the future. If an aerial application registration is requested, EFED requests notification and review of this action because of serious concerns for off-site movement of parent isoxaflutole to non-target plants from drift. It is uncertain that 5% spray drift is an accurate exposure estimate for aerial application. It may be higher. Further refinement of aerial spray drift exposure may be needed. RD should inform the registrant that lower application rates are needed to avoid high risk to non-target plants.

3. Phytotoxic Limits of Quantitation in Regards to Irrigation and Drift

Analytical methods should have detection limits that are low enough to quantify exposures that can cause ecological effects. Phytotoxicity levels of concern or triggers in ppt would be useful in monitoring of any adverse impacts of isoxaflutole on non-target plants including crops. Plants are more sensitive to foliar uptake of isoxaflutole than to root uptake. Therefore, more severe impacts may come from irrigation or drift reaching plant surfaces that would cause foliar uptake. The isoxaflutole analytical methods that have been provided to EFED do not reach levels where phytotoxicity from drift and irrigation can occur. The phytotoxicity trigger limits for soil, water, and plant residues are 2.41 ppb in plants, 21 ppt in soil, and 22 ppt in water. EFED requests that the registrant develop analytical methods that can quantify the above levels at which phytotoxic effects can occur for parent isoxaflutole, RPA 202248, and RPA 203328. The method may be either a traditional analytical method, or an immunochemical method. If the new method is immunochemical, then the registrant must follow OPP policies (see attached memo). The method needs to be publicly available.

4. Chronic Risk Concerns

Chronic risk to birds, mammals, shrimp and estuarine fish cannot be determined because data on transformation products have not been submitted.

Terrestrial

Although RPA 202248 and RPA 203328 do not show any acute toxicity to birds, chronic toxicity cannot be ruled out because there are several pesticides that do not show acute toxicity, and yet exhibit chronic toxicity. Therefore, since RPA 202248 and RPA 203328 are persistent in the terrestrial environment, EFED requests that avian reproduction studies be conducted using the mallard duck and the bobwhite quail.

EFED cannot fully assess chronic toxicity to mammals since no data are available on RPA 202248 and RPA 203328 from 2-generation rat studies. If chronic toxicity is to be assessed for mammals, then a 2-generation rat study is needed for RPA 202248 and RPA 203328.

Aquatic

One method of screening for chronic risk to aquatic organisms is to use the acute-to-chronic ratio of the parent to the transformation product. Acute data for parent and transformation product and chronic data for the parent must be available. Assuming that the calculated chronic exposure values approach the level of concern, EFED may still require chronic data on the transformation products.

Since the estuarine/marine fish acute toxicity data are outstanding on RPA 202248 and RPA 203328, EFED cannot assess chronic risk or determine the need for chronic data. **Estuarine/marine fish early life-stage studies are held in reserve pending the results of outstanding acute toxicity data.**

Minimal chronic risk to shrimp from RPA 202248 is expected based on the margin of safety in the acute-to-chronic ratio that indicates minimal chronic risk. However, since the shrimp acute toxicity data are outstanding on RPA 203328, EFED cannot make any determination of chronic data requirements or assess chronic risk. A shrimp life-cycle study is held in reserve pending the outstanding acute toxicity data on RPA 203328.

Minimal chronic risk to freshwater species are anticipated.

5

5. Water Resources

Isoxaflutole is not currently regulated under the Safe Drinking Water Act, and formal drinking water contaminant levels have not been established. EFED will complete ground and surface water assessments when HED completes its dietary assessment.

Based on incomplete laboratory and field information, the transformation products RPA 202248 and RPA 203328 have many of the characteristics of chemicals known to leach to shallow ground water or runoff to surface water. The metabolites RPA 202248 and RPA 203328 are persistent and mobile and have been observed to leach in terrestrial field dissipation studies. Since the proposed use of isoxaflutole will be widespread geographically, there is potential for widespread contamination of water resources. **If these compounds reach ground or surface water, they will be expected to persist and accumulate.**

EFED has conducted modeling and estimated the concentrations of isoxaflutole and its transformation products in surface and shallow ground water. Modeling using PATRIOT and PRZM-EXAMS estimates maximum concentrations of "hundreds of ppb" in ground water (100 ppb was used as a conservative, representative number) and 5.8 ppb in surface water (36-year maximum of RPA 203328). Irrigation water containing 22 ppt of the transformation products is assumed to be a risk to other crops. The predicted concentrations in ground and surface water exceeded 22 ppt by 4545X and 263X, respectively. These exceedences are uncertain because (1) EFED assumed that isoxaflutole residues are stable in aerobic aquatic environments and that RPA 203328 has Koc of 0.0 due to lack of data, (2) EFED assumed that the transformation products are equally as phytotoxic as parent isoxaflutole in the absence of phytotoxicity data, (3) the PRZM-EXAMS estimates did not account for outflow or dilution processes, and (4) EFED assumed 100% transformation of the parent isoxaflutole to RPA 202248, and then RPA 202248 to RPA 203328 in the PATRIOT modeling.

B. Summary of Data Reviews

The following data table summarizes the status of the environmental fate studies that were reviewed for this registration application.

Guideline Number	Study Type/ Test Material	MRID	DP Barcode	Acceptability	Guideline Status
163-1	Soil Mobility	43940301 44065801	D223678 D231444	Acceptable (core)	Partially Satisfied[1]
164-1	Terrestrial Field Dissipation	43904838 44092101	D223678	Supplemental (upgradeable)	Partially Satisfied[1]

[1] For requirements to upgrade this study, see Data Requirements section below.

A method validation report (MRID 43904840, 43904841) submitted with this package has been forwarded to the EPA Lab in Bay St. Louis, MS for validation of the analytical method.

C. Outstanding Data Requirements:

1. Ecological effects

71-4(a,b) Avian Reproduction Study using RPA 202248
71-4(a,b) Avian Reproduction Study using RPA 203328

Because RPA 202248 and RPA 203328 are persistent, the above studies using RPA 202248 and RPA 203328 are needed since the birds may be subject to repeated or continuous exposure. The preferred test species are mallard duck and bobwhite quail.

The value of these additional data is high because RPA 202248 is a biologically active primary transformation product that is very persistent in the environment. No conclusions about the overall chronic effects from the labeled use of isoxaflutole to birds can be drawn until these studies using RPA 202248 and RPA 203328 are completed and reviewed.

72-3 Acute Toxicity to Shrimp using RPA 203328

The above study is requested in order to estimate the chronic toxicity of RPA 203328. This will help determine if there is a need for chronic studies using RPA 203328.

72-3 Acute Toxicity to Estuarine Fish using RPA 202248 and RPA 203328

The above study is requested in order to estimate the chronic toxicity of RPA 202248 and RPA 203328. These estimates will help determine if there is a need for an estuarine fish early-life stage study.

123-1(a) Seedling Emergence Studies using RPA 202248
123-1(a) Seedling Emergence Studies using RPA 203328

Although the guideline is fulfilled for parent isoxaflutole, the primary chemicals to which plants will be exposed during runoff scenarios are RPA 202248 and RPA 203328. Parent isoxaflutole is not persistent in the environment. It is assumed that there will be some residual control of weeds in the field from RPA 202248 and RPA 203328 based on communication with the registrant and HED. Runoff may happen at a point in time after parent isoxaflutole has transformed to RPA 202248 and/or RPA 203328. Therefore, to assess risk to non-target plants from runoff, EFED requests seedling emergence studies on RPA 202248 and RPA 203328.

123-1(b) Vegetative Vigor Studies using RPA 202248
123-1(b) Vegetative Vigor Studies using RPA 203328

Due to the phytotoxicity of isoxaflutole, the lack of data on the transformation products (RPA 202248 and RPA 203328), the fate characteristics of the two chemicals, and a mode of action similar to clomazone; EFED requests vegetative vigor studies on RPA 202248 and RPA 203328. The data provided from the studies will be used to assess toxicity to nearby non-target plants from soil particles carried by wind and toxicity to sensitive crops from contaminated irrigation waters.

EFED has reviewed the parent isoxaflutole vegetative vigor study and finds that lettuce and ryegrass need to be retested. Because of variability in the data, a valid dose-response could not be generated and an EC_{25} could not be calculated. Isoxaflutole is one of the most phytotoxic herbicides assessed by EFED to date and drift concerns need to be addressed. Therefore, the value of core data on these species is high.

123-2 Aquatic Plant Toxicity studies (5 species) using RPA 202248
123-2 Aquatic Plant Toxicity studies (5 species) using RPA 203328

Although the guideline is fulfilled for parent isoxaflutole, the primary chemicals to which plants will be exposed during runoff scenarios are RPA 202248 and RPA 203328. Parent isoxaflutole is not persistent in the environment. Since RPA 202248 and RPA 203328 persist in the aquatic environment and may be phytotoxically active, non-target aquatic plants may be adversely affected from the proposed use of isoxaflutole. Therefore, EFED requests that aquatic plant toxicity studies be conducted on *Lemna gibba, Selenastrum capricornutum, Anabaena flos-aquae, Skeletonema costatum,* and a freshwater diatom using RPA 202248 and RPA 203328 to allow an assessment of risk to aquatic plants from runoff and long term accumulation in surface water.

2. Environmental Fate

162-4 Aerobic Aquatic Metabolism

The value of the data from this listed study is high since RPA 202248 and RPA 203328 are expected to reach surface and ground water where they will persist and accumulate. These data will be used for modeling. Also, RPA 202248 is herbicidally active. EFED has no data on aerobic aquatic metabolism of RPA 202248 or RPA 203328. The study should be conducted for long enough duration to determine half-lives for RPA 202248 and RPA 203328. The registrant has not demonstrated how RPA 202248 and RPA 203328 degrade in the environment once they leave the treated area.

163-1 Aged Mobility for RPA 203328

The value of the data from the listed study is high since RPA 203328 was formed at approximately 64 % of applied parent in the aerobic soil metabolism study (MRID 43588006). This data will be used for more accurate surface and ground water modeling estimations. The calculated half-life was 977 days, indicating that it is very persistent. RPA 203328 was detected at late as 496 days in the terrestrial field dissipation study (MRID 43904838), also indicating persistence. In addition, RPA 203328 was also detected at 6.8 % of applied in the leachate in the soil column leaching study (MRID 43588008), indicating mobility under some environmental conditions. These data indicate that once it is formed, it will persist and accumulate in the soil and aquatic environment.

164-1 Terrestrial Field Dissipation

The submitted study does not completely satisfy the data requirement. To fulfill the 164-1 data requirement, the registrant should provide pan evaporation data (if available) to determine the water balance in the field dissipation studies. The value of the data from the listed study is high since the approximate water balance in the study could not be confirmed. Although there was downward movement of the transformation products in the study, the lack of an apparent water balance adds uncertainty to the study results. Mobility to water resources would be better understood with more information on water balance.

166-1 Small-Scale Prospective Ground Water Monitoring (Reserved)

Small-Scale Prospective Ground Water Monitoring **is reserved** pending the determination of the RfD and HA by HED and pending review and evaluation of the requested fate and phytotoxicity data. The metabolites of isoxaflutole have many of the environmental fate characteristics of chemicals known to leach to ground water. The metabolites RPA 202248 and RPA 203328 are persistent and mobile and have been observed to leach in terrestrial field dissipation studies. If any residues of the above metabolites were to reach ground water, they would be expected to persist and accumulate.

Recommendations including mitigation and risk reduction:

1. **Based on our current assessment, we recommend against registration at this time.**

2. If it is registered, EFED is also recommending that the application of isoxaflutole be **RESTRICTED TO CERTIFIED APPLICATORS** because this herbicide is more toxic to non-target plants from spray drift than **PICLORAM**. PICLORAM has Restricted Use due to phytotoxicity.

3. EFED requests that the registrant develop analytical methods that can quantify levels of parent isoxaflutole, RPA 202248, and RPA 203328 at which phytotoxic effects can occur. The method may be either a traditional analytical method, or an immunochemical method. If

the new method is immunochemical, then the registrant must follow OPP policies. The method needs to be publicly available.

4. Since phytotoxic amounts are too low to be detected by current analytical methods, it is necessary to find alternative methods to monitor possible impacts to non-target plants from runoff, ground spray drift and/or irrigation from contaminated water resources. Therefore, **EFED requests that the registrant clearly identify morphological symptoms (or specific physiological responses) that can be monitored and clearly defined to determine if a plant was injured or killed specifically from isoxaflutole use.** This would rule out the effects of other herbicides or environmental damages caused by fertility or disease. The method needs to be publicly available.

5. After the morphological symptoms (or specific physiological responses) to parent isoxaflutole are clearly identified, then EFED requests that the registrant present a bioassay monitoring plan to the Agency. This plan will be used to determine whether adverse effects to non-target plants are a result of isoxaflutole use and whether appropiate action can be taken by the Agency to protect non-target plants (including other crops) from the proposed use of isoxaflutole.

6. EFED recommends that **ground spray drift reduction methods be incorporated** into the label. These measures include but are not limited to the following:

(1) not applying isoxaflutole during periods of excess wind activity or during times of inversion,
(2) application nozzles must be no more than 24 inches from the soil surface, and
(3) spray shields should be used during application.

7. The risk quotients are high for risk to non-target plants. In order to reduce the risk, the **maximum proposed rate of application should be reduced.** EFED requests that the registrant provide efficacy data on lower application rates of isoxaflutole that would still maintain acceptable levels of weed control. Different rates of application are often needed due to intensity of infestations, rainfall, soil characteristics, and topography. Therefore, EFED requests efficacy data on a regional basis in a summarized form, unless the registrant wishes to meet with EFED and BEAD to discuss the data needs.

8. EFED understands that the registrant may propose aerial application on future registrations. If an aerial application registration is requested, EFED requests notification and review of this action because of serious concerns for off-site movement of parent isoxaflutole to non-target plants. It is uncertain that 5% spray drift is an accurate estimate of exposure from aerial application. Further refinement of aerial spray drift exposure may be needed since the exposure may be higher than 5%. **Based on current data, EFED recommends that future aerial application be denied.**

9. EFED recommends monitoring of adverse impacts to non-target plants and contamination of water resources.

10. Buffer strip and/or set-backs should be provided for the protection of non-target plants and water resources. The distances for buffer strip and/or set-backs should be proposed by the registrant.

11. For the manufacturing-use products, the following label should be provided:

" Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public waters unless this product is specifically identified and addressed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA."

12. For the end-use products, the following label should be provided:

"Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark."

13. Because of ground water concerns, the following label should be provided:

"This chemical has properties and characteristics associated with chemicals detected in ground water. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination."

14. Because of surface water concerns, the following label should be provided:

"Isoxaflutole residues can contaminate surface water through spray drift. Under some conditions, isoxaflutole residues may also have a high potential for runoff into surface water (primarily via dissolution in runoff water), for several months post-application. These include poorly draining or wet soils with readily visible slopes toward adjacent surface waters, frequently flooded areas, areas over-laying extremely shallow ground water, areas with in-field canals or ditches that drain to surface water, areas not separated from adjacent surface waters with vegetated filter strips, and areas over-laying tile drainage systems that drain to surface water."

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12

1. Environmental Fate

A. Environmental fate assessment for isoxaflutole

Parent isoxaflutole (**RPA 201772; 5-cyclopropyl-4-(2-methanesulphonyl-4-trifluoromethyl benzoyl) isoxazole**) degrades rapidly to form RPA 202248 (**isoxaflutole with the isoxazole ring opened, 2-cyano-3-cyclopropyl-10(2-methylsulphonyl-4-trifluoromethylphenyl) propan-1,3-dione)**). RPA 202248 further degrades to form what appears to be the terminal, non-volatile residue in the environment, RPA 203328 (**dealkylated RPA 202248, 2-methanesulphonyl-4-trifluoromethyl benzoic acid**). The primary routes of dissipation are alkaline-catalyzed abiotic hydrolysis and microbially-mediated metabolism. Although isoxaflutole is potentially mobile in coarse-textured soils, rapid degradation in both soil and water reduces the potential for parent isoxaflutole to be transported to either ground or surface water. However, RPA 202248 and RPA 203328 are persistent and potentially mobile in terrestrial environments and may move into ground and surface water. These residues may potentially accumulate in ground and surface waters.

The degradation of parent isoxaflutole is dependent on hydrolysis and photo-induced transformation. Parent isoxaflutole hydrolyzed with half-lives of 11 days, 20 hours, and 3 hours in pH 5, 7, and 9 buffer solutions, respectively. In the aqueous photolysis study, parent isoxaflutole phototransformed with a calculated half-life of 6.7 days. Major photolytic transformation products were formed from molecular rearrangements of parent isoxaflutole. In soil photodegradation studies, however, parent isoxaflutole degradation was not dependent on photodegradation.

Isoxaflutole is not persistent in aerobic soil and anaerobic aquatic environments. The aerobic soil metabolism half-lives were 30 hours in Norfolk sandy loam soil and 56 hours in Wallasea clay soil. Major transformation products, RPA 202248 and RPA 203328, were found at maximum concentrations of 52-79 % by 7 days and 30-65 % by 1-6 months in the tested soils, respectively. Parent isoxaflutole degraded rapidly ($t_{1/2}<2$ hours) under anaerobic aquatic conditions (Eh=-420 mv). The calculated half-lives of RPA 202248 in water and of RPA 205834 (**cyano-hydrated RPA 202248, 2-aminomethylene-1-cyclopropyl-3-(2-methylsulphonyl-4-trifluoromethylphenyl)propan-1,3-dione**) in the combined system were 316 and 130 days, respectively. Bound radiolabeled residues (NaOH-extractable) increased to 17% by 365 days.

Batch equilibrium data indicate that isoxaflutole is potentially mobile in coarse textured soils. Parent isoxaflutole had Freundlich adsorption coefficients (K_d's) of 0.51 to 2.2 ml/g in sand and sandy loam soils and 0.9.3 to 14.4 ml/g in silty clay soil and loam sediment. Isoxaflutole sorption on soil is expected to be a reversible process. It also appears to depend on soil organic carbon content ($r^2=0.95$).

Freundlich adsorption coefficients (K_{ads}) for RPA 202248 ranged from 0.44 to 6.7 (Koc=94 to 159 ml/g) in five U.S. soils, three U.K. soils, and one U.S. aquatic sediment. Freundlich K_{des} values ranged from 0.77 to 8.96 (0.34 to 4.9 % OC). The 1/n values were 0.81 to 0.96 for adsorption and desorption. In an aged soil column leaching study, RPA 202248 was very mobile in sand, sandy loam, and clay loam soils with 90, 43, and 75% of applied radioactivity reaching the leachate, respectively. RPA 202248 is potentially very mobile in terrestrial environments. While no batch equilibrium data have been submitted for RPA 203328, it is potentially very mobile in terrestrial environments because it is very persistent, has a similar structure to RPA 202248 and is more water soluble and polar (anionic) than parent isoxaflutole and RPA 202248 due to the presence of carboxylic acid groups. Parent isoxaflutole was not detected in the leachate from any tested soil.

Since isoxaflutole has low vapor pressure (7.5×10^{-9} mm Hg) and Henry's Law Constant (1.84×10^{-10} torr m^3 mol^{-1}), volatilization is not expected to be a major route of dissipation.

Isoxaflutole rapidly dissipated ($t_{1/2}$'s=1.4 to 3.0 days) in field dissipation studies in Nebraska, Washington, California, and North Carolina in plots planted to corn. The half-lives for RPA 202248 were 133 days in CA and 11-17 days in NE, WA, and NC. The large discrepancy in reported half-lives may be attributed to the low moisture conditions at the CA site. The maximum depth of leaching was 12 inches in the CA study. RPA 202248 did appear to leach in the field dissipation studies in NE and NC. RPA 203328 was present as the terminal residue in the environment at all the sites, and was more persistent than RPA 202248. The maximum depth of leaching of 203328 ranged from 12-18 inches at the NC, WA, and CA sites. Since the amount of evapotranspiration was not reported, a complete field study water balance could not be determined, and the maximum depth of leaching is unknown. However, the fact that residues of RPA 202248 and RPA 203328 were mobile in the field dissipation study indicates that aged residues of isoxaflutole are likely to reach shallow ground water under some environmental conditions.

B. Environmental Fate Data Summaries

Hydrolysis (161-1)

In sterile, aqueous buffer solutions, radiolabeled isoxaflutole, at 3 μg/ml, degraded with pH-dependent half-lives of 11.1 days at pH 5, 20.1 hours at pH 7, and 3.2 hours at pH 9. The only transformation product was RPA 202248 (isoxaflutole with the isoxazole ring opened). The hydrolysis guideline requirement (161-1) is fulfilled (MRID 43573254).

Photodegradation in water (161-2)

Radiolabeled isoxaflutole, at 3 μg/ml, photodegraded in sterile pH 5 buffer solutions that were continuously irradiated with a xenon lamp for 9 days. Minimal degradation (11 % of applied) of parent was observed in the dark controls. Two major photoproducts were formed by molecular rearrangements of parent isoxaflutole: transformation products 20 and 14 (hydrated transformation product 20). The photodegradation in water guideline requirement (161-2) is fulfilled (MRID 43588004).

Photodegradation on soil (161-3)

Radiolabeled isoxaflutole, at 0.58 lb µg/g, had a degradation half-life of 23 hours on sandy loam soil that was irradiated with a xenon light source for 31 days. A similar half-life estimate (20 hours) was observed in the dark control treatment on soil. The major transformation products, RPA 202248 and RPA 203328, were detected in both the dark control and irradiated samples. Volatile and non-extractable residues did not exceed 0.2 % and 9.1 % of applied, respectively. The photodegradation on soil (161-3) guideline requirement (161-3) is fulfilled (MRID 43588005).

Aerobic soil metabolism (162-1)

Radiolabeled isoxaflutole, at 0.19 µg/g, degraded with half-lives of 30 and 56 hours in Norfolk sandy loam (pH 6.6, 0.9% OC) and Wallasea clay (pH 5.9, 4.5% OC) soils, respectively. The major non-volatile transformation products, RPA 202248 and RPA 203328, were detected at maximum concentrations of 52-79 % of the applied at 7 days posttreatment and 30-65 % of the applied in the tested soils at 1-6 months posttreatment, respectively. The EFED-calculated half-lives for RPA 202248 in sandy loam and clay soils were 115 and 186 days, respectively. The registrant-calculated half-life for RPA 203328 was 977 days. Bound residues (removable by NaOH) increased to 15-19 % in the sandy loam soil and 18-27 % in the clay soil. The major volatile degradate was CO_2, increasing to 14 % in the sandy loam and 37 % in the clay soil. The aerobic soil metabolism guideline requirement (162-1) is fulfilled (MRID 43588006).

Anaerobic aquatic metabolism (162-3)

Radiolabeled isoxaflutole, at 0.19 µg/g sediment, degraded with a half-life of <2 hours in non-sterile, anaerobic aquatic sediment:pond water incubated at 25°C for up to 365 days. Parent isoxaflutole degraded rapidly to form RPA 202248. RPA 202248 was present in water at 69 % of applied at 6 hours posttreatment, and reached approximately equal concentrations in water and sediment (43-48 % in water, 52-57% in sediment) by 28-365 days. The calculated half-lives for RPA 202248 and RPA 205834 **(cyano-hydrated RPA 202248)** in water were 316 and 13 days, respectively. Bound residues (removable by NaOH) increased from 0.18% at zero time to 17% by 365 days. The anaerobic aquatic metabolism guideline requirement (162-3) is fulfilled (MRID 43588007).

Aerobic aquatic metabolism (162-4)

Since the isoxaflutole transformation products RPA 202248 and RPA 203328 may move into surface waters, aerobic aquatic metabolism data are needed to evaluate the fate of isoxaflutole and its transformation products in aquatic environments. The study should be conducted for sufficient duration to determine the half-lives of the transformation products.

Soil adsorption/desorption (163-1)

The mobility and adsorption/desorption coefficients of parent isoxaflutole and RPA 202248 are shown in Table 1 and 2.

Table 1. Adsorption and Desorption of Parent Isoxaflutole in Soils and Sediments (MRID 43588009).

Soil (% OC)	Freundlich K_{ads} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)	Freundlich K_{des} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)
Sand (0.5 % OC)	0.51	101	1.00	None[1]	None[1]	None[1]
Sandy Loam (0.9 % OC)	1.2	131	0.90	2.6	284	0.93
Loam (2.4 % OC)	2.2	93	0.94	2.0	82	1.02
Silty Clay (7.5 % OC)	9.3	123	0.95	13.4	179	0.95
Loam Sediment	14.4	165	0.92	10.4	119	0.90

[1] Because of low Freundlich K_{ads} values, calculation of desorption values were not possible.

Based on the adsorption-desorption coefficients, parent isoxaflutole is potentially mobile in sand, sandy loam, and loam soils (Freundlich K_{ads} values of 0.5-2.2) and essentially immobile in silty clay soil and loam sediment (Freundlich K_{ads} values of 9.3-14.4). Isoxaflutole sorption on soil is expected to be a reversible process because the adsorption-desorption coefficients were similar. Sorption of isoxaflutole appears to depend on soil organic carbon content (r^2=0.95).

Table 2. Adsorption and Desorption of RPA 202248 in Soils and Sediments (MRID's 43940301, 44065801).

Soil (% OC)	Freundlich K_{ads} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)	Freundlich K_{des} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)
Sand (0.38 % OC)	0.44	117	0.95	1.1	293	0.91
Loamy Sand (0.34 % OC)	0.54	159	0.96	1.62	474	0.94
Loamy Sand (1.1 % OC)	0.63	57	0.97	0.77	70	0.93

Table 2. Adsorption and Desorption of RPA 202248 in Soils and Sediments (MRID's 43940301, 44065801).						
Soil (% OC)	Freundlich K_{ads} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)	Freundlich K_{des} (ml/g)	Koc (ml/g)	1/n (Slope of Isotherm)
Sandy Loam (1.3 % OC)	0.71	54	0.92	1.27	97	0.89
Sandy Loam (2.2 % OC)	2.18	99	0.93	3.5	159	0.92
Loam (1.9 % OC)	2.54	134	0.99	3.99	210	0.93
Loam Sediment (5.0 % OC)	6.7	135	0.89	8.96	180	0.89
Silt Loam (0.47 % OC)	0.70	149	0.95	1.56	333	0.91
Clay (1.15 % OC)	1.15	94	0.92	1.3	106	0.81

Based on the adsorption-desorption coefficients, RPA 202248 is potentially mobile in soils with low organic carbon content (r^2=0.95). Freundlich K_{ads} values for RPA 202248 ranged from 0.44-6.7 in the tested soils and sediments from the U.S. and U.K. Since adsorption and desorption partition values are comparable, RPA 202248 sorption on soil is expected to be a reversible process. Sorption of RPA 202248 appears to depend on soil organic carbon content (r^2=0.95).

In an aged soil column leaching study, [^{14}C]isoxaflutole residues were very mobile in sand, sandy loam, and clay loam soils with 0.1-2.0% OC. Parent isoxaflutole was generally not found below 6 cm of soil depth, and was not detected in the leachate from any soil. The primary residue in the leachate was RPA 202248 at 90, 43, and 75% of applied radioactivity in the sand, sandy loam, and clay soils, respectively. The remaining radioactivity was uniformly distributed throughout the soil columns. Although <2 % of applied radioactivity reached the leachate in the silty clay soil and loam sediment (7.5-8.5% OC), the radioactive residues were relatively uniform in concentration to 9 inches of depth in the soil column. In the sandy loam soil, RPA 203328 reached an average of 6.8% in the leachate, but was not found in the leachate from any other soil. MRID 43588008.

The aged soil column and adsorption/desorption studies (MRID's 43588008, 43588009, and 44065801) partially fulfill the 163-1 data requirement. To completely fulfill the 163-1 data requirement, the registrant should conduct a batch equilibrium study using RPA 203328. Since RPA 203328 exhibits properties of a mobile pesticide (carboxylic acid functional groups), batch equilibrium data are needed to complete surface and ground water assessments. RPA 203328 was the persistent, terminal transformation product in the aerobic soil metabolism (MRID 43588006), anaerobic aquatic metabolism (MRID 43588007, and terrestrial field dissipation studies (MRID 44092101) submitted to the Agency.

Terrestrial field dissipation (164-1)

Parent isoxaflutole, (applied at 0.38 lbs ai/A)[1], rapidly dissipated ($t_{1/2}$=1.4-3.0 days) in Hasting silt loam (pH 5.8, 1.5 % OC) in NE, Timmerman sandy loam (pH 7.1, 0.7 % OC) in WA, Sorrento silt loam (pH 8.9, 0.47 % OC) in CA, and Norfolk loamy sand (pH 5.9, 0.35 % OC) in NC. Residues of RPA 202248 was present at maximum soil concentrations of 0.040-0.060 ppm by 1 to 7 days posttreatment, and then declined to levels near the detection limit (0.01 ppm) at 414 days posttreatment in the CA study and 28-59 days posttreatment in the NC, WA, and NE studies. The half-lives for RPA 202248 in the surface 6 inches of soil were 133 days in the CA study and 11-17 days for the NE, WA, and NC studies. The maximum depth of leaching of RPA 202248 detected was 12 inches at 6 and 28 days (0.94-3.8 inches of rainfall/irrigation) in the CA study. RPA 203328 was detected (0.012-0.067 ppm) in all the studies. The maximum depth of leaching of RPA 203328 was 12 inches at the NC site by 30 days posttreatment (4.4 inches of rainfall/irrigation) and to 18 inches at the Washington site by 59 days posttreatment (8 inches of rainfall/irrigation). RPA 203328 was also detected to 18 inches of depth at the CA site by 356 days posttreatment (47.4 inches of rainfall/irrigation). All detections of RPA 202248 and RPA 203328 in the 12-18 inch soil layers were near the detection limit of 0.01 ppm. The guideline requirement is only partially fulfilled since the registrant did not provide data on pan evaporation to determine an approximate water balance (MRID 44092101).

[1] This application rate was phytotoxic to the corn in the NC and CA studies.

C. Water Resources

Since isoxaflutole is being registered for an ubiquitous crop such as field corn, the water resource assessment will focus on the major corn production regions. The geographic distribution of field corn is primarily associated with the following major resource land areas (MRLAs): 1) Central Feed Grains and Livestock Region; 2) Atlantic and Gulf Coast Lowland Forest and Truck Crop Region; 3) Eastern section of the South Atlantic and Gulf Slope Cash Crop, Forest, and Livestock Region; 4) Northern Atlantic Slope Truck, Fruit, and Poultry Region; 5) Lake States Fruit, Truck, 6) Dairy Region; Western Great Plains and Irrigated Region; and 7) Northern Great Plains Spring Wheat Region (Austin, 1972). These regions are predominately representative of the climatic conditions of the eastern two-thirds of the United States. The precipitation gradient can range from 50 inches in the Northern Atlantic Slope Truck, Fruit, and Poultry Region to 20 inches in the western section of Western Great Plains and Irrigated Region. Although the distribution of precipitation varies among the corn growing regions, it is generally highest from late spring to midsummer.

Further analysis of the corn production area indicates some localized regions have a high pesticide vulnerability index for contamination of shallow ground water (Kellogg et al., 1992). These regions are the coastal plains of Georgia, S. Carolina, and N. Carolina; eastern section of Nebraska; the eastern shore region of Lake Ontario; and the Delmarva

Peninsula. The most vulnerable soils for groundwater contamination appear to be associated with Psamments. The majority of the corn growing area is classified as Hydrologic Group B soils. Group B soils are characterized by moderately high to high saturated hydraulic conductivities (K_{sat}=0.36 to 3.60 cm/hr) and deep to very deep ground water. The major Group B soil subgroups are classified as Argiudolls, Hapludolls, Hapludalfs, and Dystrochepts. Small areas of concentrated Group C soils are found in Ohio, southern Iowa and Illinois, and Eastern Indiana. The major Group C soil subgroups are Hapludults and Hapludalfs. Also, the Gulf coast region of Texas consist of a high concentration of Group D soils. The major Group D soil subgroups are Ochraquults, Haplaquolls, Humaquepts, and Pelluderts. Group C and D soils are more prone to surface water runoff because of lower saturated hydraulic conductivities and/or relatively high water table.

(1) Surface Water

Surface Water Assessment

Isoxaflutole is a preemergence herbicide for the control of grassy and broadleaf weeds in field corn. The submitted label for isoxaflutole proposes a maximum single ground spray application at 0.1875 lb ai/A/season.

Since isoxaflutole is applied using ground spray methods, it is assumed that isoxaflutole can potentially drift off-site and be directly deposited into adjoining surface water bodies. The surface water assessment for isoxaflutole assumes that the spray drift potential for ground spray application methods is 1% of the applied pesticide. Isoxaflutole rapidly degrades ($t_{1/2}$ < 2.4 days) and has a relatively low soil sorption affinity in coarse textured soils. Isoxaflutole degrades to form RPA 202248. RPA 202248 further degrades to form RPA 203328. These transformation products exhibit a greater persistence and mobility potential than parent isoxaflutole in terrestrial environments.

The following data were used for input into the GENEEC and PRZM-EXAMS modeling for **Parent Isoxaflutole:**

Parameter	Value	Source
soil K_{oc}	122 ml/g[1]	MRID 43588009
Aerobic soil half-life	2.4 days	MRID 43588006
Aerobic aquatic half-life	Stable	No available data
Photolysis Half-life (pH 7)	6.7 days	MRID 43588004
Hydrolysis (pH 7)	0.83 days	MRID 43573254
Water Solubility	3.5 mg/l	MRID 42275501

[1] This value represents the mean K_{oc} partitioning coefficient.

TABLE 3a. Tier I GENEEC[1] Aquatic Estimated Environmental Concentrations for Parent Isoxaflutole

RATE (lbs ai/A/season)	PEAK EEC (ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.1875	4.05	1.72	0.34	0.13

TABLE 3b. Tier II PRZM-EXAMS Aquatic Estimated Environmental Concentrations for Parent Isoxaflutole.

RATE (lbs ai/A/season)	PEAK EEC(ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.1875	0.39[2]	0.18	0.05	0.02

[1] GENERAL: EFED calculated generic EECs using the GENeric Expected Environmental Concentration Program (GENEEC) and PRZM-EXAMS. These EECs are designed as a coarse screen and estimate expected concentrations from a few basic chemical parameters and pesticide product label application information. GENEEC is a Tier I model which uses a chemical's soil/water partition coefficient and degradation half-life values to estimate runoff from a 10-hectare field into a 1-hectare by 2-meter deep pond. GENEEC calculates both acute and chronic generic expected environmental concentration (GEEC) values. It considers reduction in dissolved pesticide concentration due to adsorption of pesticide to soil or sediment, incorporation, degradation in soil before wash-off to a water body, direct deposition of spray drift onto the water body, and degradation of the pesticide within the water body. It is designed to mimic a PRZM-EXAMS simulation.

[2] One-in-Ten-Year EEC's.

Since the transformation products of isoxaflutole, RPA 202248 and RPA 203328, are potentially phytotoxic and exhibit a greater persistence and potential mobility than parent isoxaflutole, a surface water assessment was conducted to assess the runoff potential of RPA 202248 and RPA 203328. A complete set of environmental fate data for RPA 202248 were available except for aerobic aquatic metabolism, aqueous photolysis, and hydrolysis. EFED notes the first-order half-life for RPA 202248 was estimated at 186 days from aerobic soil metabolism data (MRID 44065801). The environmental fate data for RPA 203328 is more tentative because of insufficient data on aerobic aquatic metabolism, aqueous photolysis, hydrolysis, and soil/water partitioning coefficients. Default input values for environmental fate data were selected to provide "worst-case" results ; input values were a stable degradation half-life ($k=0.0000$ $days^{-1}$) and/or no sorption to soil ($K_{oc}=0.0$ ml/g).

The following values were used for input into the GENEEC and PRZM-EXAMS Programs for **RPA 202248**:

Parameter	Value	Source
Mean soil K_{oc}	92 ml/g	MRID 44065801
Aerobic soil half-life	186 days	MRID 43588006
Aerobic aquatic half-life	Stable	No available data
Photolysis Half-life (pH 7)	Stable[1]	MRID 43588004
Hydrolysis (pH 7)	Stable[2]	MRID 43573254
Water Solubility	300 mg/l	

[1] Only minor amounts of RPA 202248 were formed in the aqueous photolysis study. Parent isoxaflutole primarily degraded to photoproducts.
[2] RPA 202248 did not appear to degrade in the hydrolysis study.

TABLE 4a. GENEEC Aquatic Estimated Environmental Concentrations for RPA 202248.

RATE (lbs ai/A/season)	PEAK EEC (ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.150[1]	6.27	6.25	6.17	6.05

TABLE 4b. Tier II PRZM-EXAMS Aquatic Estimated Environmental Concentrations for RPA 202248

RATE (lbs ai/A/season)	PEAK EEC(ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.150	2.90[2]	2.90	2.90	2.90
0.150	2.39[3]	2.39	2.39	2.39

[1] The application rate has been adjusted to account for an 80% conversion of isoxaflutole to RPA 202248 (MRID 4358806).

[2] Maximum 36-year EEC's

[3] These values are not representative of 1-in-10 year EECs because they accumulate over time in water bodies.

For risk assessment purposes, a more refined Tier II PRZM-EXAMS model is used. Since the model shows RPA 202248 to accumulate over time, the estimated 36-year maximum concentration of **2.9 ppb** is used in the Risk Assessment Section (see section 3).
The following values were used for input into the GENEEC Program for **RPA 203328**:

Parameter	**Value**	**Source**
Mean soil K_{oc}	0 ml/g	MRID 44065801
Aerobic soil half-life	977 days	MRID 43588006
Aerobic aquatic half-life	Stable	No available data
Photolysis Half-life (pH 7)	Stable	No available data
Hydrolysis (pH 7)	Stable	No available data
Water Solubility	8000 mg/l	

21

TABLE 5a. GENEEC Aquatic Estimated Environmental Concentrations for RPA 203328.				
RATE (lbs ai/A/season)	PEAK EEC (ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.150[1]	8.41	8.41	8.40	8.38

TABLE 5b. Tier II PRZM-EXAMS Aquatic Estimated Environmental Concentrations for RPA 203328				
RATE (lbs ai/A/season)	PEAK EEC(ppb)	DAY 4 EEC (ppb)	DAY 21 EEC (ppb)	Day 56 EEC (ppb)
0.150	5.80[2]	5.80	5.80	5.80
0.150	5.54[3]	5.54	5.54	5.54

[1] The application rate has been adjusted to account for an 80% conversion of isoxaflutole to RPA 203328 (MRID 4358806).

[2] Maximum 36-year EEC's

[3] These values are not representative of 1-in-10 year EECs because they accumulate over time in water bodies.

For risk assessment purposes, a more refined Tier II PRZM-EXAMS model is used. Since the model shows RPA 203328 to accumulate over time, the estimated 36-year maximum concentration of **5.8 ppb** is used in the Risk Assessment Section (see section 3).

Discussion on PRZM-EXAMS Modeling

Since the peak GENEEC EECs exceed the phytotoxic threshold level of 0.022 μg/L (see Risk Characterization Section, 5.C.), EFED conducted a Tier II surface water assessment for a corn runoff scenario on a Marshall silty clay loam (Fine-silty, mixed, Mesic Typic Hapludolls) in Pottawatamie County, Iowa. This soil is a Hydrologic Group B soil. A Hydrologic Group B soil indicates the soil may have low to moderately high runoff potential. Annual climatic data from 1948 to 1983 were obtained for the Major Land Resource Area (MRLA) 107. Thirty-six consecutive PRZM-EXAM simulations were conducted to evaluate the cumulative probability distribution for peak, 96 hour, 21 day, 60 day, and 90 day EECs.

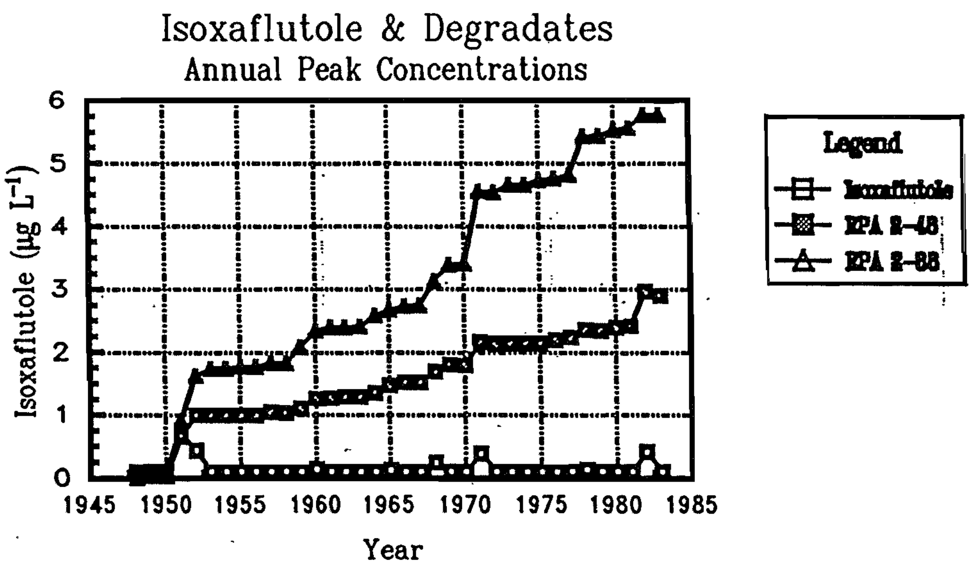
PRZM-EXAMS Results

The peak GENEEC EEC's for isoxaflutole, RPA 202248, RPA 203328 are 4.05, 6.27, and 8.41 ppb, respectively (Table 1a, 2, and 3). The one-in-10 year PRZM-EXAMS EEC's for isoxaflutole, RPA 202248, RPA 203328 are 0.39, 2.4, and 5.5 ppb, respectively. These EECs can potentially cause phytotoxic effects to non-target plants irrigated with 2 acre-inches of contaminated surface water. More refined PRZM-EXAMS modeling indicates that the 90% exceedance EEC for isoxaflutole also would exceed the phytotoxic trigger concentration for irrigation water (Table 2). PRZM-EXAMS modeling indicates that RPA 202248 and 203328 may potentially accumulate in static, surface waters (Figure 1). Exceedance EECs for RPA 202248 and RPA 203328 were not calculated because there was residue accumulation in the surface water body with successive annual applications (Figure 1). However, average annual EECs for RPA 202248 and RPA 203328 were greater than the 0.022 μg/L. ERCB/EFED notes that accumulation of isoxaflutole residues in surface waters may be an artifact of the computer simulation for several reasons: 1.) surface water hydrology of the pond does not account for outflow and/ or dilution processes; 2.) aerobic aquatic metabolism was not considered as a route of dissipation; and, 3.) the mobility of RPA 203328 was assumed to be the worst-case default value (K_{oc}=0.00). ERCB notes the K_{oc} for RPA 203328 is expected to be low because it has a carboxylic acid functional group and hence will be anionic (fully dissociated) under most environmental conditions.

Based strictly on GENEEC and PRZM-EXAMS EECs for isoxaflutole, a 50% reduction in the application rate (0.0937 lbs a.i/A) would not reduce the EEC's of isoxaflutole and its transformation products below the phytotoxicity trigger of 0.022 μg/L (See Discussion in Risk Characterization (Section 5.C.). A reduction in the application rate of isoxaflutole is expected to reduce the amount of RPA 202248 and RPA 203328 found in the aquatic environment. However, there is some uncertainty in the potential impact because of insufficient environmental fate and phytotoxicity data. Therefore, a more complete environmental fate assessment for RPA 202248 and RPA 203328 will require additional aerobic aquatic metabolism and batch equilibrium data.

23

Figure 1.



(2) Ground Water

Isoxaflutole and its degradates were evaluated for persistence and mobility in relation to its potential to leach to ground water. The following table contains the environmental fate characteristics used to determine the need for Restricted Use of parent isoxaflutole and RPA 202248.

Table 6. Mobility and Persistence of Isoxaflutole and RPA 202248 Relative to Restricted Use Criteria

FACTORS	CHARACTERISTIC	RESTRICTED USE CRITERIA	Isoxaflutole (Parent)	RPA 202248 (Transformation Product)
PERSISTENCE	Field dissipation half-life	≥ 3 weeks or	0.14-0.43 wks (1.4-3.0 d)	1.6-19 wks[1] (11-133 d.)
	Lab-derived aerobic soil metabolism half-life	> 3 weeks or	0.18, 0.33 wks (1.3, 2.4 d.)	16.4, 26.6 wks (115, 186 d.)
	Hydrolysis half-life	< 10% degraded in 30 days or	19, 1.4, 0.22 % remaining after 30 day	Stable
	Photolysis half-life (soil)	< 10% degraded in 30 days or	Stable[2]	Stable[3]

Table 6. Mobility and Persistence of Isoxaflutole and RPA 202248 Relative to Restricted Use Criteria				
FACTORS	CHARACTERISTIC	RESTRICTED USE CRITERIA	Isoxaflutole (Parent)	RPA 202248 (Transformation Product)
MOBILITY	Soil adsorption: K_d	≤ 5 ml/g or	0.51 - 14.4 ml/g	0.44 - 6.71 ml/g
	Soil adsorption: K_{oc}	≤ 500 ml/g or	82-284 ml/g	54-159 ml/g
	Depth of leaching in field dissipation study	75 cm	15 cm	30 cm

[1] The half-life in CA was 133 days (19 weeks) since no rainfall/irrigation was applied until 28 days after application. At the WA, NE, and NC sites, the half-lives were 11-17 days (1.6-2.4 weeks) since rainfall/irrigation was applied at 6-7 days at these sites. RPA 202248 did not dissipate until 3-7 inches of rainfall/irrigation was applied at all four sites.

[2] Isoxaflutole appeared to degrade by aerobic soil metabolism in both the irradiated and dark control samples, as evidenced by similar half-lives (23 and 20 hours, respectively).

[3] RPA 202248 only declined at the last sampling interval (31 days).

Shaded area indicates that parameter exceeds trigger.

The degradates RPA 202248 and RPA 203328 have the characteristics of compounds that are known to leach to ground water. RPA 202248 exceeded the criteria for persistence and mobility for ground water concerns. The registrant has not submitted adequate data to determine the persistence and mobility of RPA 203328 in the environment. However, it appears to be very persistent in the submitted studies, and exhibits physicochemical properties of mobile pesticides (e.g., carboxylic acid functional group). Since this is a new chemical, there are no reports of sampling or detections in OPP's "Pesticides and Ground Water Database" or in EFED's ground water files. Isoxaflutole and its degradates trigger the criteria for restricted use due to ground water concerns.

A Reference Dose (RfD) for isoxaflutole has not been established at this time. Because of this, it is not possible to estimate a Lifetime Health Advisory (HA) for isoxaflutole residues in drinking water. Isoxaflutole is not currently regulated under the Safe Drinking Water Act and formal drinking water contaminant levels have not been established.

<u>PATRIOT Modeling:</u>

The Pesticide Assessment Tool for Rating Investigations of Transport (PATRIOT) is designed to provide rapid analyses of ground water vulnerability to pesticides on a regional, state, or local level. PATRIOT assesses ground water vulnerability by quantifying pesticide leaching potential in terms of the pesticide mass transported to the water table.

To better understand the leaching potential of isoxaflutole and its degradates, the model PATRIOT was used to perform a comparative leaching assessment. PATRIOT incorporates the pesticide fate and transport model PRZM2 (Pesticide Root Zone Model - 2). PRZM is a one-dimensional, dynamic, compartmental model that can be used to simulate pesticide movement in unsaturated soil systems within and immediately below the plant root zone.

The scenario selected for the modeling was Iowa corn soils with very shallow ground water, about 4 1/2 ft deep. Four typical corn soils were selected to represent each of the Hydrologic soil Groups A, B, C and D in Iowa. They were: Sparta soil (Group A), Marshall soil (Group B), Grundy soil (Group C), and Webster soil (Group D).

Hydrologic Group A and B soils are more prone to leaching because they are well drained (6 to 20 inches/hr) with a water table depth usually greater than 6 feet. Group C and D soils have a moderate to high runoff potential because of a slow permeability (0.6 to 6 in/hr.) coupled with a high water table (< 1 foot).

Since there is no batch equilibrium data available for the degradate RPA 203328, the K_{oc} was assumed to be 0.01 ml/g for this modeling. This modeling assumed 100% transformation of the parent isoxaflutole to RPA 202248, and then RPA 202248 to RPA 203328. Additional assumptions and input from the PATRIOT modeling is below:

Table 7. Assumptions and other inputs for PATRIOT comparative leaching assessment.

Chemical	K_{oc} (ml/g)	Aerobic Soil half-life (days)
Isoxaflutole (parent)	122	2.4
RPA 202248 (degradate)	92	186
RPA 203328 (degradate)	0.01	977
Atrazine	89	75
Bromide tracer	0.01	9999999

<u>Model Input data:</u>

Crop: Corn (Crop #1)
State: Iowa
Rate of application: 0.1875 lb ai/a = 0.21 kg ai /HA
Incorporation depth: 2 cm.
Total Depth of Modeling: 131.0 cm.
Weather Station: Omaha (Station W14942)
Weather Data: 1961-1970
Modeling Corrected for evaporation and irrigation

24

Cropping Data

Planting date:5/1
Emergence date:5/11
Maturity date: 9/21
Harvest date:10/6

Iowa Soils:

Group A: Sparta, #22759
Group B: Marshall, #464
Group C: Grundy, #9436
Group D: Webster, #4727

Under these conditions the leaching of isoxaflutole and its degradates were compared to the potential leaching of atrazine and bromide. Atrazine was selected because it is a well characterized corn herbicide and is known to leach to ground water. Bromide was selected because it is a commonly used tracer to detect water movement.

Modeling Results:

The PATRIOT modeling predicted that parent isoxaflutole would not leach to shallow ground water in each of the representative hydrologic soil groups. This result is expected because isoxaflutole has a short half-life of 1-2.5 days in aerobic soil.

The degradate RPA 202248 was predicted to leach on the Group A and Group C soils. PATRIOT estimated that approximately 30% of the total applied mass of RPA 202248 would leach to shallow ground water when used on Group A soils. Less than 5 % of the total applied mass was predicted to leach to ground water on the Group C soil. For the Group A, B, and C soils, the predicted peak concentrations at the top of the water table would be in the tens of ppb. No RPA 202248 was predicted to leach on the Group D soil.

PATRIOT modeling predicted significant leaching of the terminal degradate RPA 203328 on all soil types. The mass leached of RPA 203328 was comparable to the bromide tracer and is much greater than from applied atrazine. The similarity in leaching to bromide may partly be an artifact of the assumption that the Koc = 0. Even with a higher Koc, because of the long half-life, EFED would still anticipate significant leaching of RPA 203328 to ground water.

Modeling on the vulnerable Group A soil estimated that greater than 90% of the total applied mass of RPA 203328 would leach to shallow ground water. Peak concentrations predicted at the top of the water table would be in the hundreds of ppbs.

27

Leaching of RPA 203328 on the Group B, C, and D was less than in the Group A soils. From 25% to 65% of the total applied mass was predicted to leach to shallow ground water on these soils. The peak concentrations predicted at the top of the water table would also be in the hundreds of ppbs.

Because RPA 203328 has an estimated aerobic soil half-life of about three years, the soil will act as a reservoir holding it until there is sufficient water to carry it through the soil profile. RPA 203328 will accumulate in the soil horizon and carry over each year thus the total mass reaching ground water may exceeded the total mass applied in that particular year. The mass of RPA 203328 estimated to leach to ground water for each year ranged from approximately 60 to 120% of the annual application.

This assessment was conducted using data from NOAA weather stations for the years 1961 to 1970. When calculating annual leaching, PATRIOT predicted limited leaching of RPA 203328, during the first several years. This was due to the low rainfall for the modeled area. In subsequent years, significant leaching of RPA 203328 was predicted due to increased precipitation. Not unexpectedly, leaching appears to be strongly controlled by the amount of precipitation received. Thus the estimates of the annual leaching of isoxaflutole degradates on Group B, C, and D soils is strongly controlled by the rainfall and total leaching each year is highly variable. To improve the use of this data, calculations are presented as ten year mean values.

Refer to Appendix 1 and 2 for graphs of the results of the comparative leaching of isoxaflutole and its degradates to atrazine and bromide. These graphs show rough estimates of the peak concentrations predicted to reach the top of the water table.

<u>Ground Water Summary:</u>

This assessment is considered to be conservative and has assumed a transformation of 100% of the parent to the degradate RPA 202248 and then 100% transformation to RPA 203328.

Modeling of the terminal degradate RPA 203328 demonstrates that it may accumulate in the soil and ground water. When used on a highly vulnerable soil with a shallow water table, RPA 203238 is expected to leach to shallow ground water. Modeling on a Group A soil (vulnerable to leaching) predicted that greater than 95% of the applied mass would leach to shallow ground water. Because of its long half-life and the carry over from year to year, the mass leached to ground water may exceed the total applied that particular year. Leaching on these soils will be strongly dependent upon water input from rainfall.

D. Method Validation

The results of the registrant's method validation data for soil that have been submitted for registration of isoxaflutole are summarized in the table below. The studies have been sent to Bay St. Louis for evaluation. EFED notes that phytotoxicity triggers (22 ppt or 0.022 ppb) noted in the Risk Characterization Section, (3.C.), are greater than 800X lower than the limits of quantitation for isoxaflutole and its transformation products (18.9 ppb).

Table 8. **Summary of the Minimum Detection Limits (MDL) and Limits of Quantitation (LOQ) for isoxaflutole and its metabolites in soil (MRID 43904840, page 31).**

	SOIL		WATER[1]	
Analyte	MDL, ppb	LOQ, ppb	MDL, ppb	LOQ, ppb
Isoxaflutole	5.425	13.974	0.5	1.0
RPA 205834	4.186	8.908	0.5	1.0
RPA 202248	3.912	12.723	0.5	1.0
RPA 203328	6.052	18.932	0.5	1.0

[1] These are preliminary limits. The registrant has not completed their internal method validation study for surface water at this time.

2. Ecological Toxicity Data

Based on the fate characteristics of parent isoxaflutole and its transformation products, the acute risk to terrestrial and aquatic animals will be determined using estimated exposure to parent isoxaflutole and/or RPA 202248. Chronic risk will be determined using estimated exposure to RPA 202248 and/or RPA 203328. Henceforth, throughout the rest of EFED Science Chapter, acute or chronic risk will be determined by the above exposures.

a. Toxicity to Terrestrial Animals

i. Birds, Acute and Subacute

An acute oral toxicity study using the technical grade of the active ingredient (TGAI) is required to establish the toxicity of isoxaflutole to birds. The preferred test species is either mallard duck (a waterfowl) or bobwhite quail (an upland gamebird). Results of this test are tabulated below.

Table 9. Avian Acute Oral Toxicity

Species	% ai	LD_{50} (mg/kg)	Toxicity Category	MRID No. Author/Year	Study Classification[1]
Mallard Duck *(Anas platyrhynchos)*	98.7	>2150	Practically non-toxic	43573232 Petersen,1994	Core
Northern bobwhite quail *(Colinus virginianus)*	98.7	>2150	Practically non-toxic	43573231 Petersen,1994	Core

[1] Core (study satisfies guideline). Supplemental (study is scientifically sound, but does not satisfy guideline)

Since the LD_{50} falls in the range of >2000 mg/kg, isoxaflutole is practically non-toxic to avian species on an acute oral basis. The guideline (71-1) is fulfilled (MRID# 43573231, 43573232).

Two subacute dietary studies using the TGAI are required to establish the toxicity of isoxaflutole to birds. The preferred test species are mallard duck and bobwhite quail. In addition, due to the persistence of RPA 202248 and RPA 203328, subacute dietary studies using RPA 202248 and RPA 203328 are required. Results of these tests are tabulated below.

Table 10. Avian Subacute Dietary Toxicity

Species	Substance Tested	% ai	5-Day LC_{50} (ppm ai)	Toxicity Category	MRID No. Author/Year	Study Classification
Northern Bobwhite Quail *(Colinus virginianus)*	isoxaflutole	98.7	>4255	slightly toxic	43573233 Petersen, 1994	core
Mallard duck *(Anas platyrhynchos)*	isoxaflutole	98.7	>4255	slightly toxic	43573234 Petersen, 1994	core
Northern Bobwhite Quail *(Colinus virginianus)*	RPA 202248	99.9	>5200	practically non-toxic	43940302 Rodgers, 1995	core

Since the LC_{50} falls in the range of 4000 to >5000 ppm, parent isoxaflutole and RPA 202248 are slightly toxic and practically non-toxic to avian species on a subacute dietary basis, respectively. Subacute dietary studies using RPA 203328 on both bobwhite quail and mallard duck and using RPA 202248 on mallard duck are required. These studies are currently outstanding. The guideline (71-2) is not fulfilled (MRID 43573233, 43573234, 43940302).

ii. Birds, Chronic

Avian reproduction studies are required for RPA 202248 and RPA 203328 because the birds may be subject to repeated or continuous exposure to these transformation products preceding or during the breeding season. The preferred test species are mallard duck and bobwhite quail. There are, currently, no data from avian reproduction studies on both of the transformation products. These studies are outstanding. The guideline is not fulfilled.

30

iii. Mammals, Acute and Chronic

Wild mammal testing is required on a case-by-case basis, depending on the results of lower tier laboratory mammalian studies, intended use pattern and pertinent environmental fate characteristics. In most cases, rat or mouse toxicity values obtained from the Agency's Health Effects Division (HED) substitute for wild mammal testing. These toxicity values are reported below.

Table 11. Mammalian Acute Toxicity

Species	Chemical	% ai	Test Type	Toxicity Value	MRID No.
Rat	parent isoxaflutole	80.0	acute oral	LD_{50}>5,000 mg/kg	Acc. #114693 and 24955
Rat	RPA 202248	99.9	acute oral	LD_{50}> 5000 ppm	MRID 44044701
Rat	RPA 203328	99.7	acute oral	LD_{50}> 5000 ppm	MRID 43904812
Rat	RPA 203328	99.7	subchronic 28-day	LOEL > 15,000 ppm	MRID 43904813

The results indicate that parent isoxaflutole and its transformation products are practically non-toxic to small mammals on an acute oral basis.

Table 12. Mammalian Chronic Toxicity for Parent Isoxaflutole

Species/ Study Duration	% ai	Test Type	Toxicity Value	Affected Endpoints	MRID No.
Sprague Dawley rat	96.6	Developmental Toxicity	LEL= 1250 ppm NOEL= 250 ppm	decrease in number of implants and live fetuses	Acc.# 249455
Rat	80	Developmental toxicity	LEL= 500 ppm NOEL= 100 ppm	increased absolute and relative liver weights, vacuolization and hypertrophy of hepatocytes	MRIDs 00039009 and 00068035
Rat	80	3-generation rat study	NOEL< 50 ppm NOEL> 250 ppm	systemic NOEL of < 50 ppm (2.5 mg/kg) based on the reduction of body weight gain in males. The NOEL for reproductive toxicity was > 250 ppm (12.5 mg/kg)	Acc. No. 249455

The results indicate that parent isoxaflutole does not affect mammal reproduction from exposure to concentration levels of at least 250 ppm. Parent isoxaflutole degrades rapidly, and therefore is not expected to persist long enough for chronic exposure. EFED expects mammals to be exposed on a chronic basis to RPA 202248 and RPA 203328, since these are persistent in the terrestrial environment. Chronic data on RPA 202248 and RPA 203328 will be needed to assess chronic risk to mammals. Currently, EFED has no data to assess chronic risk to mammals.

iv. Insects

A honey bee acute contact study using the TGAI is required for isoxaflutole because its use (corn) will result in honey bee exposure. Results of this test are tabulated below.

Table 13. Nontarget Insect Acute Contact Toxicity

Species	% ai	LD_{50} (μg/bee)	Toxicity Category	MRID No. Author/Year	Study Classification
Honey bee *(Apis mellifera)*	96.8	>100 (acute contact) >168.7 (acute oral)	practically non-toxic	43573248 Petto, 1994	core

The results indicate that isoxaflutole is practically non-toxic to bees on an acute contact and oral basis. The guideline (141-1) is fulfilled (MRID 43573248).

b. Toxicity to Freshwater Aquatic Animals

i. Freshwater Fish, Acute

Two freshwater fish toxicity studies using the TGAI are required to establish the toxicity of isoxaflutole to fish. The preferred test species are rainbow trout (a cold water fish) and bluegill sunfish (a warm water fish). In addition, due to the persistence of RPA 202248, an additional freshwater fish toxicity studies using RPA 202248 and RPA 203328 are required. Results of these tests are tabulated below.

Table 14. Freshwater Fish Acute Toxicity

Species	Substance Tested	% ai	96-hour LC_{50} (ppm ai) (measured)	Toxicity Category	MRID No. Author/Year	Study Classification
Rainbow trout *(Oncorhynchus mykiss)*	Isoxaflutole	98.7	>1.7[1]	moderately toxic	43573236 Bettencourt, 1993	core
Bluegill sunfish *(Lepomis macrochirus)*	Isoxaflutole	98.7	>4.5[1]	moderately toxic	43573235 Bettencourt, 1993	core
Rainbow trout *(Oncorhynchus mykiss)*	RPA 202248	99.9	>30.6[2]	slightly toxic	43904822 McElligott, 1995	core
Rainbow trout *(Oncorhynchus mykiss)*	RPA 203328	98.9	160[1]	practically non-toxic	43904825 Machado, 1972	core

[1] This test was conducted under flow-through conditions.
[2] This test was conducted under static renewal conditions. The solubility limit is 30.6 ppm.

Since the LC_{50} falls in the range of 1.7 - 160 ppm, isoxaflutole and it's transformation products range from practically non-toxic to moderately toxic to freshwater fish on an acute basis. The guideline (72-1) is fulfilled (MRID 43573235, 43573236, 43904822, 43904825).

32

ii. Freshwater Fish, Chronic

On the basis of comparing acute toxicity levels to EEC, as discussed later in section 3.b.ii., chronic risk to fish is not expected. Therefore, a freshwater fish early-life stage study is not requested for RPA 202248 or RPA 203328.

iii. Freshwater Invertebrates, Acute

A freshwater aquatic invertebrate toxicity test using the TGAI is required to establish the toxicity of isoxaflutole to aquatic invertebrates. The preferred test species is *Daphnia magna*. In addition, due to the persistence of RPA 202248 and RPA 203328, an additional freshwater aquatic invertebrate toxicity study using RPA 202248 and RPA 203328 are required. Results of these tests are tabulated below.

Table 15. Freshwater Invertebrate Acute Toxicity

Species	Substance Tested	% ai	48-hour EC_{50} (ppm ai measured)	Toxicity Category	MRID No. Author/Year	Study Classification
Waterflea *(Daphnia magna)*	Isoxaflutole	98.7	>1.5[1]	moderately toxic	43573237 Putt, 1993	core
Waterflea *(Daphnia magna)*	RPA 203328	99.7	>150[1]	practically non-toxic	43573241 Putt, 1994	core
Waterflea *(Daphnia magna)*	RPA 202248	99.9	>59.6[2]	slightly toxic	43904823 McElligott, 1995	core

[1] This test was conducted under flow-through conditions.
[2] This test was conducted under static renewal conditions. The limit of solubility is 59.6 ppm.

Since the EC_{50} falls in the range of 1.5 - 150 ppm, isoxaflutole and it's transformation products range from moderately toxic to practically non-toxic to aquatic invertebrates on an acute basis. The guideline (72-2) is fulfilled (MRID 43573237, 43573241, 43904823).

iv. Freshwater Invertebrate, Chronic

On the basis of comparing acute toxicity levels to EEC, as discussed later in section 3.b.ii., chronic risk to freshwater invertebrate is not expected. Therefore, a freshwater invertebrate life-cycle study is not requested for RPA 202248 or RPA 203328.

c. Toxicity to Estuarine and Marine Animals

i. Estuarine and Marine Fish, Acute

Acute toxicity testing with estuarine/marine invertebrates using the TGAI is required for isoxaflutole because the end-use product is intended for application sites near coastal counties. In addition, due to the persistence of RPA 202248 and RPA 203328, additional estuarine/marine fish toxicity studies using these transformation products are required. The preferred test species is sheepshead minnow. Results of these tests are tabulated below.

Table 16. Estuarine/Marine Fish Acute Toxicity for Parent Isoxaflutole

Species	% ai	96-hour LC_{50} (ppm ai)	Toxicity Category	MRID No. Author/Year	Study Classification
Sheepshead minnow *(Cyprinodon variegatus)*	96.8	6.4[1] (measured)	moderately toxic	43573238 Bettencourt, 1994	core

[1] This test was conducted under flow-through conditions.

Since the LC_{50} is about 6.5 ppm, isoxaflutole is moderately toxic to estuarine/marine fish on an acute basis. There are no data on RPA 202248 and RPA 203328. The guideline (72-3a) is not fulfilled (MRID 43573238). Studies on RPA 202248 and RPA 203328 are outstanding.

ii. Estuarine and Marine Fish, Chronic

Since there are no acute data on RPA 202248 and RPA 203328, no chronic risk determination or chronic data requirements can be made. Estuarine/marine fish early life-stage study on RPA 202248 and RPA 203328 are held in reserve pending acute data on these transformation products.

iii. Estuarine and Marine Invertebrates, Acute

Acute toxicity testing with estuarine/marine invertebrates using the TGAI is required for isoxaflutole because the end-use product is intended for corn which is grown in coastal counties. In addition, due to the persistence of RPA 202248 and RPA 203328, additional estuarine/marine invertebrate toxicity studies on shrimp using these transformation products are required. The preferred test species for parent isoxaflutole are mysid shrimp and eastern oyster. Results of these tests are tabulated below.

Table 17. Estuarine/Marine Invertebrate Acute Toxicity

Species	Substance Tested	% ai.	96-hour LC_{50}/EC_{50} (ppm ai)	Toxicity Category	MRID No. Author/Year	Study Classification
Eastern oyster (embryo-larvae) *(Crassostrea virginica)*	Isoxaflutole	96.8	3.3[1]	moderately toxic	43573239 Dionne, 1994	core
Mysid shrimp *(Mysidopsis bahia)*	Isoxaflutole	96.8	0.018[1]	highly toxic	43573240 Bettencourt, 1994	core
Mysid shrimp *(Mysidopsis bahia)*	RPA 202248	99.9	3.6[2]	moderately toxic	43904824 Collins, 1995	core

[1] This test was conducted under flow-through conditions with the results mean measured.
[2] This test was conducted under static renewal conditions with the results mean measured.

Since the LC_{50} or EC_{50} values fall in the range of 0.018 - 3 ppm, isoxaflutole and RPA 202248 are classified as moderately toxic to highly toxic to estuarine/marine invertebrates on an acute basis. There are no data on acute toxicity of RPA 203328 to shrimp. The guideline is not fulfilled (MRID 43573239, 43573240, 43904824). Data on RPA 203328 using shrimp is outstanding.

iv. Estuarine and Marine Invertebrate, Chronic

An estuarine/marine invertebrate life-cycle toxicity test using the TGAI of isoxaflutole is tabulated below.

Table 18. Aquatic Invertebrate Life-Cycle Toxicity

Species	% ai	NOEC (ppb ai)	LOEC (ppb ai)	MATC (ppb ai)	Parameters affected	MRID # Author/Year	Study Classification
Mysid shrimp (*Mysidopsis bahia*)	96.8	1.0	1.9	1.4[1]	survival	43904821 Sousa, 1995	core

[1] This study was conducted under flow-through conditions and the results are mean measured.

On the basis of comparative acute toxicity for RPA 202248 and the acute-to-chronic ratio calculation for estuarine invertebrates, chronic risk to estuarine invertebrates due to the RPA 202248 are not expected. Therefore, an estuarine invertebrate life-cycle study is not requested for RPA 202248. However, due to the lack of acute shrimp data on RPA 203328, an acute-to-chronic ratio was not performed with RPA 203328. In order to determine chronic risk to estuarine invertebrates from exposure to the terminal transformation product, RPA 203328, data on acute toxicity to shrimp from RPA 203328 is needed. Therefore, until acute data is provided for RPA 203328, the shrimp life-cycle study is held in reserved. For further discussion, please see section 3.c.

d. Toxicity to Plants

i. Terrestrial

Terrestrial plant testing (seedling emergence and vegetative vigor) is required because isoxaflutole has a non-residential outdoor use patterns and it may move from the application site by spray drift or runoff.

For seedling emergence and vegetative vigor testing the following plant species and groups should be tested: (1) six species of at least four dicotyledonous families, one species of which is soybean (*Glycine max*), and the second of which is a root crop, and (2) four species of at least two monocotyledonous families, one of which is corn (*Zea mays*).

Terrestrial Tier II studies are required for all low dose herbicides (those with the maximum use rate of 0.5 lbs ai/A or less) and any pesticide showing a negative response equal to or greater than 25% in Tier I tests. Tier II tests measure the response of plants, relative to a control, and five or more test concentrations. Results of Tier II toxicity testing on the technical/TEP material are tabulated below.

Parent isoxaflutole degrades rapidly, and therefore is not expected to persist in the terrestrial environment. Information available to EFED indicates that phytotoxicity is expected to continue in the environment after parent isoxaflutole has degraded. EFED expects RPA 202248 and RPA 203328 to have some phytotoxicity in order to have seasonal control of the targeted weeds. Therefore, terrestrial plant data (seedling emergence and vegetative vigor) studies are required for RPA 202248 and RPA 203328.

Table 19. Nontarget Terrestrial Plant Seedling Emergence Toxicity (Tier II)

Species	% ai	EC_{25} (lb ai/A)	EC_{25} Endpoint Affected	EC_{05}/NOEC (lb ai/A)	EC_{05}/NOEC Endpoint Affected	MRID No. Author/Year	Study Classification
Monocot- Corn	96.8	>0.19	shoot length	0.045	shoot length	43573242 Hoberg, 1994	core
Monocot- onion	96.8	0.01576	shoot length	0.012	shoot length	same as above	core
Monocot- oat	96.8	0.02109	shoot length	0.0071	shoot length	same as above	core
Monocot- ryegrass	96.8	0.07967	shoot length	0.021	shoot length	same as above	core
Dicot- cucumber	96.8	0.00454	shoot length	<0.0020	shoot length	same as above	core
Dicot- lettuce	96.8	0.00066	shoot length	0.00049	shoot length	same as above	core
Dicot- cabbage	96.8	0.00149	shoot length	0.0011	shoot length	same as above	core
Dicot- soybean	96.8	0.01857	shoot length	0.0071	shoot length	same as above	core
Dicot- turnip	96.8	0.00047	shoot length	0.00011	shoot length	same as above	core
Dicot- tomato	96.8	0.00570	shoot length	0.0038	shoot length	same as above	core

For Tier II seedling emergence, turnip is the most sensitive dicot (EC_{25}= 0.00047 lb ai/A) and onion is the most sensitive monocot (EC_{25}= 0.01576 lb ai/A). The guideline (123-1a) is fulfilled for parent isoxaflutole (MRID 43573242). Data on RPA 202248 and RPA 203328 are outstanding.

Table 20. Nontarget Terrestrial Plant Vegetative Vigor Toxicity (Tier II)

Species	% ai	EC_{25} (lb ai/A)	EC_{25} Endpoint Affected	EC_{05}/NOEC (lb ai/A)	EC_{05}/NOEC Endpoint Affected	MRID No. Author/Year	Study Classification
Monocot- Corn	96.8	0.04379	shoot weight	<0.0790	shoot weight	43895801 Heldreth, 1996	supplemental
Monocot- onion	96.8	0.00274	shoot weight	<0.0047	shoot weight	same as above	supplemental
Monocot- ryegrass	96.8	[1]	[1]	[1]	[1]	same as above	supplemental
Monocot- oat	96.8	0.00210	shoot weight	0.00048	Shoot weight	same as above	supplemental
Dicot- cucumber	96.8	0.00316	root weight	0.0013	root weight	same as above	supplemental
Dicot- cabbage	96.8	0.00005[2]	root weight	<0.00012	root weight	same as above	supplemental
Dicot- turnip	96.8	0.00001	root weight	<0.00012	root weight	same as above	supplemental
Dicot- soybean	96.8	0.00183	shoot weight	0.00130	shoot weight	same as above	supplemental
Dicot- lettuce	96.8	[1]	[1]	[1]	[1]	same as above	supplemental
Dicot- tomato	96.8	0.00062	root weight	0.00048	root weight	same as above	supplemental

[1] Lettuce and ryegrass EC_{25} and EC_{50} values lack any certainty of confidence since the 95% CL includes infinity.

For Tier II vegetative vigor, turnip is the most sensitive dicot (EC_{25}= 0.00001 lb ai/A) and oat is the most sensitive monocot (EC_{25}= 0.00210 lb ai/A). The guideline (123-1b) is not fulfilled (MRID 43895801) because lettuce and ryegrass need to be retested. The ryegrass and lettuce data were too variable to provide a valid EC_{25} calculation. Another deviation in the study was that no raw data was submitted.

Data on RPA 202248 and RPA 203328 are outstanding.

ii. Aquatic Plants

Aquatic plant testing (tier II) is required for isoxaflutole because it has outdoor non-residential terrestrial uses that may move off-site by runoff and by aerial spray drift. The following species should be tested at Tier II: *Kirchneria subcapitata (Selenastrum capricornutum)*, *Lemna gibba*, *Skeletonema costatum*, *Anabaena flos-aquae*, and a freshwater diatom. Results of Tier II toxicity testing on the technical/TEP material are tabulated below.

Table 21. Nontarget Aquatic Plant Toxicity (Tier II)

Species	Substance Tested	% ai	EC_{50} (ppm ai)	EC_{05}/NOEC (ppm ai)	MRID No. Author/Year	Study Classification
Vascular Plants						
Duckweed *Lemna gibba*	Isoxaflutole	96.8	0.0049	0.0011	43573246 Hoberg, 1994	core
Nonvascular Plants						
Green algae *Kirchneria subcapitata*	Isoxaflutole	98.7	0.14	0.016	43573243 Hoberg, 1993	core
Green algae *Kirchneria subcapitata*	RPA 203328	98.9	5.9	2.4	43904826 Hoberg, 1995	core
Marine diatom *Skeletonema costatum*	Isoxaflutole	96.8	0.11	0.0022	43573247 Hoberg, 1994	core
Freshwater diatom *Navicula pelliculosa*	Isoxaflutole	96.8	0.38	0.0031	43573244 Hoberg, 1994	core
Blue-green algae *Anabaena flos-aquae*	Isoxaflutole	96.8	0.18	0.0086	43573245 Hoberg, 1994	core

The Tier II results indicate that *Skeletonema costatum* is the most sensitive nonvascular aquatic plant. The vascular plants (*Lemna gibba*) EC_{50} value is 4.9 ppb (0.0049 ppm). The guideline (123-2) is fulfilled (MRID 43573243, 43573244, 43573245, 43573246, 43573247, 43904826).

Data on RPA 202248 and RPA 203328 are outstanding.

3. Exposure and Risk Characterization

Risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic.

RQ = EXPOSURE/TOXICITY

RQs are then compared to OPP's levels of concern (LOCs). These LOCs are criteria used by OPP to indicate potential risk to nontarget organisms and the need to consider regulatory action. The criteria indicate that a pesticide used as directed has the potential to cause adverse effects on nontarget organisms. LOCs currently address the following risk presumption categories: (1) **acute high** - potential for acute risk is high, regulatory action may be warranted in addition to restricted use classification (2) **acute restricted use** - the potential for acute risk is high, but this may be mitigated through restricted use classification (3) **acute endangered species** - the potential for acute risk to endangered species is high, regulatory action may be warranted, and (4) **chronic risk** - the potential for chronic risk is high, regulatory action may be warranted. Currently, EFED does not perform assessments for chronic risk to plants, acute or chronic risks to nontarget insects, or chronic risk from granular/bait formulations to mammalian or avian species.

The ecotoxicity test values (i.e., measurement endpoints) used in the acute and chronic risk quotients are derived from the results of required studies. Examples of ecotoxicity values derived from the results of short-term laboratory studies that assess acute effects are: (1) LC_{50} (fish and birds) (2) LD_{50} (birds and mammals (3) EC_{50} (aquatic plants and aquatic invertebrates) and (4) EC_{25} (terrestrial plants). Examples of toxicity test effect levels derived from the results of long-term laboratory studies that assess chronic effects are: (1) LOEC (birds, fish, and aquatic invertebrates) (2) NOEC (birds, fish and aquatic invertebrates) and (3) MATC (fish and aquatic invertebrates). For birds and mammals, the NOEC value is used as the ecotoxicity test value in assessing chronic effects. Other values may be used when justified. Generally, the MATC (defined as the geometric mean of the NOEC and LOEC) is used as the ecotoxicity test value in assessing chronic effects to fish and aquatic invertebrates. However, the NOEC is used if the measurement end point is production of offspring or survival.

Risk presumptions, along with the corresponding RQs and LOCs are tabulated below.

Table 22. Risk Presumptions for Terrestrial Animals

Risk Presumption	RQ	LOC
Birds		
Acute High Risk	EEC[1]/LC_{50} or LD_{50}/sqft[2] or LD_{50}/day[3]	0.5
Acute Restricted Use	EEC/LC_{50} or LD_{50}/sqft or LD_{50}/day (or LD_{50} < 50 mg/kg)	0.2
Acute Endangered Species	EEC/LC_{50} or LD_{50}/sqft or LD_{50}/day	0.1
Chronic Risk	EEC/NOEC	1
Wild Mammals		
Acute High Risk	EEC/LC_{50} or LD_{50}/sqft or LD_{50}/day	0.5
Acute Restricted Use	EEC/LC_{50} or LD_{50}/sqft or LD_{50}/day (or LD_{50} < 50 mg/kg)	0.2
Acute Endangered Species	EEC/LC_{50} or LD_{50}/sqft or LD_{50}/day	0.1
Chronic Risk	EEC/NOEC	1

[1] abbreviation for Estimated Environmental Concentration (ppm) on avian/mammalian food items

[2] $\frac{mg/ft^2}{LD_{50} * \text{wt. of bird}}$

[3] $\frac{\text{mg of toxicant consumed/day}}{LD_{50} * \text{wt. of bird}}$

Table 23. Risk Presumptions for Aquatic Animals

Risk Presumption	RQ	LOC
Acute High Risk	EEC[1]/LC_{50} or EC_{50}	0.5
Acute Restricted Use	EEC/LC_{50} or EC_{50}	0.1
Acute Endangered Species	EEC/LC_{50} or EC_{50}	0.05
Chronic Risk	EEC/MATC or NOEC	1

[1] EEC = (ppm or ppb) in water

Table 24 Risk Presumptions for Non-Target Plants

Risk Presumption	RQ	LOC
	Terrestrial Plants	
Acute Risk	EEC[1]/EC_{25}	1
Endangered Species	EEC/EC05 or NOEC	1
	Aquatic Plants	
Acute Risk	EEC[2]/EC_{50}	1
Endangered Species	EEC/EC05 or NOEC	1

[1] EEC = lbs ai/A
[2] EEC = (ppb or ppm) in water

a. Exposure and Risk to Nontarget Terrestrial Animals

For pesticides applied as a nongranular product (e.g., liquid, dust), the estimated environmental concentrations (EECs) on food items following product application are compared to LC_{50} values to assess risk. The predicted 0-day maximum and mean residues of a pesticide that may be expected to occur on selected avian or mammalian food items immediately following a direct single application at 1 lb ai/A are tabulated below.

Table 25. Estimated Environmental Concentrations on Avian and Mammalian Food Items (ppm) Following a Single Application at 1 lb ai/A)

Food Items	EEC (ppm) Predicted Maximum Residue[1]	EEC (ppm) Predicted Mean Residue[1]
Short grass	240	85
Tall grass	110	36
Broadleaf/forage plants, and small insects	135	45
Fruits, pods, seeds, and large insects	15	7

[1] Predicted maximum and mean residues are for a 1 lb ai/a application rate and are based on Hoerger and Kenaga (1972) as modified by Fletcher *et al.* (1994).

The following exposure tables for birds and mammals contain exposure values (ppm) for their food items that were calculated using the predicted maximum residues from Hoerger and Kenaga (1972) as modified by Fletcher *et al.* (1994) and the maximum labeled rate of application (0.1875 lb ai/A).

41

i. Birds

The acute risk quotients for broadcast applications of nongranular isoxaflutole products are tabulated below.

Table 26. Avian Acute Risk Quotients for Single Application of Nongranular Products (Broadcast) Based on a (bobwhite quail and mallard duck) LC_{50}> 4255 ppm ai.

Site/ App. Method	App. Rate (lbs ai/A)	Food Items	Maximum EEC (ppm)	LC_{50} (ppm)	Acute RQ (EEC/LC_{50})
Corn (ground application)	0.1875	Short grass	45	4255	0.01
		Tall grass	21	4255	<0.01
		Broadleaf plants/Insects	25	4255	0.01
		Seeds	3	4255	<0.01

The results indicate that for a single broadcast application of isoxaflutole, no avian levels of concern are exceeded at registered maximum application rate.

Parent isoxaflutole degrades rapidly, and therefore it is not expected to persist long enough for chronic exposure. Therefore, no avian reproduction studies are needed for the parent isoxaflutole. However, EFED expects birds to be exposed on a chronic basis to RPA 202248 and RPA 203328, since these are persistent in the terrestrial environment. Avian reproduction studies are required for RPA 202248 and RPA 203328 because the birds may be subject to repeated or continuous exposure to these transformation products preceding or during the breeding season. The preferred test species are mallard duck and bobwhite quail. Avian reproduction studies are outstanding on the two transformation products.

ii. Mammals

Birds and mammals have similar responses to xenobiotics, their differences being more quantitative rather than qualitative. Since parent isoxaflutole does not present an acute risk to endangered birds, mammals are also presumed to be protected on an acute basis.

The chronic risk quotients for broadcast applications of parent isoxaflutole are tabulated below.

Table 27. Mammalian Chronic Risk Quotients for Multiple Applications of Nongranular Products (Broadcast) Based on a rat NOEC of 50 ppm in a 3-generation rat study.

Site/Application Method	Application Rate in lbs ai/A	Food Items	Maximum EEC[1] (ppm)	NOEC (ppm)	Chronic RQ (EEC/NOEC)
Corn (ground)	0.1875	Short grass	45	50	0.90
		Tall grass	21	50	0.42
		Broadleaf plants/Insects	25	50	0.50
		Seeds	3	50	0.06

[1] Based on Fletcher without degradation.

The above results indicate that for broadcast applications of parent isoxaflutole, the mammalian EEC approaches the level of concern for short grass food item. Since parent isoxaflutole degrades very rapidly in the environment, chronic exposure will likely be to RPA 202248 and RPA 203328. However, EFED has no chronic toxicity data for mammals on RPA 202248 and RPA 203328. Therefore, EFED cannot provide any chronic risk assessment to mammals.

iii. Insects

Currently, EFED does not assess risk to nontarget insects. Results of acceptable studies are used for recommending appropriate label precautions. Since isoxaflutole is practically non-toxic to honey bees, a label advisory is not recommended.

b. Exposure and Risk to Nontarget Freshwater Aquatic Animals

In the surface water assessment (Environmental Fate Assessment section), EFED estimated aquatic concentrations (EEC's) of parent isoxaflutole and RPA 202248 using the GENEEC model, a Tier I screening model. EFED also calculated EEC's for parent isoxaflutole and two transformation products, RPA 202248 and RPA 203328 using PRZM-EXAMS, a more refined Tier II model. For acute and chronic risk assessments, EFED compared toxicity values with the higher tier exposure model (PRZM-EXAMS). Acute risk assessments use peak EEC values for a single application. Chronic risk assessments use the 21-day EEC for invertebrates and 60-day EEC for fish.

EFED normally uses a 1-in-10-year EEC from PRZM-EXAMS to estimate exposure to aquatic organisms. However, since the model shows RPA 202248 and RPA 203328 to accumulate over time, the estimated 36-year maximum concentrations of **2.9 ppb for RPA 202248 and 5.8 ppb for RPA 203328** were used. For acute risk assessments, the immediate maximum concentrations for parent isoxaflutole and RPA 202248 were 0.4 and 2.9 ppb, respectively. Peak EEC values were calculated for RPA 202248 because parent isoxaflutole is expected to quickly degrade into RPA 202248, which is persistent in the environment. For chronic risk assessment, the 21- and 60-day EEC for RPA 202248 is 2.9 ppb and for RPA 203328 is 5.8 ppb.

The one-in-10 year PRZM-EXAMS EEC's for isoxaflutole, RPA 202248, RPA 203328 are 0.39, 2.4, and 5.5 ppb, respectively.

i. Freshwater Fish

Acute

A "worst case" scenario for acute risk, direct application of isoxaflutole to 6 inches of water, should result in the highest possible exposure to aquatic organisms from the proposed use of isoxaflutole. One pound of active ingredient in 6 inches of water over an acre results in a concentration of 724 ppb. Adjusting for the maximum application rate of isoxaflutole (0.1875 lbs ai/A), the concentration to which organisms would be exposed in this scenario is 135 ppb or 0.135 ppm (724 ppb x 0.1875 lb ai/A) assuming no degradation. The lowest LC_{50} for fish is 1.7 ppm for rainbow trout. The risk quotient (RQ), derived by dividing the exposure (0.135 ppm) by the toxicity value (1.7 ppm), is 0.08 for freshwater fish. This exceeds the level of concern (LOC) for endangered species of fish. However, because the modeled EEC for RPA 202248 of 2.9 ppb (PRZM-EXAMS) takes into account some degradation processes, it is assumed that the proposed use of isoxaflutole would not cause acute concerns for non-endangered or endangered species of freshwater fish.

Chronic

No data on chronic toxicity to freshwater fish was submitted for isoxaflutole or its transformation products. On the basis of comparing acute toxicity levels to EECs, the margin of safety is great enough that, chronic risk to fish due to RPA 202248 and RPA 203328 is not expected. Therefore, a freshwater fish early-life stage study is not requested for RPA 202248 or RPA 203328.

ii. Freshwater Invertebrates

Acute

A "worst case" scenario for acute risk, direct application of isoxaflutole to 6 inches of water, should result in the highest possible exposure to aquatic organisms from the proposed use of isoxaflutole. One pound of active ingredient in 6 inches of water over an acre results in a concentration of 724 ppb. Adjusting for the maximum application rate of isoxaflutole (0.1875 lbs ai/A), the concentration to which organisms would be exposed in this scenario is 135 ppb or 0.135 ppm (724 ppb x 0.1875 lb ai/A). The lowest LC_{50} for freshwater invertebrates is 1.5 ppm for *Daphnia magna*. The risk quotient (RQ), derived by dividing the exposure (0.135 ppm) by the toxicity value (1.5 ppm), is 0.09 for freshwater invertebrates. This exceeds the level of concern (LOC) for endangered species of freshwater invertebrates. However, because the modeled EEC for RPA 202248 of 2.9 ppb (PRZM-EXAMS) takes into account some degradation processes, it is assumed that the proposed use of isoxaflutole would not cause acute concerns for non-endangered or endangered species of freshwater invertebrates.

Chronic

No data on chronic toxicity to freshwater invertebrates was submitted for isoxaflutole or its transformation products. On the basis of comparing acute toxicity levels to EECs, the margin of safety is great enough that, chronic risk to freshwater invertebrates due to RPA 202248 and RPA 203328 is not expected. Therefore, a freshwater invertebrates life-cycle study is not requested for RPA 202248 or RPA 203328.

c. Estuarine and Marine Animals

Table 28. Risk Quotients (RQ) for Estuarine and Marine Organisms[1] from Isoxaflutole (Parent).

Use Site	Application Rate (lb ai/A)	Species	Chronic RQ	Acute RQ (96-hr)
Corn	0.1875	oyster	------	<0.01
		shrimp	0.04[2]	0.02
		fish	------	<0.01

[1] Acute shrimp EC_{50} is 18 ppb under flow-through conditions. Acute oyster (embyro larvae) EC_{50} is 3300 ppb and acute fish is 6400 ppb, both are under flow-through conditions.
[2] The shrimp chronic toxicity study uses parent isoxaflutole. Chronic shrimp MATC = 1.4 ppb with survival as the parameter most affected. The exposure value from PRZM-EXAMS is the 21 day value of 0.05 ppb for parent isoxaflutole.

Acute

Although EFED has no model specifically for estimating EEC's to estuaries, PRZM-EXAMS was run to provide a rough approximation of EEC's. The acute RQ is calculated by dividing the exposure (0.4 ppb for parent isoxaflutole) by the acute toxicity value (18 ppb). The RQ (0.02) show there are no exceedances for shrimp.

The mysid shrimp study using RPA 202248 was tested under static conditions (MRID 43904824). The EC_{50} value was 3600 ppb. This value is similar to the oyster EC_{50} value. Therefore, it is assumed that there will be minimal adverse acute affects to shrimp from RPA 202248.

Shrimp acute data on RPA 203328 are not available to assess acute risk to shrimp from RPA 203328. These data are outstanding.

Estuarine/marine fish acute toxicity data on RPA 202248 and RPA 203328 are outstanding. EFED cannot provide an acute risk assessment on RPA 202248 and RPA 203328.

Chronic

Since the estuarine/marine fish acute toxicity data are outstanding, EFED cannot make any determination of chronic data requirements or chronic risk assessment. Estuarine/marine fish early life-stage studies are held in reserve pending the outstanding acute toxicity data.

Shrimp chronic RQ on parent isoxaflutole shows minimal concern for estuarine/marine invertebrates.

Chronic data for the parent are available for shrimp. Acute data for RPA 202248 on shrimp are available but there are no chronic toxicity data. By using the concept of acute-to-chronic ratios, predictions can be made concerning the chronic toxicity of RPA 202248 to the same tested species in most cases.

An acute-to-chronic ratio is based on a wide range of pesticides tested for effects to aquatic organisms in which a consistent ratio of acute and chronic toxicity between the parent material and their transformation product(s) has been observed. Shrimp was the most sensitive species of the aquatic animals tested with parent isoxaflutole, and all of the transformation products were less toxic than the parent in acute tests. Therefore, if a chronic risk to shrimp from RPA 202248 is not identified, then such risk will probably not exist for other aquatic animals. However, if the EEC approaches the chronic toxicity concentration level for shrimp, then additional chronic testing may be required using RPA 202248 on shrimp to confirm the potential for chronic risk.

The acute-to-chronic ratio formulae is shown below:

$$\frac{\text{Parent (acute toxicity)}}{\text{Parent (chronic toxicity)}} = \frac{\text{Degradate (acute toxicity)}}{\text{Degradate (chronic toxicity)}}$$

The toxicity endpoints for the formulae are as follows:

Acute shrimp EC_{50} = 18 ppb for parent isoxaflutole
Chronic shrimp MATC = 1.4 ppb for parent isoxaflutole
Acute shrimp EC_{50} = 3600 ppb for RPA 202248
Chronic shrimp MATC = unknown for RPA 202248

In solving the equation below for RPA 202248 (chronic) where X = the chronic toxicity value of RPA 202248 to shrimp, EFED calculated the chronic toxicity of RPA 202248 to be 280 ppb.

46

The calculations are as follows:

$$\text{X ppb (RPA 202248 chronic)} = \frac{\text{(parent chronic) 1.4 ppb x (RPA 202248 acute) 3600 ppb}}{\text{(parent acute) 18 ppb}}$$

RPA 202248 chronic = 280 ppb

The value of 280 ppb for the estimated chronic toxicity of RPA 202248 to shrimp is much greater than the predicted EEC in aquatic environments (2.9 ppb for RPA 202248 from PRZM-EXAMS). Therefore, it can be reasonably assumed that a chronic study for shrimp using RPA 202248 is not needed. Chronic risk to estuarine/marine invertebrates is unlikely.

Chronic data for the shrimp using RPA 203328 is needed for assessing long term chronic risk. Acute shrimp toxicity data for RPA 203328 are not available. Since shrimp chronic data for RPA 203328 are not available, an acute-to-chronic ratio of shrimp could be calculated. EFED cannot provide a chronic risk assessment for RPA 203328.

Shrimp life-cycle study for RPA 203328 will be held in reserved pending acute shrimp data on RPA 203328.

d. Exposure and Risk to Nontarget Plants

i. Terrestrial and Semi-aquatic Areas

Plants may be exposed to pesticides from runoff, spray drift or volatilization. Plants may inhabit semi-aquatic areas such as low-lying wet areas that may be dry at certain times of the year. EFED's runoff scenario is: (1) based on a pesticide's water solubility and the amount of pesticide present on the soil surface and its top one inch (2) characterized as "sheet runoff" (one treated acre to an adjacent acre) for terrestrial areas (3) characterized as "channelized runoff" (10 treated acres to a distant low-lying semi-aquatic acre) and (4) based on % runoff values of 0.01, 0.02, and 0.05 for water solubility of <10 ppm, 10-100 ppm, and >100 ppm, respectively.

Spray drift exposure from ground application is assumed to be 1% of the application rate. Spray drift from aerial application is assumed to be 5% of the application rate.

EECs are calculated for unincorporated ground applications. Formulae for calculating EECs for terrestrial plants inhabiting areas adjacent to treatment sites and EECs for plants inhabiting wet, low-lying semi-aquatic areas are in an addendum.

Estimated environmental concentrations (EEC) of Parent Isoxaflutole for plants inhabiting terrestrial and semi-aquatic plants are tabulated below.

47

Table 29. Estimated Environmental Concentrations (lbs ai/A) For Plants in Terrestrial and Semi-Aquatic Areas for Parent Isoxaflutole

Site/ Application Method/ Rate of Application in lbs ai/A	Minimum Incorpor. Depth (in)	Runoff Value	Sheet Run-off (lbs ai/A)	Channelized Runoff (lbs ai/A)	Drift (lbs ai/A)	Total Loading to Adjacent Area (Sheet Run-off+Drift)	Total Loading to Semi-aquatic Area (Channel Run-off+ Drift)
Corn (Unincorporated Ground) 0.1875	0	0.01	0.002	0.02	0.002	0.004	0.022

The EC_{25} value of the most sensitive species in the seedling emergence study is compared to runoff plus drift exposure to determine the risk quotient (EEC/toxicity value). The EC_{25} value of the most sensitive species in the vegetative vigor study is compared to the drift exposure to determine the acute risk quotient.

EECs and acute high risk quotients for plants inhabiting terrestrial and semi-aquatic areas based on a single application are tabulated below.

Table 30. Acute High Risk Quotients from a Single Application for Plants Based On a (Turnip) Seedling Emergence EC_{25} of 0.00047 lb ai/A and a (Turnip) Vegetative Vigor EC_{25} of 0.00001 lb ai/A.

Site, Method and Rate of Application (lbs ai/A)	Seedling Emergence EC_{25} (lbs ai/A)	Vegetative Vigor EC_{25} (lbs ai/A)	Drift (lbs ai/A)	Total Loading to Adjacent Area (Sheet Runoff+ Drift)	Total Loading to Semi-aquatic Area (Channel Runoff+ Drift)	Runoff RQ Terres-trial Area	Runoff RQ Semi-Aquatic Area	Drift RQ
Corn (Unincorporated Ground) 0.1875	0.00047	0.00001	0.002	0.004	0.022	8.5	46.8	187.5

The results indicate that for a single application, acute risk and endangered species levels of concern are exceeded for plant inhabiting terrestrial and semi-aquatic areas (including endangered species) at the proposed application rate for parent isoxaflutole.

There are no plant data for RPA 202248 and RPA 203328. EFED cannot conduct plant risk assessments for RPA 202248 and RPA 203328. Plant data for RPA 202248 and RPA 203328 are outstanding.

Currently, EFED does not perform assessments for chronic risk to plants inhabiting terrestrial and semi-aquatic areas.

ii. Aquatic Plants

Exposure to nontarget aquatic plants may occur through runoff or spray drift from adjacent treated sites. An aquatic plant risk assessment for acute risk is usually conducted for aquatic vascular plants from the surrogate duckweed, *Lemna gibba*. Non-vascular acute aquatic plant risk assessments are performed using either algae or a diatom, whichever is the most sensitive species. An aquatic plant risk assessment for endangered species is usually conducted for aquatic vascular plants from the surrogate duckweed, *Lemna gibba*. To date there are no known non-vascular plant species on the endangered species list. Runoff and drift exposure are computed using PRZM/EXAMS. The risk quotient is determined by dividing the pesticide's initial or peak concentration in water by the plant EC_{50} value.

Acute risk quotients for vascular and non-vascular plants are tabulated below.

Table 31. Acute Risk Quotients for Aquatic Plants based upon a duckweed (*Lemna gibba*) EC_{50} of 0.0049 ppm ai and a nonvascular plant (*Skeletonema costatum*) EC_{50} of 0.11 ppm ai. For endangered species, the *L. gibba* NOEC of 0.0011 ppm ai.

Site/ Application Method/ Rate of Application (lbs ai/A)	Species	EC_{50} (ppm)	EEC[1] (ppm)	NOEC (ppm)	Endangered Species RQ EEC/NOEC	Drift[2] RQ	Non-target plant RQ (EEC/EC_{50})
Corn (Ground)	duckweed	0.0049	0.039	0.0011	35.45	<0.01	7.96
0.1875	algae or diatom	0.11	0.039	[3]	[3]	<0.01	0.35

[1] The EEC is based on PRZM/EXAMS for parent isoxaflutole (39 ppb).

[2] The drift RQ = $\frac{1\% \text{ (ground spray drift) x 0.724 ppm (one lb ai in 6 acre-inches) x rate of application.}}{EC_{50}}$

[3] There are no endangered species of algae or diatoms listed.

The LOC for non-target aquatic vascular plants are exceeded from runoff. The LOC for algae or diatoms are not exceeded. The LOC for endangered species of aquatic vascular plants are exceeded. (Non-vascular endangered species are not known to exist at this time).

There are no plant toxicity data for RPA 203328 and RPA 202248. EFED cannot conduct risk assessments for RPA 203328 and RPA 202248. Aquatic plant data on these transformation products are outstanding.

4. Endangered Species

Endangered species LOCs are exceeded for isoxaflutole. The endangered species that may be affected from the proposed use of isoxaflutole are terrestrial and aquatic plants. There is insufficient data to assess chronic toxicity to endangered species of aquatic and terrestrial organisms.

Attached to this Science Chapter is a listing of endangered species of crustaceans and plants that inhabit the counties where corn is grown. The registrant is a member of the industry's Endangered Species Task Force and may be able to provide data on the protection of endangered species through this task force.

49

4. Labeling Requirements

All pesticides must have labeling for manufacturing-use products and end-use products. These labeling statements are uniform and standard statements.

a. Manufacturing-Use Products

" Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public waters unless this product is specifically identified and addressed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA."

b. End-use Products

"Do not apply directly to water, or to areas where the surface water is present or to intertidal areas below the mean high-water mark, Drift and runoff may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water when disposing of equipment washwater or rinsate."

c. Ground Water Labeling

Since isoxaflutole transformation products are expected to leach through the soil profile to groundwater, the following statement should appear on the label:

"This chemical has properties and characteristics associated with chemicals detected in ground water. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination."

d. Surface Water Labeling

Since isoxaflutole transformation products are expected to move as runoff and spray drift to surface water, the following statement should appear on the label:

"Isoxaflutole residues can contaminate surface water through spray drift. Under some conditions, isoxaflutole residues may also have a high potential for runoff into surface water (primarily via dissolution in runoff water), for several months post-application. These include poorly draining or wet soils with readily visible slopes toward adjacent surface waters, frequently flooded areas, areas over-laying extremely shallow ground water, areas with in-field canals or ditches that drain to surface water, areas not separated from adjacent surface waters with vegetated filter strips, and areas over-laying tile drainage systems that drain to surface water."

S

5. Risk Characterization

A. Executive Summary of Risk

Parent isoxaflutole degrades rapidly and sequentially in the environment to the primary transformation product, RPA 202248, and what appears to be the terminal transformation product, RPA 203328. The transformation products are expected to reach surface water and shallow ground water where they will persist and accumulate. There is evidence to show that RPA 202248 is biologically active. Since parent isoxaflutole is not expected to persist long enough in the environment for animals to be chronically exposed, the EEC's to animals in the environment are based on the transformation products. There are no data available to assess chronic risk to animals from the tranformation products. Therefore, EFED is not able to provide a complete chronic risk assessment at this time. Acute risk to birds, mammals, aquatic organisms, and beneficial insects is expected to be minimal from parent isoxaflutole and its transformation products. Terrestrial plants are expected to be highly vulnerable to runoff and spray drift from ground application.

- There is phytotoxicity risk to non-target terrestrial plants from ground spray drift of parent isoxaflutole. Compared to sulfonylureas (which have similar phytotoxicity) and picloram (the only herbicide to have restricted use based on phytotoxicity) this chemical poses more risk to non-target plants because the application rate is higher. However, minimal adverse affects to non-target aquatic plants are expected from spray drift.

- There is phytotoxicity risk to non-target aquatic and terrestrial plants from runoff of parent isoxaflutole and it's transformation products.

- Endangered plant species may be affected from the proposed use of isoxaflutole.

- Chronic risk to birds, mammals, shrimp and estuarine fish cannot be determined because data on the transformation products have not been submitted.

- EFED expects that the transformation products will persist and accumulate in surface water and shallow ground water surrounding treated areas.

- A Reference Dose (RfD) for isoxaflutole has not been established at this time. Therefore, it is not possible to estimate a Lifetime Health Advisory (HA) for isoxaflutole residues in drinking water.

- There is a potential risk to other crops from the presence of potentially phytotoxic transformation products in irrigation water. However, the major areas of corn production that use irrigation (Western U. S. corn belt) have deep aquifers with slow recharge rates that are not likely to have sufficient concentrations of the transformation products to adversely affect other crops. In other parts of the U.S.

where corn is also grown and where shallow ground water is used for irrigation, sporadic irrigation is used for other crops. Crops such as soybeans, which are rotated with corn and are sensitive to irrigation waters containing isoxaflutole residues, could be adversely affected.

- Estimated maximum concentrations of isoxaflutole residues in ground water exceed the phytotoxic triggers to non-target plants (e.g. other crops) up to 4500 times, presuming that the transformation products are as toxic as parent isoxaflutole.

B. Background

Isoxaflutole, 5-cyclopropyl-4-(2-methylsulphonyl-4-trifluoromethylbenzoyl) isoxazole, is to be used for control of both grasses and broadleaf weeds in corn. The formulation is a 75% water dispersible granule ground applied at the maximum use rate of 0.1875 lb ai/acre at either preemergence or preplant time. Aerial application is **not** being requested in this registration.

According to the summary document associated with the submitted studies, isoxaflutole is a member of a class of herbicides that disrupts pigment biosynthesis in plants. The specific mode of action is inhibition of 4-hydroxyphenylpyruvate dioxygenase, preventing the formation of a quinone required for carotenoid biosynthesis. Emerging weeds are bleached as the herbicide is taken up by the root system.

C. Fate and Transport

Parent isoxaflutole (RPA-201772) degrades quickly via hydrolysis and microbial metabolism in the field to RPA 202248. RPA 202248 slowly degrades via microbial metabolism to RPA 203328, the terminal residue in the environment. Both RPA 202248 and RPA 203328 were found to be persistent and potentially mobile in the laboratory and in the field. Therefore, EFED expects that they will persist and accumulate in surface water and shallow ground water resources surrounding treated areas. GENEEC and PRZM-EXAMS modeling support this conclusion.

Table 32.	GENEEC			PRZM-EXAMS (Maximum EEC)	
Chemical	Peak EEC (ppb)	21-day EEC (ppb)	56-day EEC (ppb)	one-in-10 year EEC (ppb)	year-36 EEC (ppb)
Parent Isoxaflutole	4.1	0.3	0.1	0.4	0.1
RPA 202248	6.3	6.2	6.1	2.4[1]	2.9
RPA 203328	8.4	8.4	8.4	5.5[1]	5.8

[1] These values are not representative of 1-in-10 year EECs because they accumulate over time in water bodies.

(1) Surface Water Modeling Results (PRZM-EXAMS)

While corn is an ubiquitous crop, the highest geographical concentration is in the Midwest. Therefore, the modeling for isoxaflutole was conducted for the Midwest (Iowa). The other major geographical areas include the Mid-Atlantic area, the Southeast, and the Mid-South.

A reduction in the application rate of isoxaflutole is expected to reduce the amount of RPA 202248 and RPA 203328 found in the aquatic environment, however a 50% reduction in the application rate (0.0937 lbs a.i/A) would not reduce the EEC's of isoxaflutole and its transformation products below the phytotoxicity trigger of 0.022 μg/L (see 5.D. of this section).

Surface water modeling (PRZM-EXAMS) indicates that long-term accumulation of total isoxaflutole residues may occur in surface water bodies. EFED notes that accumulation of isoxaflutole residues in surface waters may be an artifact of the computer simulation for several reasons: 1.) surface water hydrology of the pond does not account for outflow and/ or dilution processes; 2.) aerobic aquatic metabolism was not considered as a route of dissipation; and, 3.) the mobility of RPA 203328 was assumed to be the worst-case default value (K_{oc}=0.00). EFED notes the K_{oc} for RPA 203328 is expected to be low because it has a carboxylic acid functional group and hence will be anionic (fully dissociated) under most environmental conditions. Insufficient environmental fate and phytotoxicity data also create some uncertainty in the potential impact. Therefore, a more complete environmental fate assessment for RPA 202248 and RPA 203328 will require additional aerobic aquatic metabolism, batch equilibrium, and phytotoxicity data.

(2) Ground Water Modeling Results (PATRIOT)

Estimated (PATRIOT) concentrations (maximum of 100 ppb) of isoxaflutole residues in shallow ground water underlying Group A, B, C, and D soils in Iowa exceeded the phytotoxic threshold of 22 ppt by factors of 1,000-5,000. Between 25 to 90 % of applied isoxaflutole reached shallow ground water as the transformation products. This modeling is slightly uncertain since the K_{oc} of RPA 203328 was assumed to be zero for this modeling (no data are available) and since EFED assumed 100% transformation of the parent isoxaflutole to RPA 202248, and then RPA 202248 to RPA 203328. Additional assumptions and input from the PATRIOT modeling may be found in the Ground Water Assessment Section of the Environmental Fate Assessment (Section 1.C.(2)).

RPA 202248 was predicted to leach in the Group A and Group C soils. PATRIOT estimated that approximately 30% of the total applied mass of RPA 202248 would leach to shallow ground water when used on Group A soils. Less than 5 % of the total applied mass was predicted to leach to ground water underlying the Group C soil. For the Group A, B, and C soils, the predicted peak concentrations at the top of the water table would be in the tens of ppb. No RPA 202248 was predicted to leach on the Group B or D soils. The graphical representation of this data is found in the Appendix at the end of this chapter.

PATRIOT modeling predicted significant leaching of RPA 203328 on all soil hydrologic types. The mass leached of RPA 203328 was comparable to the bromide tracer and much greater than atrazine. Modeling on the vulnerable Group A soil estimated that >90% of the total applied mass of RPA 203328 would leach to shallow ground water. **Peak concentrations predicted at the top of the water table would be about 100 ppb.** In the group B, C, and D soils, 25% to 65% of the total applied mass was predicted to leach to shallow ground water underlying these soils. **The peak concentrations predicted at the top of the water table would also be roughly 100 ppb.** Overall, the mass of RPA 203328 estimated to leach to ground water for each year ranged from approximately 60 to 120% of the annual application. The modeled results exceeded 100 % of applied because the soil will act as a reservoir, holding it until there is sufficient water to carry it through the soil profile. The similarity in leaching to bromide may partly be an artifact of the assumption that the $K_{oc}=0$. However, even with a higher K_{oc}, EFED would still anticipate significant leaching of RPA 203328 to ground water because of the long half-life of 977 days. EFED needs a batch equilibrium study on RPA 203328 to improve modeling estimations.

(3) Drinking Water

Because the Reference Dose (RfD) and Lifetime Health Advisory (HA) have not yet been determined by HED, comprehensive ground and surface water assessments cannot be completed at this time. Isoxaflutole is not currently regulated under the Safe Drinking Water Act, and formal drinking water contaminant levels have not been established. However, the transformation products of isoxaflutole have many of the environmental fate characteristics of chemicals known to leach to ground water. RPA 202248 and RPA 203328 are persistent and mobile in laboratory and field studies. **Therefore, if any residues of RPA 202248 and RPA 203328 were to reach ground or surface water, they would be expected to persist and accumulate in ground or surface water over time.** Since the proposed use of isoxaflutole will be widespread geographically, it is assumed that widespread contamination of water resources may be observed.

D. Method Validation and Phytotoxic Trigger Exposures

Executive Summary

Analytical methods should have detection limits that are low enough to quantify levels of parent isoxaflutole, RPA 202248, and RPA 203328 that can cause ecological effects. Phytotoxicity levels of concern or triggers in ppt would be useful in monitoring of any adverse impacts of isoxaflutole on non-target plants including crops. Plants are more sensitive to foliar uptake of isoxaflutole than to root uptake. Therefore, more severe impacts may come from irrigation or drift reaching plant surfaces that would cause foliar uptake. The isoxaflutole analytical methods that have been provided to EFED do not reach levels where phytotoxicity can occur. The table below shows the margin by which the estimated exposures exceed the phytotoxic triggers for drift and irrigation. Residues in the water medium could impact crops from irrigation. Residues on plants and soil indicate that spray drift of isoxaflutole would likely cause adverse effects to non-target plants.

The registrant should provide analytical methods that will quantify residues for monitoring the impacts of isoxaflutole on non-target plants. EFED therefore requests that the registrant develop analytical methods that can detect levels of parent isoxaflutole, RPA 202248, and RPA 203328 at which phytotoxic effects can occur. The method may be either a traditional analytical method, or an immunochemical method. If the new method is immunochemical, then the registrant must follow OPP policies (see attached memo). The method needs to be publicly available.

<u>Calculations of Phytotoxic Limits in Soil</u>

The calculated phytotoxic level in soil is 21 ppt, and was determined by the following means:

(1) According to USDA soil charts, application of 1 lb ai/A results in 0.73 ppm in the top 3 inches of soil. Therefore, residues of isoxaflutole in the top one inch of soil would be 0.411 ppm (411 ppb), given the application rate of 0.1875 lbs ai/A (0.73 ppm x 3 x 0.1875);

(2) One percent spray drift from ground application is expected to lead to concentrations of 4 ppb (0.01 x 411 ppb) in the top one-inch of soil off-site. In order to determine the phytotoxic levels of parent isoxaflutole and its transformation products in soil residues, the inverse of the LOC (1/187) times the 4 ppb in the top one-inch of soil off-site will provide the phytotoxic level, which is 0.021 ppb, or 21 ppt from 1 % spray drift.

<u>Calculations of Phytotoxic Limits in Plant Residues</u>

Pesticide residues on plants are needed to monitor the adverse impacts of isoxaflutole on non-target plants (e.g., other crops). The following calculation is used to estimate the concentration of isoxaflutole residues on plant surfaces that would result in sufficient exposure to cause adverse effects on non-target plants (vegetative vigor EC_{25} value):

0.1875 lb ai/A (application rate) x 1% spray drift = 0.001875 lb ai/A

The above calculated value of 0.001875 lb ai/A is the amount of isoxaflutole residue that would be expected to be on plant surfaces from the ground application spray drift. The amount of residues found on plant surfaces would be 240 ppm x 0.001875 = 0.45 ppm (450 ppb). The predicted maximum residues are for a 0.1875 lb ai/a application rate and are based on Hoerger and Kenaga (1972) as modified by Fletcher *et al.* (1994).

The amount of isoxaflutole residues on plants that is expected to cause an adverse effect on sensitive plants is calculated by:

450 ppb (predicted maximum residues on plants) / 187 (RQ for 1% spray drift to terrestrial plants) = **2.41 ppb**

Calculations of Phytotoxic Limits in Water Resources

Since EFED does not have phytotoxicity data on the transformation products, an assumption is made that they will be equivalent to parent isoxaflutole phytotoxicity. The following calculation was used to estimate the ground water or surface water concentration in overhead irrigation water that would result in sufficient exposure to cause adverse effects on non-target plants (vegetative vigor EC_{25} value):

62.36 lb water/ft^3 x 43,560 ft^2/acre x 0.167 ft depth (two inches) =
453,639 lb water irrigated/acre

The above calculation assumes that two inches of irrigation water are used. The amount of water required to irrigate an acre with two inches of water is 453,639 lbs.

Assuming the vegetative vigor EC_{25} is 0.00001 lb ai/A, the concentration of isoxaflutole transformation products in two inches of irrigation water required to deliver this EC_{25} dose is:

[(0.00001 lb ai/A) / 453,639 lb water/A] x 10^9 ppb= **0.022 ppb (22 ppt)**

It is likely that ground water contamination (about 100 ppb) from the transformation products will exceed the level of concern (22 ppt).

Discussion

The limits of analytical methods submitted for soil are 3.9-6.1 ppb (Minimum Detection Limit; MDL) and 12.7-18.9 ppb (Limit of Quantitation; LOQ). The preliminary limits of analytical methods submitted for water are 0.5 ppb for the MDL and 1.0 ppb for the LOQ. The limits of quantitation needed are 0.022 ppb in water, 0.021 ppb in soil, and 2.41 ppb in plant residues for parent isoxaflutole, RPA 202248, and RPA 203328.

When comparing modeled levels in ground and surface water to phytotoxic limits, the calculated exceedences were >4500X for ground water and >250X for surface water. This assumes that the transformation products are equally as phytotoxic as parent isoxaflutole and that RPA 203328 does not bind to soil (K_{oc}=0). If the rate of application was lowered by 250 times, there would still be exceedences from ground water used for irrigation.

- **There is risk to other crops from presence of potentially phytotoxic transformation products in irrigation water. However, the major areas of corn production that use irrigation (Western U. S. corn belt) have deep aquifers with slow recharge rates that are not likely to have sufficient concentrations of the**

transformation products to adversely affect other crops. In other parts of the U.S. where corn is also grown and where shallow ground water is used for irrigation, sporadic irrigation is used for other crops and could adversely affect those crops such as soybeans, which is rotated with corn and is sensitive to irrigation waters containing isoxaflutole residues.

Table 33. Estimated Water Concentrations and Phytotoxic Trigger Exceedances per Medium Sampled

Medium	GW Conc. (ppb)[1]	Phytotoxic[2] Exceed GW	SW Conc. (ppb)[3]	Phytotoxic[2] Exceed SW
soil	100	4,761X[4]	5.8	276X[4]
water	100	4,545X[4]	5.8	263X[4]

[1] PATRIOT model maximum results of "hundreds of ppb" for top of ground water (GW) table for RPA 203328. The representative number used is 100 ppb.
[2] Phytotoxic triggers are 0.022 ppb (water) and 0.021 ppb (soil) based on turnip vegetative vigor EC_{25} of 0.00001 lb ai/A.
[3] PRZM-EXAMS model 36-year maximum for RPA 203328 in surface water (SW).
[4] The calculations for the exceedances are as follows: Water Conc. (ppb) / phytotoxic trigger (ppb)

E. Ecological Effects

(1) Plants

The primary risk from isoxaflutole is non-target phytotoxicity from spray drift of parent isoxaflutole, from runoff of the parent and it's transformation products and the presence of the transformation products, RPA 202248 and RPA 203328 in water used for irrigation. Non-target plants inhabiting terrestrial and semi-aquatic areas including endangered plants are expected to be highly sensitive to isoxaflutole residues. This assessment is based on environmental fate and transport data, ecological toxicity data, and surface and ground water modeling.

The uncertainities of this plant risk characterization is based on lack of plant data for RPA 202248 and RPA 203328. For risk assessment, EFED assumed that the transformation products are as phytotoxic as the parent isoxaflutole.

Plant Risk Runoff

Runoff from a single application at the maximum rate will exceed the levels of concern for acute risk to non-target plants inhabiting terrestrial and semi-aquatic areas by 10 and 55 times, respectively. The proposed use of isoxaflutole may affect endangered species of plants. Buffer strips may possibly minimize adverse effects from runoff.

Plant Risk Spray Drift

Even though the proposed registration is only for ground application, adverse effects to non-target plants from runoff and spray drift are anticipated. The vegetative vigor EC_{25} value (0.00001 lb ai/A) is based on turnip root weight.

Compared to sulfonylureas (which have similar phytotoxicity) and picloram (the only herbicide to have restricted use based on phytotoxicity) this chemical poses a **higher risk to non-target plants from drift**.

The following table compares both the ground and aerial spray drift RQ of sulfonylureas and picloram with parent isoxaflutole:

Table 34. Comparative Analysis of Phytotoxicity

Chemical Name	Trade Name	Shaun.#	EC_{25} lb ai/A	Appl. Rate lb ai/A	1% Drift RQ	5% Drift[1] RQ	Crop
Rimsulfuron	Matrix	129009	0.000030	0.032	11	53	corn, potato
Metsulfuron methyl	Ally	122010	0.000018	0.003	2	8	wheat, non-food
Triasulfuron	Amber	128969	0.000034	0.3	88	441	wheat
Tribenuron methyl	Express	128887	0.000390	0.0156	0.4	2	wheat
Bensulfuron methyl	Londax	128820	0.000127	0.0625	5	25	rice
Primisulfuron methyl	Beacon	128973	0.000127	0.036	3	14	corn
Sulfometuron methyl	Oust	122001	0.000030	0.1875	62	312	non-food
Triflusulfuron methyl	Upbeet	129002	0.000087	0.031	4	18	sugar beet
Prosulfuron methyl	Exceed	129031	0.001600	0.4	3	13	corn
Picloram TIPA salt		005103	0.000200	2.2	110	550	non-food
Isoxaflutole	Balance[2]	123000	0.000010	0.1875	187	938	corn

[1] EFED assumed 1 % drift for ground application and 5 % drift for aerial application. These do not include runoff, which is discussed in the Risk Assessment section.

[2] Balance is a proposed trade name for isoxaflutole.

As the table shows, the phytotoxicity (EC_{25}) and risk quotients (1 and 5 % spray drift) of parent isoxaflutole are greater than the most toxic of the sulfonylureas (Oust™), as well as picloram. Non-target plants are expected to be adversely affected from the proposed use of isoxaflutole.

Aerial Application

EFED understands that the registrant is expected to request aerial application in future registration requests. If an aerial application registration is requested, EFED requests notification and review of this action because of serious concerns for off-site movement of parent isoxaflutole to non-target plants. The table above shows aerial application RQ to exceed the LOC by 938 times. It is uncertain that 5% spray drift is an appropriate estimate exposure of aerial application. Further refinement of aerial spray drift exposure may be needed. RD should inform the registrant that lower application rates are needed to avoid high risk to non-target plants.

Restricted Use

EPA registered the active ingredient picloram as a Restricted Use herbicide because of the phytotoxicity concerns toward non-target plants. Only certified applicators could apply picloram due to the relatively high exceedences of risk to non-target plants. Since isoxaflutole shows greater exceedences of risk to non-target plants than picloram, EFED requests that the same restricted use be applied to isoxaflutole.

Morphological Phytotoxic Analysis

Isoxaflutole is a member of a class of herbicides that disrupts pigment biosynthesis in plants. The specific mode of action is inhibition of 4-hydroxyphenylpyruvate dioxygenase, preventing the formation of a quinone required for carotenoid biosynthesis. Emerging weeds and existing plants are bleached as the herbicide is taken up by root and foliar systems. In comparison with other herbicide mode of action classes, this class of herbicides has symptoms that are specific to each chemical.

Since phytotoxic amounts are too low to be detected by current analytical methods, it is necessary to find alternative methods to monitor possible impacts to non-target plants from runoff, ground spray drift and/or irrigation from contaminated water resources. Therefore, EFED requests that the registrant clearly identify morphological symptoms that can be monitored and clearly defined to determine if a plant was injured/killed by isoxaflutole use. This would rule out the effects of other herbicides or environmental damages caused by fertility or disease.

Risk Reduction Measure for Ground Application

Spray Drift from ground application will affect non-target plants (RQ=187.5). One method of reducing the spray drift from ground application is (1) to not apply isoxaflutole during periods of wind activity, (2) to specify that application nozzles must be no more than 24 inches from the soil surface, and (3) to specify that spray shields should be used during application. EFED requests that these ground spray drift reduction methods be incorporated into the label.

Efficacy Data Needed to Determine Lower Maximum Rates

The risk quotients are high for risk to non-target plants. In order to reduce the risk, the **maximum proposed rate of application should be reduced.** EFED requests that the registrant provide efficacy data on lower rates of isoxaflutole that would still maintain acceptable levels of weed control. Rates of application are often determined by intensity of infestations, rainfall, soil characteristics, and topography. Therefore, EFED requests the efficacy data on a regional basis in a summarized form, unless the registrant wishes to meet with EFED and BEAD otherwise.

Plant Studies for Transformation Products

Based on the lack of persistence of parent isoxaflutole and expected season-long control of weeds, it appears that the transformation products RPA 202248 and RPA 203328 may be phytotoxic. Therefore, EFED requests that Tier II terrestrial plant studies be conducted for these transformation products. The seedling emergence study (123-1 a) is needed to assess risk to non-target plants from runoff. The vegetative vigor study (123-1 b) is needed to assess risk from wind-blown soil particles containing residues of these transformation products and from irrigation water used for crops other than corn. In addition, aquatic plant studies (123-2) for five species are requested for RPA 202248 and RPA 203328 to assess risk to non-target aquatic plants from runoff.

(2) Animals

Acute Risk

The proposed use of isoxaflutole was determined to cause minimal acute risk to animals from parent isoxaflutole.

Acute toxicity data on RPA 203328 to shrimp is needed.

Acute toxicity data on RPA 202248 and RPA 203328 to estuarine fish is needed.

Avian toxicity data shows that RPA 202248 has similar toxicity as parent isoxaflutole to birds. Since parent isoxaflutole does not present an acute risk to birds, mammals are also assumed to have minimal risk. Therefore, acute risk to birds and mammals from RPA 202248 and RPA 203328 are not anticipated.

Chronic Risk

Terrestrial Animals

Chronic exposure to terrestrial organisms is expected to occur from RPA 202248 and RPA 203328. EFED lacks data to conduct a chronic risk assessment to terrestrial and aquatic organisms from RPA 202248.

Although RPA 202248 and RPA 203328 do not show any acute toxicity to birds, chronic toxicity cannot be ruled out because there are several pesticides that do not show acute toxicity and yet have very sensitive chronic toxicity endpoints. Therefore, due to the persistence of these transformation products in the terrestrial environment, EFED requests avian reproduction studies be conducted using the mallard duck and the bobwhite quail.

EFED cannot assess chronic toxicity to mammals since no data are available on RPA 202248 and RPA 203328 from 2-generation rat study. If chronic toxicity is to be assessed for mammals, then a 2-generation rat study is needed for RPA 202248 and RPA 203328.

Aquatic Animals

Minimal chronic risk to freshwater species are anticipated.

Since the estuarine/marine fish acute toxicity data are outstanding on RPA 202248 and RPA 203328, EFED cannot assess chronic risk or determine the need for chronic data. Estuarine/marine fish early life-stage studies are held in reserve pending the results of outstanding acute toxicity data.

Minimal chronic risk to shrimp from RPA 202248 is expected. However, since the shrimp acute toxicity data are outstanding on RPA 203328, EFED cannot make any determination of chronic data requirements or chronic risk assessment. Shrimp life-cycle study is held in reserve pending the outstanding acute toxicity data on RPA 203328.

PLANT RISK ADDENDUM:

EEC Formulae

Calculating EECs for terrestrial plants inhabiting areas adjacent to treatment sites

Unincorporated ground application:
Runoff = maximum application rate (lbs ai/A) x runoff value
Drift = maximum application rate x 0.01
Total Loading = runoff (lbs ai/acre) + drift (lbs ai/A)

Incorporated ground application:
Runoff = [maximum application rate (lbs ai/A) ÷ minimum incorporation depth (in.)] x runoff value
Drift = maximum application rate x 0.01
(Note: drift is not calculated if the product is incorporated at the time of application.)
Total Loading = runoff (lbs ai/A) + drift (lbs ai/A)

Aerial, airblast, forced-air, and chemigation applications:
Runoff = maximum application rate (lbs ai/A) x 0.6 (60% application efficiency assumed) x runoff value
Drift = maximum application rate (lbs ai/A) x 0.05
Total Loading = runoff (lbs ai/A) + drift (lbs ai/A)

Calculating EECs for semi-aquatic plants inhabiting wet, low-lying areas

Unincorporated ground application:
Runoff = maximum application rate (lbs ai/A) x runoff value x 10 acres
Drift = maximum application rate x 0.01
Total Loading = runoff (lbs ai/A) + drift (lbs ai/A)

Incorporated ground application:
Runoff = [maximum application rate (lbs ai/A)/minimum incorporation depth (in.)] x runoff value x 10 acres
Drift = maximum application rate x 0.01
(Note: drift is not calculated if the product is incorporated at the time of application.)
Total Loading = runoff (lbs ai/A) + drift (lbs ai/A)

Aerial, airblast, and forced-air applications:
Runoff = maximum application rate (lbs ai/acre) x 0.6 (60% application efficiency assumed) x runoff value x 10 acres
Drift = maximum application rate (lbs ai/A) x 0.05
Total Loading = runoff (lbs ai/A) + drift (lbs ai/A)

Kellogg, R.L., M.S. Maizel, and D.W. Goss. 1992. Agricultural Chemical Use and Ground Water Quality: Where are the Problem Areas?. USDA-SCS-ERS-CSRS-NCRI Publication.

Isoxaflutole Comparative Leaching Assessment for Corn