February 5, 1998

Memorandum

Subject: **Isoxaflutole - 123000**: Health Effects Division Risk Characterization Document for the First Food Use of Isoxaflutole in/on Corn (6F4664).

PRATS Case Numbers: 046754 and 287353.
PRATS DP Barcode Numbers: D223677, D227942, D234214, D237697, D239590, D241042, D241043 and D241047.

From: Barbara Madden
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Karen Whitby, Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

TO: Daniel Kenny/Joanne Miller PM Team 23
Herbicide Branch
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational, residential and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the use of isoxaflutole in/on corn.

A summary of the findings and an assessment of human risk resulting from the proposed uses for isoxaflutole are provided in this document. The hazard assessment was provided by Sanjivani B. Diwan, Ph.D., of Toxicology Branch II, the residue chemistry data review by George F. Kramer, Ph.D. of Registration Action Branch I, the dietary risk assessment by Brian Steinwand of Chemistry and Exposure Branch I (CEB I), the worker risk assessment by Tracy Keigwin of CEB I and the water exposure assessment by James Breithaupt of the Environmental Fate and Effects Division (EFED).

I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue chemistry data submitted by Rhone-Poulenc Ag Company in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158. The data were submitted to support the registration of an end-use

product formulation containing the active ingredient (ai) isoxaflutole as well as the establishment of permanent tolerances in/on corn (6F4664).

Isoxaflutole is a new chemical and is not currently registered. Technical Isoxaflutole (264-LAA) is to be formulated into an end-use product formulation (Balance WDG Herbicide, 264-LAT), a 75% water dispersible granular herbicide. Balance is proposed for a single early preplant or preemergence broadcast application to field corn. The maximum use rate is 0.14 lbs ai/A. (The maximum proposed rate was originally 0.19 lbs ai/A but was reduced by the registrant due to ecological concerns.) Only one application may be made per season.

Isoxaflutole is proposed for use on broadleaf and grass weeds in corn. Some of the weeds controlled by isoxaflutole include: Chamomile spp., Dandelion, Galinsoga, Jimsonweed, Kochia, Common lambsquarters, Wild mustard, Marestail, Eastern black nightshade, Black nightshade, Barnyardgrass, Large crabgrass, Woolly Cupgrass, Giant foxtail, Green foxtail, Fall panicum, Wild proso millet, Broadleaf signalgrass and Field sandbur. Presently, there are no proposed residential uses of isoxaflutole.

The toxicological data base for isoxaflutole is complete and of acceptable quality. The residue chemistry data base for isoxaflutole is complete and of acceptable quality.

Tolerances should be established for: "the combined residues of the herbicide isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione and 2-methylsulfonyl-4-trifluoromethyl benzoic acid, calculated as the parent compound, in/on Corn, field, grain, stover and forage. Isoxaflutole residues do not appear to concentrate in processed corn commodities. Therefore, tolerances in corn processed commodities are not required. No concentration of combined residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 were observed in aspirated grain fractions. Therefore, no tolerance for aspirated grain fractions is required at this time. Tolerances for meat and milk should be for: "the combined residues of the herbicide isoxaflutole and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione, calculated as the parent compound, in/on milk, liver of cattle, goat, hogs, horses and sheep, and meat byproducts (except liver) of cattle, goat, hogs, horses and sheep. The poultry liver tolerance should be for: "the combined residues of the herbicide isoxaflutole and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione, calculated as the parent compound, in/on poultry liver.

The appropriate tolerances are:

Corn, grain	0.2 ppm
Corn, stover	0.5 ppm
Corn, forage	1.0 ppm
Milk	0.02 ppm
Liver*	0.50 ppm
Meat Byproducts (except liver)*	0.10 ppm
Poultry, Liver	0.30 ppm
Meat	0.20 ppm
Fat**	0.20 ppm
Eggs	0.01 ppm

*of cattle, goat, hogs, horses and sheep
**of cattle, goat, hogs, and sheep

Field accumulation studies in rotational crops are required to determine the appropriate plantback intervals and/or the need for rotational crop tolerances. These studies should be performed in accordance with OPPTS Test Guidelines 860.1900. Until limited field trial data are submitted, reviewed and found acceptable, crop rotation restrictions are required. The end-use product label should contain a statement limiting the planting of rotational crops to 6 months after application.

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of isoxaflutole and its metabolites in corn. Therefore, a compatibility issue is not relevant to the proposed tolerance.

Parent isoxaflutole is not expected to persist in surface water or to reach ground water. However, the metabolites RPA 202248 and RPA 203328 are expected to reach both ground and surface water, where they are expected to persist and accumulate.

For chronic (non-cancer) dietary risk, using tolerance level residues and assuming 100 percent crop treated, non-nursing infants (< 1 year old) is the subgroup that utilized the greatest percentage of the RfD at 81%. By refining the chronic dietary risk assessment assuming 34 percent of the corn crop treated and anticipated residues (ARs) for corn, animal RACs and processed commodities, less than 1 percent of the RfD for the general population and 1 percent of the RfD for nursing infants, the subgroup with the greatest percentage of the RfD, is used.

A preliminary DRES run assuming 100 percent crop treated and tolerance level residues resulted in a cancer risk (3×10^{-6}) which exceeded HED's level of concern. Therefore, more refined dietary risk assessments for cancer were conducted using ARs for isoxaflutole and 34 percent crop treated information. A non-linear (MOE) methodology for the estimation of human cancer risk resulted in a margin of exposure (MOE) of 250,000. A linear approach, using a Q_1* of 0.0114 resulted in an upper bound cancer risk of 9.3×10^{-8}. This linear risk estimate, for use of isoxaflutole on corn is below HED's level of concern for life time cancer risk and is considered protective.

An acute dietary endpoint of concern was identified for use in risk assessment for females 13+. The appropriate MOE for acute dietary risk assessment for females 13+ is 3000. An acute dietary endpoint of concern was also identified for the general population including infants and children. The appropriate MOE for acute dietary risk assessment for the general population including infants and children is 1000. The high end MOE for the subgroup of Females, 13+ was 500, and is cause for concern given the need for a MOE of 3000. The high end MOEs for the general population, infants and children all exceed 1000, and demonstrate no acute dietary concern.

Isoxaflutole is a new chemical, proposed for use on corn. Therefore, there are no residential uses associated with the use of this chemical at this time.

For occupational exposure, risk assessments were recommended for short term (1 to 7 days) and intermediate term (1 week to several months) dermal and inhalation exposures and chronic both cancer and non-cancer. Chronic exposure is not expected. Therefore, HED did

not assess chronic non-cancer and cancer (non-linear) risk. For short and intermediate exposures the only exposure scenario with an unacceptable MOE is the commercial mixer/loader. Exposure can be reduced to acceptable levels with the addition of a chemical resistant apron when mixing/loading and cleaning equipment. It should be noted that "acceptable" is strictly for this use scenario only. Should the registrant propose other methods of application (e.g. - aerial application) projected exposures and risk will need to be reassessed. HED also assessed the potential cancer (linear) risk to workers resulting from exposure to isoxaflutole. Cancer risk for workers ranged from 2.0×10^{-7} to 8.2×10^{-8}. These risk estimates, all greater than 1×10^{-6}, do not exceed HED's level of concern and are considered protective of adult workers.

HED has calculated drinking water levels of concern (DWLOC) for the general population and children for acute exposures to isoxaflutole in surface and ground water. The maximum estimated concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface and ground water were less than HED's levels of concern for acute exposure in drinking water. Therefore, HED concludes with reasonable certainty that residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in drinking water do not contribute significantly to the aggregate acute human health risk for the general population and children at the present time considering the uses proposed in this action for registration. HED does have concern for the aggregate acute human health risk for females 13+ since the acute risk from food sources alone exceeds HED's level of concern.

Since there are no residential exposures expected with this proposed use, short and intermediate aggregate risk assessments were not conducted.

HED has calculated DWLOC for chronic (non-cancer) exposures to isoxaflutole in surface and ground water. The estimated annual average concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface and ground water were less than HED's levels of concern for chronic (non-cancer) exposure in drinking water. Therefore, HED concludes with reasonable certainty that residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in drinking water do not contribute significantly to the aggregate chronic (non-cancer) human health risk at the present time considering the present uses and uses proposed in this action for registration.

A non-linear cancer aggregate risk assessment has not been conducted since the point of departure for non-linear cancer risk assessment (2 mg/kg/day) is the same endpoint as the RfD and the aggregate cancer linear risk assessment using the Q* is considered more restrictive unless a MOE of greater than 20,000 is warranted. HED has calculated DWLOC for chronic (cancer) exposures to isoxaflutole in surface and ground water. The estimated concentrations of isoxaflutole and its metabolite RPA 202248 in ground and surface water were less than HED's levels of concern. However, the estimated concentrations of metabolite RPA 203328 in surface water (9.3 ppb) and in ground water (6.1 ppb) were greater than HED's levels of concern for chronic (cancer) exposure in drinking water. Therefore, HED concludes that residues of metabolites RPA 203328 in surface water and ground water used as drinking water may contribute significantly to the aggregate human health risk at the present time considering the proposed corn use. Because there are no available, appropriate, and reliable monitoring data to use in a more-refined quantitative exposure and risk assessment, and because HED has concerns regarding the impacts of metabolite RPA 203328 on drinking water, mitigation

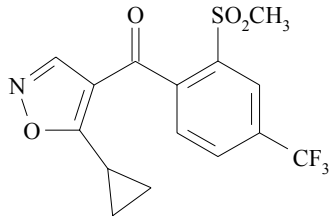
measures and monitoring requirements should be imposed as a condition of registration. RD, EFED and HED should meet to discuss what type of data should be required.

II. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

Isoxaflutole is the ANSI accepted name for the active ingredient 5-cyclopropyl-4-isoxazolyl [2-(methylsulfonyl)-4-trifluoromethyl) phenyl] ketone. The OPP pesticide chemical code for isoxaflutole is 123000. Isoxaflutole is also identified as RPA 201772. The registrant has identified isoxaflutole as one of a new class of benzoylisoxazoles.

The chemical structure for isoxaflutole is:



1. Identification of Active Ingredient

Rhone-Poulenc Ag Company submitted product chemistry data for 98% isoxaflutole technical grade active ingredient (TGAI). Findings from review of this data are in the Table 1 below.

Table 1. Physical and Chemical Properties for Rhone-Poulenc 98% TGAI.

Color	MRID 43573203	yellow
Physical State	MRID 43573203	granular powder
Odor	MRID 43573203	slight acetic acid-like odor
Melting Point	MRID 43573203	135-136 ± 1 C (decomposes at 160 C)
Boiling Point	MRID 43573203	solid at room temperature
Density, Bulk Density, or Specific Gravity	MRID 43573203	1.419 20 C/20 C (specific gravity) 1.416 g/mL at 20 C (density)

Table 1. Physical and Chemical Properties for Rhone-Poulenc 98% TGAI.		
Solubility	MRID 43573205	0.00062 g/100 mL in water (pH 5.5) 0.00068 g/100 mL in pH 5 buffer 29.3 g/100 mL in acetone 23.3 g/100 mL in acetonitrile 14.2 g/100 mL in ethyl acetate 34.6 g/100 mL in dichloromethane 0.010 g/100 mL in hexane 3.12 g/100 mL in toluene 1.38 g/100 mL in methanol 0.076 g/100 mL in 1-octanol
Vapor Pressure	MRID 43573208	1.0×10^{-6} Pa at 25 C
Dissociation Constant	MRID 43573204	not determined: solubility in 3% acetonitrile or methanol was too low for potentiometric determination.
Octanol/Water Partition Coefficient	MRID 43573206	P = 219 (log P = 2.34) at 20 C
pH	MRID 43573204	4.6 at 25 C (1% w:v aqueous suspension containing 2% acetonitrile, v:v)
Stability	MRID 43573207	Stable for 14 days at elevated temperatures (54 C) and under simulated sunlight; stable in the presence of iron, tin, and aluminum powders at 30-150 C; degradation occurred in the presence of ferric chloride at 40-90 C.

B. Human Risk Assessment

1. Hazard Assessment

The registrant has submitted toxicology data to support the registration of isoxaflutole. All toxicology studies discussed below are acceptable unless otherwise noted.

a. Acute Toxicity

The acute toxicity data on technical grade isoxaflutole and its metabolites are summarized in Table 2 and 3 below.

Table 2. Acute Toxicity of TGAI Isoxaflutole

§ No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral	43573212	LD50 >5,000 mg/kg	IV
81-2	Acute Dermal	43573213	LD50 >2,000 mg/kg	III
81-3	Acute Inhalation	43573214	LC50 >5.23 mg/L	IV

81-4	Primary Eye Irritation	43573215	Non-irritating	IV
81-5	Primary Skin Irritation	43573216	Non-irritating	IV
81-6	Dermal Sensitization	43573217	Non-sensitizer	NA

Table 3. Acute Toxicity of Metabolites of Isoxaflutole

§ No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral - RPA 202248	43904810	LD_{50} >5,000 mg/kg	IV
81-1	Acute Oral- RPA 203328	43904812	LD_{50} >5,000 mg/kg	IV

b. Subchronic Toxicity

In a 21-day dermal toxicity study (MRID 43573219) in rats, 8 CD rats/sex/group were treated topically with dosages of either 10, 100 or 1000 mg/kg/day of isoxaflutole eight hours per day for 21 days. The test material was applied using 0.5% w/v methylcellulose in purified water daily at a volume-dosage of 2 ml/kg bodyweight. Treatment-related marginal increase in relative liver weight was observed in both sexes of rats at 1000 mg/kg/day. This finding was considered as an adaptive response to isoxaflutole treatment. There were no differences between the control and treated groups in any of the other parameters measured. The systemic toxicity lowest observable effect level (LOEL) is greater than 1000 mg/kg/day for males and females; the systemic toxicity no observable effect level (NOEL)is 1000 mg/kg or greater for males and females. The dermal toxicity LOEL is greater than 1000 mg/kg/day for males and females; the dermal toxicity NOEL is 1000 mg/kg/day or greater for males and females.

In a 28-day oral subchronic toxicity study (MRID 43904813), RPA 203328 (a metabolite of isoxaflutole) was administered in the diet to male and female Charles River France, Sprague-Dawley rats (10/sex/dose) at dosage levels of 0, 150, 500, 5,000, or 15,000 ppm (0, 11.14,37.57, 376.96 or 1,117.79 mg/kg/day in males and 12.68, 42.70, 421.53 or 1268.73 mg/kg/day in females, respectively) for 28 days. Among males, a slightly lower urinary pH at 15,000 ppm and minimally higher urinary refractive index at 500 and 15,000 ppm were noted. In the absence of adverse effects on other parameters, these changes were considered as a normal physiological response to ingestion of an acidic compound. There were no compound related adverse effects on survival, clinical signs, body weight, food consumption, clinical chemistry, hematology, and gross or microscopic pathology. The LOEL is greater than 1,117.79 mg/kg/day in males and 1,268.73 mg/kg/day in females (15,0000 ppm). The NOEL for both sexes is 1,117.79 mg/kg/day in males and 1,268.73 mg/kg/day in females (15,0000 ppm).

c. Chronic Toxicity/Carcinogenicity

In a chronic toxicity study (MRID 43573218), isoxaflutole was administered to five beagle dogs/sex/dose in the diet at dose levels of 0, 240, 1,200, 12,000, or 30,000 ppm (0,

7

8.56, 44.81, and 453 mg/kg/day, respectively, for males; 0, 8.41, 45.33, 498, or 1,254 mg/kg/day, respectively, for females) for 52 weeks. The 52 week mean intake value for males in the 30,000 ppm treatment group was not available because all dogs in that group were sacrificed after 26 weeks due to severe chronic reaction to the test substance. The LOEL is 453 mg/kg/day for males; 498 mg/kg/day for females (12,000 ppm), based on reduced weight gains compared to controls and intravascular hemolysis with associated clinical chemistry and histopathological findings. The NOEL is 44.81 mg/kg/day for males; 45.33 mg/kg/day for females (1,200 ppm).

In a combined chronic toxicity/carcinogenicity study (MRID 43904806), isoxaflutole was continuously administered to 75 Sprague-Dawley rats/sex/dose at dietary levels of 0, 0.5, 2, 20 or 500 mg/kg/day for 104 weeks. An additional 20 rats/sex/group were treated for 52 weeks, after which 10 rats/sex/group were sacrificed and the remainder were held for a maximum of eight weeks without treatment in order to assess reversibility of treatment-related changes. Evidence of systemic toxicity observed at 500 mg/kg/day in one or both sexes included: abnormal gait, limited use of limbs, lower body weight gains and food consumption, decreased food efficiency during the first 14 weeks of the study, elevated cholesterol levels throughout the 104-week study, increased absolute and relative liver weights, and thyroid hyperplasia. Increased incidence of periacinar hepatocytic hypertrophy, portal tract (senile) bile duct changes, focal cystic degeneration of the liver was observed in males at 20 mg/kg/day and greater, females at 500 mg/kg/day. Eye opacity, gross necropsy changes in eyes, corneal lesions, degeneration of sciatic nerve and thigh muscles was observed in males at 20 mg/kg/day and higher doses and in females at 500 mg/kg/day. The chronic LOEL is 20 mg/kg/day based on liver, thyroid, ocular, and nervous system toxicity in males and liver toxicity in females. The chronic NOEL is 2.0 mg/kg/day.

Under the conditions of this study, isoxaflutole induced benign and malignant tumors of the liver in both sexes at 500 mg/kg/day hepatocellular adenomas (in 14/75 in males and 29/74 in females vs. 2/75 and 4/74 in the control group rats) and hepatocellular carcinomas (17/75 and 24/74 vs. 5/75 and 0/74 in the controls, respectively). Combined incidences of liver adenoma/carcinoma in males and females were 31/75 and 46/74, respectively, with animals bearing carcinomas in the majority. Thyroid follicular adenomas occurred with increased frequency in 500 mg/kg/day males (15/75 vs 3/74 in controls). The above tumor incidences exceeded the historical incidence of these tumors for this strain in this laboratory. The study demonstrated that isoxaflutole is carcinogenic to rats at a dose of 500 mg/kg/day. The chemical was administered at a dose sufficient to test its carcinogenic potential. At 500 mg/kg/day, there were alterations in most of the parameters measured including clinical signs of toxicity, body weight gain, food consumption, food conversion efficiency, and clinical as well as post-mortem pathology. Thyroid stimulating hormone (TSH) was not measure in this study. However, special study (MRID 43904818) investigating the mechanism of action of isoxaflutole on the thyroid, (discussed in section j. Other Toxicological Considerations) tested at the same doses as this study, TSH was indirectly measured since there was a significant reduction in T_4 level and thyroid gland weights were significantly increased. These results were sufficient to support the hypothesis that isoxaflutole may have induced thyroid tumors in male rats through a disruption in the thyroid-pituitary hormonal feedback mechanisms.

In a 78-week carcinogenicity study (MRID 43904807), isoxaflutole was fed in diet to 64 or 76 mice/sex/dose at dose levels of 0, 25, 500, or 7,000 ppm daily (means of 0, 3.2, 64.4, or 977.3 mg/kg/day, respectively, for males; and 0, 4.0, 77.9, or 1161.1 mg/kg/day, respectively,

for females). Interim sacrifices were made at 26 weeks (12 mice/sex at the 0 and 7,000 pm doses) and at 52 weeks (12 mice/sex at all dose levels). Isoxaflutole had no significant effect on the survival of animals. Systemic signs of toxicity in the treated groups included: decreased body weight gain in both sexes at 500 ppm and 7,000 ppm and for females at 25 ppm group; food consumption was unaffected except food efficiency was lower for both sexes at 7000 ppm during the first 14 weeks of the study; absolute and relative/body liver weights were significantly increased in both sexes at 7,000 ppm and at 500 ppm relative liver weight was increased in males at 52 weeks and in females at 78 weeks; gross necropsy at 78-week sacrifice revealed increased occurrences of liver masses in both sexes at 7,000 ppm; non-neoplastic lesions of the liver occurred at 52-week sacrifice in males at 500 ppm and in males and females at 7,000 ppm. At termination, the 500 ppm group males exhibited increased incidence of hepatocyte necrosis. At 7,000 ppm, significant increase in non-neoplastic lesions in both sexes included periacinar hepatocytic hypertrophy, necrosis, and erythrocyte-containing hepatocytes. In addition, males at the high dose had pigment-laden hepatocytes and Kupffer cells, basophilic foci, and increased ploidy; extramedullary hemopoiesis in the spleen was noted in both sexes; increase incidences of hepatocellular adenoma and carcinoma were observed in both sexes at 7,000 ppm in the 52-week and 78-week studies.

Among scheduled and unscheduled deaths in the 78-week study, there were significant occurrences of hepatocellular adenomas in 27/52 males (52%) and 15/52 females (29%), and carcinomas in 17/52 males (33%) and 4/52 females (8%;non-significant). The incidences of these tumors exceeded the corresponding historical incidence with this species, in this laboratory. Combined adenoma and carcinoma incidences at 7,000 ppm were 73% for males and 35% for females. At 500 ppm, the incidences of 17% adenomas and 15% carcinomas in males and 2% adenomas in females were not statistically significant, but exceeded the means for historical controls. The 52- and 78-week studies revealed a dose-related decrease in the first occurrence of carcinomas in males; the earliest carcinomas were observed at 78, 71, 52, and 47 weeks at the 0 through 7,000 ppm doses. There were no carcinomas in females up to 78 weeks at 0, 25, or 500 ppm, although, the earliest finding at 7000 ppm was at 60 weeks.

The LOEL for this study is 64.4 mg/kg/day for males and 77.9 mg/kg/day for females (500 ppm), based on decreased body weight gains, increased liver weights, and increased incidences of histopathological liver changes. The NOEL is 3.2 mg/kg/day for males and 4.0 mg/kg/day for females (25 ppm). Although body weight was decreased marginally in females at 25 ppm, there were no corroborating findings of toxicity at this dose.

Under conditions of this study, isoxaflutole appears to induce hepatocellular adenomas and carcinomas in male and female CD-1 mice. The chemical was tested at doses sufficient to measure its carcinogenic potential.

d. Developmental Toxicity

In a developmental toxicity study (MRID# 43573220) isoxaflutole was administered to twenty-five female Sprague-Dawley rats by gavage at dose levels of 0, 10, 100, or 500 mg/kg/day from gestational days 6–15, inclusive. Maternal toxicity, observed at 500 mg/kg/day, was manifested as an increased incidence of salivation; decreased body weight, weight gain, and food consumption during the dosing period. The maternal LOEL is 500 mg/kg/day, based on increased incidence of clinical signs and decreased body weights, body weight gains and food consumption. The maternal NOEL is 100 mg/kg/day.

Developmental toxicity, observed at 100 and 500 mg/kg/day, were manifested as increased incidences of fetuses/litters with various anomalies: growth retardations (decreased fetal body weight; increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals). In addition, an increased incidence of vertebral and rib anomalies and high incidence of subcutaneous edema were observed at 500 mg/kg/day. The incidences of these anomalies were higher than the concurrent control values and in some cases exceeded the range for historical controls. The LOEL for developmental toxicity is 100 mg/kg/day, based on decreased fetal body weights and increased incidences of skeletal anomalies. The developmental NOEL is 10 mg/kg/day.

In a developmental toxicity study (MRID# 43904808), isoxaflutole was administered to twenty-five female New Zealand White Rabbits by gavage at dose levels of 0, 5, 20, or 100 mg/kg/day from gestational days 6–19, inclusive. Maternal toxicity, observed at 100 mg/kg/day, was manifested as increased incidence of clinical signs (little diet eaten and few feces) and decreased body weight gain and food consumption during the dosing period. The maternal LOEL is 100 mg/kg/day, based on increased incidence of clinical signs, decreased body weight gains and food consumption. The maternal NOEL is 20 mg/kg/day.

Developmental toxicity, observed at 5 mg/kg/day consisted of increased incidence of 27th pre-sacral vertebrae. Additional findings noted at 20 and 100 mg/kg/day were manifested as increased number of postimplantation loss and late resorptions, as well as growth retardations in the form of generalized reduction in skeletal ossification, and increased incidence of 13 pairs of ribs. At 100 mg/kg/day, an increased incidence of fetuses with incisors not erupted was also observed. Incidences of these anomalies, on a litter basis, were higher than the concurrent control values and in some cases exceeded the range for historical controls. The LOEL for developmental toxicity is 5 mg/kg/day, based on increased incidence of fetuses with 27th pre-sacral vertebrae. The developmental NOEL was not established.

e. Reproductive Toxicity

In a 2-generation reproduction study (MRID 43904809), isoxaflutole was administered to Charles River Crl:CD®BR VAF/Plus® rats (30/sex/group) at nominal dietary levels of 0, 0.5, 2, 20 or 500 mg/kg/day (actual levels in males: 0, 0.45, 1.76, 17.4 or 414 mg/kg/day; females: 0, 0.46, 1.79, 17.7 or 437 mg/kg/day, respectively). Evidence of toxicity was observed in the male and female parental rats of both generations: at 20 and 500 mg/kg/day, increased absolute and relative liver weights associated with liver hypertrophy was observed; at 500 mg/kg/day (HDT), decreased body weight, body weight gain and food consumption during premating and gestation, and increased incidence of subacute inflammation of the cornea of the eye in F_0 adults as well as keratitis in F_1 adults were reported. There were no other systemic effects that were attributed to treatment, nor was there any indication, at any treatment level, of an effect on reproductive performance of the adults. Treatment-related effects were observed in F_1 and F_2 offspring: at 20 and 500 mg/kg/day, reduction in pup survival was noted; at 500 mg/kg/day, decrease in body weights of F_1 and F_2 pups throughout lactation, increased incidence of chronic keratitis, low incidence of inflammation of the iris, as well as retinal and vitreous bleeding in F_2 pups and weanlings were observed. Necropsy of F_1 and F_2 pups culled on Day 4 revealed an increased number of pups with no milk in the stomach and underdeveloped renal papillae. The Systemic LOEL is 17.4 mg/kg/day for males and females, based upon increased liver weights and hypertrophy and the Systemic NOEL is 1.76 mg/kg/day for males and females. The

Reproductive LOEL is greater than 437 mg/kg/day, based on lack of reproductive effects and the Reproductive NOEL is greater than or equal to 437 mg/kg/day.

f. Mutagenicity

Isoxaflutole (RPA 201772):

Salmonella typhimurium reverse gene mutation assay (MRID 43588002): Independently performed tests were negative in S.typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 up to insoluble doses (≥500 µg/plate +/- S9) and was non-cytotoxic.

Mouse lymphoma L5178Y forward gene mutation assay (MRID 43573222): Independently performed tests were negative up to insoluble (≥150 µg/mL +/-S9) or soluble (≤75 µg/mL +/-S9) doses.

In vitro cytogenetic assay in cultured human lymphocytes (MRID 43573221). The test was negative up to insoluble concentrations (≥300 µg/mL -S9; 600 µg/mL +S9) and was non-cytotoxic.

Mouse micronucleus assay (MRID 43573223): The test was negative in male or female CD-1 mice up to the highest administered oral gavage dose (5000 mg/kg). No evidence of an overt toxic response in the treated animals or a cytotoxic effect on the target cells was observed.

Major Metabolite (RPA 202248):

Salmonella typhimurium reverse gene mutation assay (MRID 43904811): Independently performed plate incorporation or preincubation modification to the standard plate incorporation tests were negative in S. typhimurium strains TA1535, TA1537, TA98, TA100 and TA102 up to the highest dose assayed (5000 µg/plate +/- S9).

Minor Metabolite (RPA 203328)

Salmonella typhimurium reverse gene mutation assay (MRID 43904814): Independently performed plate incorporation tests were negative in S. typhimurium strains TA1535, TA1537, TA98, and TA100 up to cytotoxic doses (≥2500 µg/plate +/- S9).

These acceptable studies satisfy the new mutagenicity initial testing battery guidelines. Based on the findings of the acceptable studies, there is no concern for mutagenicity at this time.

g. Metabolism

In a metabolism study (MRID 43573224), ^{14}C-isoxaflutole was administered to groups (5/sex/dose) of male and female Sprague-Dawley (CD) rats by gavage at a single low oral dose (1 mg/kg), repeated low oral dose (1 mg/kg/day as a final dose in a fifteen day repeat dose series), and a single high dose (100 mg/kg). In addition, pharmacokinetics in blood was investigated using two groups of 10 rats (5/sex/dose) that received a single oral dose of 1 or

100 mg/kg of ^{14}C–isoxaflutole. Urine and feces were collected at 24, 48, 96, 120, 144, and 168 hour after dosing, and tissues were collected at 168 hours post-dosing. Metabolite analysis was performed on the urine and feces of all dose groups, and on the liver samples of the two low dose group male and female rats.

^{14}C-isoxaflutole was rapidly and extensively absorbed and metabolized. RPA 202248, a major metabolite, a diketonitrile derivative, represented 70% or more of the radioactivity excreted in the urine and feces from the two low dose groups. The other minor metabolite, RPA 203328, was more polar. Elimination was rapid and dose-dependent. The mean total recovery ranged from 98.09% to 99.84% (mean 99.21%). Urinary elimination (males: 61.16% to 66.65%, females: 58.80% to 67.41%) was predominant in the two low dose groups while the major portion of radiolabel was excreted via the feces (males: 62.99%, females: 55.23%) in the high dose group. The higher fecal elimination possibly resulted from the saturation of absorption resulting in elimination of unchanged parent compound. The majority of the radiolabel was eliminated in the first 24 and 48 hours for the low and the high dose groups, respectively. The extensive systemic clearance of the radiolabel was reflected in the low levels of radioactivity found in tissues at 168 hours post-dosing. For the two low dose groups, liver (0.172 to 0.498 ppm) and kidneys (0.213 to 0.498 ppm) accounted for the major portion of the administered dose found in tissues. In the high dose group, the highest level of radioactivity was found in decreasing order in blood, plasma, liver, and kidney. Sex-related differences were observed in the excretion and distribution pattern among high dose rats. The elimination half-lives were similar among single low and high dose groups, with an estimated mean blood half-life of 60 hours. No sex differences were observed in the metabolism of ^{14}C-isoxaflutole.

In a comparative metabolism study (MRID 43904815), isoxaflutole was administered to groups (5/species) of male Sprague-Dawley (CD) rats and CD-1 mice by gavage at a single dose (10 mg/kg) followed one hour later with a single oral dose of ^{14}C-Tyrosine (500 mg/kg). The total radioactivity in the urine and expired CO_2 was estimated at 0-5, 5-12, 12–24, and 12–48 hour intervals. Metabolite analysis was performed on the urine of the rat and the mouse to analyze the quantitative differences in their ability to utilize a by-pass metabolic route for the blocked tyrosine pathway via hydroxyphenyl lactic acid (HPLA) and hydroxyphenyl acetic acid (HPAA).

For both species, a major portion of ^{14}C-Tyrosine administered dose was eliminated via urine and expired air. Urinary elimination (mice: 46.79%, rats: 15.70%) was predominant in the mouse while a significant portion of radiolabel was predominantly excreted via the expired air as CO_2 in the rat (mice: 6.47%, rat: 17.04%) during the first 48 hours following administration of ^{14}C-Tyrosine. HPLC analysis of ^{14}C-Tyrosine metabolites found in the urine of both species revealed higher amounts of two major metabolites, HPLA and HPAA, in the mouse than those in the rat. The enzymatic hydrolysis of conjugates indicated that some metabolites were excreted as glucuronides and/or sulfates in urine; these did not include HPLA and HPAA.

This study demonstrated species-related qualitative and quantitative differences in the excretion of tyrosine following single simultaneous administrations of isoxaflutole and ^{14}C-Tyrosine to male mice and rats. The findings of the study further suggests differential ability of the two species to alternatively utilize a by-pass metabolic route for the blocked tyrosine pathway via HPLA and HPAA.

This comparative metabolism study using *rats* and *mice* is classified as ***Unacceptable*** however, it is not a required guideline study. It can be upgraded provided the registrant provides clarification of the following issues:

1. It is not clear why there was an absence of a control group in this study, specifically, that there were groups of rats and mice dosed only with radiolabelled tyrosine. This could have facilitated comparison of disposition observed after dosing with the combination of tyrosine and isoxaflutole. The co-administration of tyrosine and isoxaflutole might have also influenced the disposition of tyrosine accounting in part for the observed difference in disposition between rats and mice.

2. It is also unclear why only a single dose of isoxaflutole was used. A series of doses could have better delineated possible differences between rats and mice in sensitivity. The only major difference in this study was noted in the percentage of HPLA and HPAA excreted from 0-5 hours post-dose in rats and mice, where mice showed higher percentages of these metabolites in urine. The differences in percentages of these metabolites at later times of excretion was not major, i.e. from 0.13-0.5% greater in mice vs. rats.

3. There are no individual animal data to verify the summary data on metabolite fractions presented in Tables 5 and 6 of the submitted report, pages 23 and 24. It is unclear what is meant by the term "individual" samples as stated in the heading to Table 5. Individual animal data should be submitted to verify the summary data.

4. There appears to be a shift in the retention time for HPLA and HPAA metabolites using the same HPLC method on individual and pooled samples. In Table 5 of the report, the HPLA and HPAA metabolites are listed as fractions 5 and 6, respectively, while for the pooled samples, the same metabolites are listed as fractions 6 and 8. The reason for this apparent shift needs explanation.

h. Neurotoxicity

In an acute neurotoxicity study (MRID 43904804), CD rats (10/sex/group) received a single oral gavage administration of isoxaflutole in 0.5% aqueous methylcellulose at doses of 0 (vehicle only), 125, 500 or 2000 mg/kg body weight. No treatment-related effects were observed on survival, body weight, body weight gain or food consumption. There were significant decreases in landing foot splay measurements in males at 2000 mg/kg during FOB tests indicating impairment of neuromuscular function. At 500 mg/kg, males exhibited significant decreases in landing foot splay measurements on day 15. The LOEL was 500 mg/kg based on significant decreases in landing foot splay on day 15. The NOEL was 125 mg/kg.

In a subchronic neurotoxicity study (MRID 43904805), isoxaflutole was administered to CD rats (10/sex/group) at dietary levels of 0, 25, 250 or 750 mg/kg/day for 90 days. Treatment-related effects observed in high-dose males consisted of decreases in body weight and body weight gain. The LOEL was established at 25 mg/kg/day based on significant decreases in mean hind limb grip strength in male rats at 25 mg/kg/day (LDT) during both trials at week 13 as well as a non significant decrease in mean forelimb grip strength at week 13.

i. Dermal Absorption

In a dermal absorption study ^{14}C-Isoxaflutole(99.7%) as a 1% carboxy methylcellulose aqueous suspension was administered to male Crl:CDBR rats (4/dose) as a single dermal application at 0.865, 7.32 or 79 mg/cm^2. Dermal absorption was measured after 0.5, 1, 2, 4, 10 and 24 hours of exposure. Results are summarized below:

	Percent Absorbed		
Average Dose	1 hour	10 hours	24 hours
0.865 mg/cm^2	<1	**3.46**	4.42
7.32 mg/cm^2	<1	<1	<1
7.9 mg/cm^2	<1	<1	<1

j. Other Toxicological Considerations (special studies)

Isoxaflutole has been found to produce corneal lesions in male rats but not in mice or dogs of either sex. Additionally, isoxaflutole blocks the oxidative breakdown of tyrosine. Because high doses of tyrosine itself or the administration of a compound that blocks the oxidative breakdown of tyrosine (NTBC) also produce corneal lesions in rats, the registrants are postulating, based on the special studies discussed below, that the corneal toxicity by isoxaflutole results from its blockage of tyrosine breakdown (presumably by allowing tyrosine to reach toxic levels in tissues).

The registrant also conducted three additional special studies discussed below, to investigate the mixed function oxidase system with respect to liver enlargement in rats and mice and to investigate the mechanism of action of isoxaflutole on the thyroid. These studies were considered by the Cancer Peer Review Committee in determining the carcinogenicity of isoxaflutole and mechanism of toxicity.

In an exploratory study (MRID 43904816), groups of 5 male and 5 female CD rats, Brown Norway rats and CD-1 mice received 0, 2 or 5% tyrosine (0, 1,000 or 2,500 mg/kg/day for rats and 0, 2,600 or 6,500 mg/kg/day for mice, respectively) in their diet for 14 days. Within 48 hours of dietary administration of 5% tyrosine, corneal opacities with superficial keratitis were observed in 3 of 5 male CD rats; by Day 7, corneal opacities developed in all five rats. At study termination, these corneal lesions were found to be associated with elevated plasma tyrosine levels. One of five male Brown Norway rats receiving 5% tyrosine had slight bilateral opacities at 14 days accompanied by a high plasma tyrosine level. Histopathology revealed changes characteristic of corneal opacity involving various corneal layers and ciliary processes. These effects were not seen in female rats or mice of either sex. Dietary administration of 2% tyrosine failed to produce similar effects in any group or in any female rats and both sexes of mice. There were no differences between the control and treated groups in any of the other parameters measured.

In a comparative tyrosine tolerance study (MRID 43904817), isoxaflutole or RPA 200261 [99.8% a.i.; also called 2-(2-Nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione or NTBC], a therapeutic agent, were administered in the diet to male Sprague-Dawley rats (5/dose) at dosage levels of 0 and 10 mg/kg/day for one week. The animals then received 500 mg/kg/day tyrosine on the day of treatment, and on Days 2, 3 and 8 after the test substance administration. Urine collected at 4, 8 and 24 hours was analyzed for tyrosine metabolites. Administration of tyrosine to rats pretreated with isoxaflutole or NTBC, increased the urinary excretion of tyrosine metabolites, N-acetyl tyrosine (NAT), 4-hydroxyphenyl acetate (4-HPAA) and 4-hydroxyphenyl lactate (4-HPLA). The effect of isoxaflutole was reversible within 48 hours after administration while that of NTBC was not. The results of this functional assay suggests that both isoxaflutole and NTBC affect the main catabolic pathway for tyrosine by inhibiting 4-Hydroxy phenyl pyrorate dioxygenase.

A special study (MRID 43904819) in rats was also conducted to establish the dose response and to investigate the role of the mixed function oxidase system with respect to liver enlargement in isoxaflutole treated rats. Groups of 5 male Sprague-Dawley rats received isoxaflutole in the diet at dosage levels of 0, 10, 100, or 400 mg/kg/day for 14 days. Isoxaflutole administration caused an increase in absolute and relative liver weights in rats at 100 and 400 mg/kg/day. This increase was attributed to induction of mixed function oxidase (MFO) enzymes in the liver. The total cytochrome P-450 levels were increased in a dose-dependent manner. The specific forms of isoenzymes responsible for this increase were PROD and BROD enzymes, which may be attributed to the induction of P-450 2B family (i.e., phenobarbital type). Therefore, isoxaflutole appears to function as a phenobarbital type inducer of the P-450 2B family. There was no increase in other P-450 isoenzyme levels including MROD and EROD nor did the test compound induce lauric acid hydroxylases that are associated with peroxisome proliferation. Thus, isoxaflutole appears to be a phenobarbital type inducer of liver enzymes. The LOEL is 10 mg/kg/day based on induction of P-450 enzymes in male rats. In addition, at greater than or equal to 100 mg/kg/day liver enlargement was also seen.

The registrant conducted a special study in mice (MRID 43904820) to establish the dose response and to investigate the role of the mixed function oxidase system with respect to liver enlargement in isoxaflutole treated mice. Groups of 25 male CD-1 mice received isoxaflutole in the diet at dosage levels of 0, 175, 700, 2800 or 7000 ppm (0, 23, 91, 364 or 910 mg/kg/day, respectively) for 14 days. Isoxaflutole administration caused increase in absolute and relative liver weights in rats at 700 ppm and greater. This increase was attributed to the induction of mixed function oxidase enzymes in the liver. The total cytochrome P-450 levels were increased in a dose-dependent manner. The specific forms of isoenzymes responsible for this increase included pentoxyresorufin O-diethylase (PROD) and benzoxyresorufin O-diethylase (BROD), which may be attributed to induction of the P-450 2B family. Therefore, isoxaflutole appears to function as a phenobarbital type inducer. There was no significant increase in other P-450 isoenzyme levels including methoxyresorufin O-diethylase (MROD) and ethoxyresorufin O-diethylase (EROD) nor did the test compound induce lauric acid hydroxylases, that are associated with peroxisome proliferation. The LOEL was 23 mg/kg/day (175 ppm) based on induction of the P-450 enzyme, BROD, in male mice. In addition, at 91 mg/kg/day (700 ppm) and greater a dose-related increase in liver enlargement and induction of PROD was seen.

A study (MRID 43904818) in which the mechanism of action of isoxaflutole on the thyroid was investigated in male Sprague-Dawley rats was submitted. In this study isoxaflutole was administered in the diet to male Crl:CD (SD) rats (14/dose) at dosage levels of 0 or 500

mg/kg/day for 14 days. A third group (positive control) of rats received 80 mg/kg/day sodium phenobarbital by gavage and an untreated diet. Following the treatment period, the liver enzyme activities including cytochrome P-450 and p-nitrophenol uridine 5'-diphosphatase-glucuronyltransferase (UDPGT) as well as thyroxine levels were monitored and thyroid weights were determined. The rate of T_4 disappearance from blood was measured in rats after intravenous administration of sodium ^{125}I-thyroxine. The effect on blood concentration half-life, thyroid gland iodine uptake and thyroid weights were measured.

Isoxaflutole administration caused more than two-fold increase in cytochrome P-450 dependent mixed-function oxidase system and UDPGT activity which resulted in increased clearance of ^{125}I-thyroxine from the blood as indicated by shorter half-life and decreases in plasma T_4 level. In addition, there were increases in liver and thyroid weights. The plasma T_3 level was unaffected. The significant reduction in the level of circulating T_4 was possibly the result of enhanced glucuronidation by hepatic UDPGT and a rapid systemic clearance of total radioactive ^{125}I-thyroxine in the isoxaflutole treated group. Following intravenous administration of ^{125}I-thyroxine, the thyroid iodine uptake was slightly higher and thyroid weights were significantly higher than controls in isoxaflutole treated rats. The effects observed in this study are supportive of the hypothesis that isoxaflutole may have induced thyroid tumors in male rats (MRID 43904806) through a disruption in the thyroid-pituitary hormonal feedback mechanisms.

2. Dose Response Assessment

The HED RfD/Peer Review Committee met on April 24, 1997 to discuss and evaluate the toxicology data base for isoxaflutole and determine the appropriate Reference Dose (RfD) to be used in risk assessment. The HED Toxicology Endpoint Selection Committee considered the available toxicology data for isoxaflutole at a meeting held on April 29, 1997. Based upon a review of the toxicology data base for isoxaflutole, toxicology endpoints and dose levels of concern were identified for use in risk assessments.

On December 4, 1997, the risk assessment document on Isoxaflutole was reviewed by HED's Risk Assessment Review Committee (RARC). The RARC recommended that the Hazard Identification Review Committee (HIARC) re-evaluate the rationale used for recommended additional uncertainty factor (UF) of 3 x. The RARC was unsure as to whether the 3 x applied for the lack of a NOEL in the critical study and/or because of the observance of increased sensitivity *in utero* developmental toxicity studies in rats and rabbits. The RARC also needed clarification on the need for the developmental neurotoxicity study in light of the increased sensitivity observed in rats and rabbits .

Consequently, on December 12, 1997, the HIARC: 1) re evaluated the toxicology data base; 2) re-assessed the doses and endpoints selected; 3) determined the MOEs for the various exposure scenarios (dietary as well as occupational exposure risk assessments); 4) addressed the enhanced sensitivity of infants and children as required by FQPA; and 5) determined the need for a developmental neurotoxicity study in rats.

a. Special Sensitivity to Infants and Children

The HIARC determined that for isoxaflutole, the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. This conclusion was based on the following factors.

(i) There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposures in prenatal developmental toxicity studies. In both species, the developmental effects were seen at doses which were not maternally toxic. (i.e., developmental NOELs were less than the maternal NOELs). In rats, increased sensitivity manifested as growth retardation characterized as decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals. In rabbits, increased sensitivity was manifested as fetuses with increased pre-sacral vertebrae at the lowest dose tested as well as fetuses with increased incidences of skeletal anomalies at the next two higher doses tested; also a NOEL for developmental toxicity was not established in this study.

(ii) There is concern for the developmental neurotoxic potential of isoxaflutole. This is based on the demonstration of neurotoxicy in FOB measurements in the acute and subchronic neurotoxicity as well as evidence of neuropathology in the combined chronic toxicity/ carcinogenicity studies.

(iii) A developmental neurotoxicity study is required based on the evidence of neurotoxicity as well as the lack of assessment of susceptibility of the offspring in functional/neurological development in the standard developmental/reproduction toxicity studies. Although the recommendation of the 5/29/97 RfD Peer Review Committee was that a developmental neurotoxicity study in rats would not be required, a reevaluation of the neurotoxicity studies by the HIARC identified significant neurobehavioral findings, supported by neuropathology observed in the chronic study in rats following long term exposure. With this information considered in the weight-of-the-evidence evaluation, the HIARC revised the previous conclusion and recommended that a developmental neurotoxicity study in rats with isoxaflutole would be required. The following information was considered in support of this decision:

Evidence that support requiring a developmental neurotoxicity study:

- Isoxaflutole is a neurotoxic chemical.
- Neurobehavioral findings were observed in the acute and subchronic neurotoxicity studies in rats. These included decreased foot splay in the acute and subchronic studies and decreased hind- and forelimb grip strength in the subchronic study.
- Increased incidences of axonal/myelin degeneration of the sciatic nerve were observed in the chronic toxicity study in rats. Focal degeneration/inflammation of the thigh muscle was seen at the same treatment levels.

b. Reference Dose (RfD)

For chronic dietary risk assessment, the RfD Committee selected a NOEL of 2 mg/kg/day based on hepato, thyroid, ocular and neurotoxicity in males as well as hepatotoxicity in females at 20 mg/kg/day (LOEL) following dietary administration of Isoxaflutole (99.2%) at 0, 0.5, 2, 20 or 500 mg/kg/day for 104 weeks to male and female Sprague-Dawley rats (MRID No.

43904806). The NOEL/LOEL of this study is supported by the parental systemic toxicity NOEL of 1.76 mg/kg/day and the LOEL of 17.4 mg/kg/day established in the two-generation reproduction study in rats; the LOEL was based on increased liver weights and hypertrophy in both sexes in both generations.

The RfD Committee applied a UF of 300 to the NOEL of 2 mg/kg/day to derive the RfD of 0.0067 mg/kg/day (2 mg/kg/day ÷ 300 = 0.0067 mg/kg/day). The UF of 300 included 10 x for inter, 10 x for intra-species variations and an additional 3 x for the lack of a NOEL in the developmental rabbit study and the potential for increased sensitivity to fetuses following *in utero* exposure. Because of the clarification needed on the UF of 300, this RfD was re-assessed by the HIARC. The HIARC concurred with the RfD Committee on the dose and endpoint selected but did not concur on the UF of 300. Instead, the HIARC determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Thus, for chronic dietary risk assessment an UF of 1000 is required (10 x for inter-species variation, 10 x for intra-species variation, and 10 x for FQPA). Consequently the revised RfD is 0.002 mg/kg/day (NOEL of 2 mg/kg/day ÷ UF of 1000 = RfD, 0.002 mg/kg/day) and supersedes the previous RfD.

Refer to the section above on Special Sensitivity to Infants and Children for discussion on why the FQPA 10x factor should be retained.

c. Carcinogenic Classification and Risk Quantification

The HED Carcinogenicity Peer Review Committee (CPRC) met on May 14, 1997 to discuss and evaluate the weight-of-the-evidence on isoxaflutole with particular reference to its carcinogenic potential. In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 23, 1996), isoxaflutole was characterized as "likely to be a human carcinogen", based on statistically significant increases in liver tumors in both sexes of mice and rats, and statistically significant increases in thyroid tumors in male rats. Also, the liver tumors in male mice had an early onset.

Administration of isoxaflutole in the diet to CD-1 mice for 78 weeks resulted in statistically significant increases in hepatocellular adenomas and combined adenoma/carcinoma in both sexes at the highest dose (7000 ppm, equivalent to 977.3 mg/kg/day for males; 1161.1 mg/kg/day for females). There were also positive significant trends for hepatocellular adenomas, carcinomas and combined adenoma/carcinoma in both sexes. In male mice there was also a statistically significant increase in hepatocellular carcinomas at the highest dose with a positive significant trend and, at the 53-week sacrifice, there was evidence of early onset for hepatocellular adenomas. The incidences of hepatocellular tumors exceeded that for historical controls in both sexes.

The CPRC agreed that the highest dose in this study was adequate and not excessive.

Administration of isoxaflutole in the diet to Sprague-Dawley rats for 2 years resulted in statistically significant increases in hepatocellular adenomas, carcinomas and combined adenoma/carcinoma in both sexes at the highest dose (500 mg/kg/day). There were also positive significant trends for hepatocellular carcinomas, adenomas and combined adenoma/carcinoma in both sexes. The incidences of hepatocellular adenomas and carcinomas exceeded that for historical controls in both sexes.

In male rats there was also a statistically significant increase in thyroid follicular cell adenomas, carcinomas and combined adenoma/carcinoma at the highest dose, and positive significant trends for these adenomas and combined adenoma/carcinoma. The incidences of thyroid adenomas and carcinomas exceeded that of historical controls in male rats.

The CPRC agreed that the highest dose in the rat study was adequate and not excessive.

There was no evidence of mutagenicity in the studies submitted and no structurally related analogs could be identified, since isoxaflutole is a member of a new class of chemicals.

The studies (MRIDs 43904819 & -20) submitted by the registrant to show a mechanistic basis for the liver tumors were considered by the CPRC to be suggestive, but not convincing. The CPRC agreed that the mechanistic evidence (MRID 43904818) presented for the thyroid tumors appeared to be scientifically plausible and consistent with EPA current policy.

CPRC recommended that for the purpose of risk characterization, a non-linear (MOE) approach be applied to the most sensitive precursor lesion in the male rat thyroid, and that a linear low-dose extrapolation be applied for the tumors of the rat liver.

On August 26, 1997 members of HED, William Burnam, Sanjivani Diwan, Barbara Madden, Hugh Pettigrew and Esther Rinde met to further discuss issues regarding the Carcinogenicity Peer Review of isoxaflutole. As stated above, CPRC recommended that for the purpose of risk characterization, a non-linear (MOE) approach be applied to the most sensitive precursor lesion in the male rat thyroid, and a linear low-dose extrapolation be applied for the tumors of the rat liver. In the August 26, 1997 meeting, upon review of the data and CPRC document it was recommended that the NOEL of 2 mg/kg/day in males from a 104 week combined chronic toxicity/carcinogenicity study in rats (MRID 43904806) be used for the non-linear (MOE) cancer risk assessment. The endpoint of concern and LOEL was 20 mg/kg/day based on thyroid hyperplasia. Tumors first appear in this study at the 500 mg/kg/day dose.

It was also decided that there was no reason not to include the results from the 78-week feeding/carcinogenicity study in mice (MRID 3904807) when determining the Q_1^* to be used for risk assessment for the linear low-dose extrapolation. It was recommended that a Q_1^* be developed for the female mouse liver, female rat liver, male mouse liver and male rat liver and the Q_1^* with the highest unit of potency be used for risk assessment.

The four resulting estimates of unit potency were:

	Unit Potency (95% upper bound (Q_1^*)) [per mg/kg/day]
Female CD-1 Mouse liver	3.55E-003
Female Rat liver	3.84E-003
Male CD-1 Mouse liver	1.14E-002
Male Rat liver	5.27E-003

The unit risk, Q_1^* $(mg/kg/day)^{-1}$ of isoxaflutole, based upon male mouse liver (adenomas and or carcinomas) tumors is 1.14×10^{-2} in human equivalents, converted from animals to humans by use of the 3/4's scaling factor (1994, Tox_Risk, 3.5-K.Crump). The dose levels used in the 79 week mouse study were 0, 3.2, 64.4 and 977.3 mg/kg/day of isoxafluotle. The corresponding tumor rates for the male mice were 13/47, 15/50, 14/48 and 38/49.

d. Other Toxicological Endpoints

i. Dermal Absorption

In a dermal absorption study (MRID 44044702) ^{14}C-Isoxaflutole as a 1% carboxy methylcellulose aqueous suspension was administered to rats as a single dermal application at 0.865, 7.32 or 79 mg/cm^2. The estimated absorption at 10 hours is 3.5%. Therefore, the HIARC determined that a dermal absorption rate of 3.5% should be used for risk assessment.

ii. Acute Dietary

The HIARC identified the developmental LOEL of 5 mg/kg/day from the developmental toxicity study (MRID 43904808) in rabbits as the acute dietary endpoint to be used for risk assessments. The LOEL is based on increased incidence of fetuses with 27th pre-sacral vertebrae; a NOEL was not established. The fetal incidence of this anomaly was dose-depended and exceeded the concurrent as well as the historical control incidences. Also at the next higher dose (20 mg/kg/day) there was an increased incidence of fetuses with reduced ossification. It was noted that the developmental anomalies occurred below the dose that caused maternal toxicity (100 mg/kg/day).

The TESC selected this dose and endpoint and recommended a MOE of 300 for this risk assessment because of the use of a LOEL. The HIARC re-affirmed the dose and endpoint and the additional UF of 3 x under FIFRA. The HIARC, however, determined that for acute dietary risk assessment for this sub population (13+), the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Thus, a MOE of 3000 is required. This MOE of 3000 includes: the conventional 100; 10 x for FQPA; and 3 x for FIFRA (lack of NOEL).

Refer to the section above on Special Sensitivity to Infants and Children for discussion on why the FQPA 10x factor should be retained.

The HIARC also identified the NOEL of 125 mg/kg/day from the acute neurotoxicity study (MRID 43904804) as the endpoint of concern to be used in acute dietary risk assessment for the general population including infants and children. The NOEL is based on significant decreases in landing foot splay on day 15.

The HIARC determined that for acute dietary risk assessment for the general population, the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Thus, a MOE of 1000 is required and includes the conventional 100 and 10 x for FQPA. Since a NOEL was used the FIFRA factor is not applicable. Refer to the section

above on Special Sensitivity to Infants and Children for discussion on why the FQPA 10x factor should be retained.

iii. Short Term (1-7 days) and Intermediate Term (1 week to several months) Dermal Occupational and Residential

The TESC in their April, 1997 meeting did not select doses or endpoints for these risk assessments due to the lack of dermal or systemic toxicity in the 21-dermal toxicity study in rats following repeated dermal applications at doses up to and including 1000 mg/kg/day (Limit-Dose)(MRID 43573219). Although the HIARC recognized the lack of systemic toxicity in the 21-day dermal toxicity study as well as the low absorption potential, the LOEL of 5 mg/kg/day from the developmental toxicity study (MRID 43904808) in rabbits was chosen for use as an endpoint in short and intermediate term risk assessments. The developmental LOEL was selected because: 1) of the concern for the increased sensitivity observed following *in utero* exposures in rats and rabbits; 2) developmental LOEL was lower than maternal NOEL in rabbits; 3) fetal effects can occur after a single exposure; 4) developmental effects are not evaluated in the dermal study and 5) adequate protection is needed for pregnant occupational workers.

Since an oral dose was selected a dermal absorption rate of 3.5% should be used in risk assessments.

The HIARC determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. An additional UF of 3 x was applied under FIFRA because of the use of the LOEL (i.e., lack of a NOEL in the critical study) for these risk assessments. Thus, a MOE of 3000 is required. The MOE of 3000 includes: the conventional 100; 10 x for FQPA; and 3 x for FIFRA. Although there are no residential uses, the FQPA factor still applies to ensure protection against female occupational workers.

iv. Chronic (Non-Cancer)(Several Months to a Lifetime) Dermal Occupational and Residential

The NOEL of 2 mg/kg/day was selected as the endpoint of concern for chronic (non-cancer) risk assessment from a combined chronic/oncogenicity study in rats (MRID 43904806). The NOEL is based on increased liver weights and hypertrophy in both sexes in both generations.

The HIRAC determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Thus, for these risk assessments a MOE of 1000 is required. The MOE of 1000 includes the conventional 100 and 10 x for FQPA. In addition, although there are no residential uses, the FQPA factor still applies to ensure protection against female occupational workers.

v. Inhalation (Any Time Period)

Although the LC_{50} of >5.26 mg/L (Toxicity Category IV) indicates low inhalation toxicity potential, the HIARC identified doses and endpoints for inhalation risk assessment due to the potential exposure via this route for occupational workers. The developmental LOEL of 5 mg/kg/day from the developmental toxicity study (MRID 43904808) in rabbits should be used as an inhalation endpoint for short-and intermediate-term exposure. The oral systemic NOEL of 2 mg/kg/day from the combined chronic/oncogenicity study in rats (MRID 43904806) should be used as an inhalation endpoint for chronic inhalation exposure.

HIARC selected these doses, the same doses used in respective dermal risk assessments, due to the lack of appropriate inhalation toxicity studies and the concern for the toxicity seen via the oral route. Since the doses identified for these (inhalation) risk assessments are oral dose the risk assessment should be as follows:

Step I. The inhalation exposure component (i.e., mg/L) using a 100 % absorption rate (default value) should be converted to an equivalent oral dose (mg/kg/day).

Step II. The dermal exposure component (i.e., mg/kg/day) using 3.5% dermal absorption should be combined with this converted oral equivalent dose (mg/kg/day).

Step III. This combined oral equivalent dose should then be compared to the oral LOEL of 5 mg/kg/day for short- and intermediate-term exposure and the NOEL of 2 mg/kg/day for chronic exposures to calculate the MOE.

Table 4. Summary of Toxicological Endpoints for Isoxaflutole

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	Females 13+ : LOEL of 5 mg/kg/day based on increased incidence of 27th pre-sacral. MOE of 3000 General Population including infants and children: NOEL of 125 mg/kg/day based on significant decreases in landing foot spay on day 15. MOE of 1000
Short-Term (1-7 days) & Intermediate-Term (one week to several months) Occupational/Residential	Dermal & Inhalation	LOEL of 5 mg/kg/day based on increased incidence of 27th pre-sacral. MOE of 3000
Chronic (non-cancer) (several months to a lifetime) Occupational and Residential	Dermal & Inhalation	NOEL of 2 mg/kg/day based on hepato, thyroid, ocular, and neurotoxicity in amles and hepatotoxicity in females. MOE of 1000

Cancer	Dietary/Dermal /Inhalation	NOEL of 2 mg/kg/day for the non-linear (MOE) approach - based on statistically significant increases in thyroid tumors in male rats. Q* of 1.14E-002 from the male CD-1 mouse liver for the linear low-dose extrapolation based on statistically significant increases in liver tumors in both sexes of mice and rats.
Chronic (non-cancer)	Dietary	RfD of 0.002 mg/kg/day based on the chronic rat study with a NOEL of 2 mg/kg/day. At the next higher dose level of 20 mg/kg/day, liver, thyroid, ocular, and nervous system toxicity were observed in males and liver toxicity was observed in females. UF of 1000 to account for special sensitivity of infants and children (developing fetuses), interspecies and intraspecies extrapolation.

3. Dietary Exposure and Risk Characterization

a. Dietary Exposure - Food Source

i. Directions for Use

Isoxaflutole is formulated as Balance WDG Herbicide (264-LAT), a water-dispersible granule containing 75% a.i. Balance is proposed for a single early preplant or preemergence broadcast application to field corn. The maximum use rate is 0.19 lbs. ai/A. Only one application may be made per season.

ii. Nature of the Residue - Plants

Rhone-Poulenc submitted data (MRID 43573249) depicting the metabolism of [phenyl-^{14}C]isoxaflutole in field corn. The test substance was prepared by mixing [phenyl-^{14}C]isoxaflutole (specific activity 18.35 mCi/mmol, radiochemical purity 98.7%) with [carbonyl-^{13}C]isoxaflutole and non-labeled isoxaflutole to a final specific activity of 37,600 dpm/µg. The test substance was applied to container-grown field corn as a single preplant incorporated application (PPI) or a single preemergence application (PRE); PPI applications were made immediately prior to planting, and PRE applications were made following planting. Application rates for the PPI mode of treatment were 0.187 lb ai/A (1x the maximum proposed application rate for preplant application) or 0.586 lb ai/A (3x; exaggerated rate). Application rates for the PRE mode of treatment were 0.203 lb ai/A (1.7x the maximum proposed application rate for preemergence application) or 0.960 lb ai/A (8.2x; exaggerated rate).

The petitioner also submitted a discussion (MRID 43573250) of their rationale for conducting the metabolism study with isoxaflutole labeled in the phenyl ring. The petitioner stated that they conducted numerous preliminary metabolism studies, with plants, soil, and animals, in which isoxaflutole was labeled in the phenyl ring, in the isoxazole ring, or at the carbonyl carbon. Based on these studies, the petitioner observed that RPA 203328 is the major

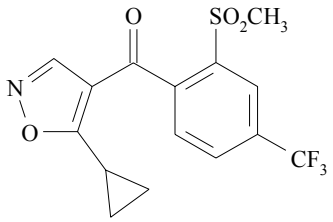
metabolite, that the isoxazole ring is highly unstable and hydrolyzes rapidly to form RPA 202248, and that the cyclopropyl moiety metabolizes/degrades to cyclopropane carboxylic acid. The petitioner concluded that the metabolism of isoxaflutole results in the formation of RPA 203328 and cyclopropane carboxylic acid, and that no additional information would be obtained from a study in which the molecule was labeled in the isoxazole ring or the cyclopropyl ring, due to the short half-life of the isoxazole ring and the metabolism/degradation of the cyclopropyl ring into compounds of little toxicological significance.

The nature of the residue in plants is adequately understood. The major terminal residues of regulatory concern are the parent compound, isoxaflutole (RPA 201772), and its metabolites, 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione (RPA 202248), and 2-methylsulfonyl-4-trifluoromethyl benzoic acid (RPA 203328). RPA 202248 and RPA 203328 were the **only** components of the residue identified, generally accounting for 30-100% of the total radioactive residue (TRR). The metabolism of isoxaflutole in corn proceeds via: 1) the hydrolysis of the isoxazole ring to form RPA 202248; 2) further hydrolysis to produce RPA 203328.

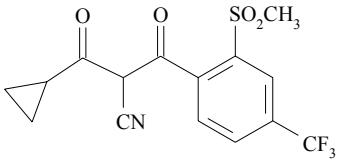
It was determined at an Ad Hoc Metabolism Committee Premeeting (7/17/97) that there is no scientific objection to establishing the plant tolerances in terms of isoxaflutole and its metabolites RPA 202248 and RPA 203328, calculated as the parent compound. The HED Metabolism Committee met on September 4, 1997 and agreed with this conclusion and determined that there was no conclusive evidence to suggest that metabolites 202248 and 203328 are any less toxic than the parent and therefore, are considered toxicology equivalent to the parent. The Committee also decided that the residues of concern in drinking water are isoxaflutole and its metabolites RPA 202248 and RPA 203328.

The structure of isoxaflutole and its metabolites are shown below:

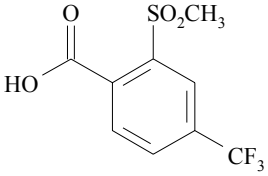
ISOXAFLUTOLE



RPA 202248



RPA 203328



iii. Nature of the Residue - Livestock

The nature of the residue in ruminants is considered to be understood. A study (MRID 43904827) entitled "^{14}C)-RPA201772: Absorption, Distribution, Metabolism and Excretion Following Repeat Oral Administration to the Dairy Goat" was submitted. [Phenyl(U)-^{14}C]-isoxaflutole (18.4 mCi/mmol) was isotopically diluted, placed in a gelatin capsule and administered orally to lactating goats (weight of 63-87 kg, age <8 years) with the aid of a balling gun. The goats were dosed at a total rate of 1 ppm, 10 ppm or 50 ppm per day. Doses were administered twice daily for 7 consecutive days. The animals were sacrificed approximately 24 hours after administration of the final dose.

Of the administered radioactivity, 28-31% was recovered in feces, less than 1% in the milk and 9-11% in the tissues. Extractable residues were analyzed by HPLC and the retention times compared with those of possible metabolites. RPA 202248 was generally the major component of the residue, accounting for 24-86% of the TRR. RPA 207048 and RPA 205834 were also identified, accounting for 10-26% and 0-15% of the TRR, respectively. The metabolism of isoxaflutole thus proceeds via: 1) the hydrolysis of the isoxazole ring to form RPA 202248 and RPA 205834; 2) further hydrolysis to produce RPA 207048.

For compounds with multiple rings, HED generally requires that metabolism studies be performed with each ring labeled. However, as the metabolism of isoxaflutole in ruminants proceeds via opening of the isoxazole ring, HED concludes that a goat metabolism study using isoxaflutole labeled in this ring will not be required.

A study (MRID 43904827) entitled "(^{14}C)-RPA201772: Absorption, Distribution, Metabolism and Excretion Following Repeat Oral Administration to the Laying Hen" was submitted. [Phenyl(U)-^{14}C]-isoxaflutole (18.4 mCi/mmol) was isotopically diluted, placed in a gelatin capsule and administered orally to laying hens (weight of 1.5-2.1 kg, age 22 weeks). The hens were dosed at a rate of 1 ppm or 10 ppm. There were five birds in each dosing group. Doses were administered daily for 14 consecutive days. The animals were sacrificed approximately 24 hours after administration of the final dose.

Of the administered radioactivity, 88-100% was recovered in excreta, 0.2% in the eggs and less than 2% was recovered in the tissues. Extractable residues were analyzed by HPLC and the retention times compared with those of possible metabolites. RPA 202248 was generally the major component of the residue, accounting for 6-93% of the TRR. RPA 207048 and RPA 205834 were also identified, accounting for up to 49% and up to 28% of the TRR, respectively. The metabolism of isoxaflutole in poultry is thus very similar to that in ruminants.

The HED Metabolism Committee concluded RPA 207048 and RPA 205834 are the major portion of the residue of concern in animal commodities and therefore these metabolites need to be included in the dietary risk assessment. The committee also concluded that metabolites RPA 207048 and RPA 205834 are likely to be of comparable toxicity to the parent. Since RPA 207048 and RPA 205834 are a major portion of the residue in animal commodities, these metabolites need to be included in the risk assessment. However, since another major metabolite, RPA 202248 is measured by the proposed enforcement method, RPA 207048 and RPA 205834 need not be included in the tolerance expression for animals; i.e., RPA 202248 is serving as a marker compound for the total toxic residue.

iv. Residue Analytical Methods

Plants

The registrant submitted residue analytical methods (MRID 43573253,43588003 and 43904829) using a modification of the GC/MSD method entitled "Analytical Method for the Determination of Residues of RPA 201772, RPA 202248, and RPA 203328 in Maize Grain and Fodder." The method involves hydrolysis of residues of isoxaflutole to RPA 202248, conversion of RPA 202248 residues to RPA 203328, and then derivatization of RPA 203328 to a methyl ester for GC analysis. The limit of quantitation (LOQ) is 0.01 ppm.

Rhone-Poulenc submitted data (MRID 43573251) pertaining to independent laboratory validation (ILV) of the proposed enforcement method for the determination of residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in/on field corn forage, fodder, and grain. The method used was entitled "Analytical Method for Determination of Residues of RPA 201772, RPA 202248, and RPA 203328 in Corn Forage, Silage, Grain, and Fodder," and it is essentially identical to the method used for residue data collection. The validation was conducted by ABC Laboratories (Pan-Ag Division, Madera, CA), and field corn grain was chosen as the representative matrix for validation. The submitted data are adequate to satisfy the requirements for independent laboratory validation (as per PR Notice 88-5) of the proposed enforcement method.

The OPP Analytical Chemistry Laboratory Branch (ACLB) performed a PMV on the following method “Analytical Method for the Determination of Residues of RPA 201772, RPA 202248, and RPA 203328 in Corn Grain and Fodder (MRID 43573251). The recoveries of isoxaflutole are acceptable (Memo, G. Kramer 8/20/96; D228481). However, the petitioner should submit a revised version of the proposed analytical enforcement method as specified in conclusions 1-5 of the aforementioned Memo. Until the receipt of the revised method, the requirements for analytical enforcement methodology will remain unfulfilled.

Animals

The registrant submitted “Isoxaflutole- Validation of Method of Analysis for Isoxaflutole and Its Metabolite in Animal Tissues” (MRID 44169004) as the proposed enforcement method. Isoxaflutole is converted to RPA 202248 by base hydrolysis. RPA 202248 is with HPLC. The LOQ is 0.01 ppm for milk and eggs; 0.40 ppm for beef and poultry liver, 0.20 ppm for beef and poultry muscle and fat; and 0.20 ppm for beef kidney.

Rhone-Poulenc submitted data (MRID 44169005) pertaining to ILV of the proposed enforcement method for the determination of residues of isoxaflutole and its metabolites in milk, eggs, liver, kidney, muscle and fat tissues. This method was performed by Mckenzie Labs, Phoenix, AZ. Acceptable recoveries were obtained by the laboratory.

The proposed analytical enforcement method for animal RACs has been validated by ACL, Beltsville (Memo, M. Law 11/4/97). However, minor revisions of the method are required. Until the receipt of the revised method for animal RACs, the requirements for analytical enforcement methodology will remain unfulfilled.

An HPLC/MS/MS method was used to analyze the tissue samples from the feeding studies. The method was shown to extract 53% of the TRR. Therefore, in order to obtain an accurate interpretation of the residue data from the ruminant and poultry magnitude of residue studies, adjustments in the results from the LC-MS-MS data gathering method were made to correct for the lower extraction efficiency.

v. Multiresidue Methods

Data pertaining to the recovery of isoxaflutole and its metabolites RPA 202248 and RPA 203328 using FDA multiresidue methods were submitted (MRID 43573252). These multiresidue screening data were forwarded to FDA.

vi. Storage Stability Data

The registrant submitted storage stability data (MRID 43904834). Samples of corn grain, forage, fodder, and silage with field-incurred residues stored frozen at less than -10 ○C. Samples were maintained frozen and two subsamples were removed and analyzed at various intervals for residues using the proposed enforcement method over the course of 13 months. Each analysis included two freshly fortified controls. The results demonstrate that the total residues of isoxaflutole and its metabolites are stable during storage in corn RACs up to 13 months. The petitioner has provided adequate storage stability data for corn RACs. The total residues of isoxaflutole and its metabolites are stable during frozen storage in corn RACs for up to 13 months.

An additional storage stability study (MRID 44169005) was submitted. Samples of corn processed commodities were fortified with residues of isoxaflutole, RPA 202248, and RPA 203328 and stored frozen at less than -10○C. Samples were maintained frozen and two subsamples were removed and analyzed after 3 months for residues using the proposed enforcement method. Each analysis included two freshly fortified controls. The results demonstrate that the total residues of isoxaflutole and its metabolites are stable during storage in corn processed fractions for 3 months. The storage stability results indicated that there were no significant losses of isoxaflutole, RPA 202248, or RPA 203328 in any of the matrices during storage under freezer conditions.

A storage stability study (MRID 44169007) entitled “Isoxaflutole: Storage Stability of Residues in Dairy Cow and Poultry Matrices” was submitted. Samples of animal commodities were fortified with residues of isoxaflutole, RPA 202248, RPA 205834, RPA 207048, and RPA 203328 and stored frozen at <-10 ○C. Samples were maintained frozen and two subsamples were removed and analyzed after 0.5, 1, 2, 3 and 4 months for residues using the data gathering method. Each analysis included a freshly fortified control. The results for milk indicate that RPA 202248, RPA 205834 and RPA 203328 are stable or show no indication of degradation during the conditions of the study. The parent compound, isoxaflutole appears to degrade with an estimated half life of approximately 111 days. The results for the tissues indicate that RPA 207048 does degrade in some tissue matrices. The other analytes appear to be stable in the kidney, muscle and fat tissues. For liver, isoxaflutole and RPA 202248 appear to be generally stable, whereas RPA 205834 and RPA 207048 appear to degrade with an estimated half life of about 3 months. The results for egg indicate that RPA 202248 is stable in the egg matrix. As indicated in the feeding studies, the parent isoxaflutole is immediately converted to RPA 202248 in the egg matrix, so that no fresh recovery of isoxaflutole is possible.

vii. Crop Field Trials

Rhone-Poulenc has submitted residue data (MRID 43588003) from ten field trials conducted in IL(2), IN(2), IA(1), MN(2), MO(1), NE(1), and OH(1) depicting residues of

isoxaflutole and its metabolites RPA 202248 and RPA 203328 in/on field corn commodities. Field corn was treated with a single preemergence broadcast application of isoxaflutole (50.8% WP formulation) at 0.134 (0.124-0.139) or 0.223 (0.217-0.239) lb ai/A (0.7x or 1.2x the maximum proposed application rate on the label; 1.1x or 1.9x the maximum proposed application rate for this type of application) in 10.2-21.1 gal/A of water using a CO_2 backpack sprayer, a tractor mounted sprayer, or a bicycle sprayer. Three treated samples and one untreated sample were harvested per trial. Forage samples were harvested 55-60 days after treatment. Corn silage samples were harvested at the dent stage of growth, 99-126 days after treatment. Corn grain and fodder samples were collected at crop maturity, 123-161 days after treatment.

The registrant also submitted results from an additional twenty two field residue trials (MRID 43904837) conducted in 1994 in 13 different states. These trials were located in Regions 1 (1 trial), 2 (1 trial), 6 (1 trial) and 5 (19 trials). A single preemergence broadcast application of isoxaflutole (75 WG) was performed at a rate of 0.223 lbs. ai/A (1.2X). The spray volume was 15-20 gal/A. Three replicate samples were harvested from each treated plot 55-61 (forage), 93-145 (silage) and 114-183 (fodder and grain) days after application. The samples were frozen. All samples were analyzed within 319 days of harvest. Sample analysis for isoxaflutole and its metabolites was performed using the proposed enforcement method. The method was validated over a range of 0.01-1.4 ppm. The average recovery was 111 ± 4.9% in forage; 104 ± 9.8% in silage; 99.7 ± 6.9% in fodder; 96.1 ± 10.4% in grain. Analysis of the treated samples showed that the maximum residues were 0.88 ppm in forage, 1.1 ppm in silage, 0.40 ppm in fodder, and 0.11 ppm in grain.

HED concludes that the 32 field corn trials were conducted in accordance with the *EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances, 6/2/94*. The maximum residues were 0.88 ppm in forage, 1.1 ppm in silage, 0.40 in fodder, and 0.11 ppm in grain. Based on these data, the appropriate tolerances for isoxaflutole and its metabolites are 0.2 ppm in grain, 0.5 ppm in stover and 1.0 ppm in forage.

Tolerances should be established for: "the combined residues of the herbicide isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione and 2-methylsulfonyl-4-trifluoromethyl benzoic acid, calculated as the parent compound, in/on Corn, field, grain, stover and forage.

HED notes that one value (1.1 ppm) in excess of the proposed forage tolerance was observed in silage (NE-2). However, as the residues other two silage samples from this site were well below 1.0 ppm and the residues in the other 191 forage and silage samples were below 1.0 ppm, the appropriate tolerance for forage appears to be 1.0 ppm.

viii. Processed Food/Feed

Rhone-Poulenc has submitted data (MRID 43573253) depicting the concentration of residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in field corn processed commodities. In two tests conducted in IN and NE in 1993, field corn grain was harvested 166-180 days following a single preemergence broadcast application of the 50.8% WP formulation at 0.223-1.116 lb ai/A (1.2-6x the proposed maximum application rate) using ground equipment. Three replicate treated grain samples and one untreated control sample were harvested from plots treated at 0.67 lb ai/A (3.6x the proposed maximum application rate).

This was the highest application rate that exhibited no phytotoxicity. Although grain was harvested from both IN and NE tests sites, only field corn grain samples from the NE test site were used for processing.

Isoxaflutole residues do not appear to concentrate in processed corn commodities. The registrant submitted storage stability data (MRID 44169005) indicating that there were no significant losses of isoxaflutole, RPA 202248, or RPA 203328 in any processed corn commodity during storage under freezer conditions. Therefore, tolerances in corn processed commodities are not required.

At the Engineering Biosciences Research Center of Texas A&M University (Bryan, TX), aspirated grain fractions were collected, and samples of field corn were processed into germ, hulls, coarse gluten-starch, gluten, starch, presscake, crude oil, refined oil, and soapstock using a small-scale wet milling commercial procedure, and into germ, hulls, grits, flour, meal, presscake, crude oil, refined oil, and soapstock using a small-scale dry milling commercial procedure. The registrant submitted adequate material balance information and descriptions of the field corn processing procedures. Aspirated grain fraction collection procedures simulated commercial techniques.

Adequate data pertaining to aspirated grain fractions of corn were collected in connection with the field corn processing study. No concentration of combined residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 was observed in aspirated grain fractions collected from field corn grain samples bearing detectable residues (average combined residues were 0.039 ppm) following a single preemergence broadcast application of the 50.8% WP formulation at 3.7x. Based on these data, no tolerance for aspirated grain fractions is required at this time.

ix. Meat, Milk, Poultry, Eggs

A study entitled “Isoxaflutole: Magnitude of the Residues in Milk and Tissues of Lactating Dairy Cows” (MRID 43904835) was submitted. Holstein dairy cows were dosed daily with isoxaflutole levels of 0, 4.6, 13.8, and 46 ppm in the diet. Each treatment group had four cows; the control group, 2. Milk samples were taken for analysis twice weekly. The cows were sacrificed on day 42. The maximum sample storage interval was 87 days. Samples of tissues were analyzed with LC/MS method described above; milk, with the proposed enforcement method. The method was validated in milk over a range of 0.02-0.10 ppm. The average recoveries were 87 ± 11%, 98 ± 11, and 94 ± 8% for isoxaflutole, RPA 202248, and RPA 205834, respectively. The method was validated in tissues over a range of 0.05-2.0 ppm. The average recoveries were 84 ± 10%, 93 ± 9%, 95 ± 11%, and 92 ± 17% for isoxaflutole, RPA 202248, RPA 205834, and RPA 207048, respectively. At the 4.6 ppm dietary burden, quantifiable residues were observed only in liver (up to 0.8 ppm), milk (up to 0.03 ppm), and kidney (up to 0.2 ppm). At the highest dose level, quantifiable residues of isoxaflutole or RPA 202248 were not observed in fat or muscle.

Based on the estimated maximum dietary burden of 1.2-1.4 ppm, the dietary feeding levels in this study were ≈3X, ≈10X and ≈35X. The samples from the feeding studies were stored for a maximum of 3 months. The results of the feeding study have been recalculated, correcting for the ≈50% extraction efficiency of the LC-MS-MS data gathering method and the decline of residues observed in some tissue/metabolite combinations The appropriate tolerances are:

Milk	0.02 ppm
Liver*	0.50 ppm
Meat Byproducts (except liver)*	0.10 ppm
Poultry, Liver	0.20 ppm
Fat**	0.20 ppm

*of cattle, goat, hogs, horses and sheep
** of cattle, goat, hogs, and sheep

Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are required for meat and fat of cattle, goat, hogs, and sheep. The required tolerances for these commodities, 0.20 ppm for meat and fat, are based on the LOQ of the proposed analytical enforcement method.

The tolerance expression proposed by the petitioner included RPA 203328. However, this metabolite is neither found in animals nor is it measured in the proposed enforcement method for animal tissues. Tolerance for meat and milk should be for: "the combined residues of the herbicide isoxaflutole and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione, calculated as the parent compound, in/on milk, liver of cattle, goat, hogs, horses and sheep, and meat byproducts (except liver) of cattle, goat, hogs, horses and sheep.

A magnitude of the residue study (MRID 43904836) in poultry was also submitted. White Leghorn laying hens were dosed daily with isoxaflutole at levels of 0, 0.18, 0.54 and 1.8 ppm in the diet. Each group had 15 hens. Egg samples were taken daily. The animals were sacrificed on day 42. The maximum sample storage interval was 83 days. Samples of tissues were analyzed with LC/MS method described above; eggs, with the proposed enforcement method. The method was validated in eggs at 0.05 ppm. The average recovery was 92 ± 3%. The method was validated in tissues over a range of 0.05-1.0 ppm. The average recoveries were 83 ± 18%, and 84 ± 9% for isoxaflutole and RPA 202248, respectively. At the 1.8 ppm dietary burden, quantifiable residues were observed only in liver (up to 0.6 ppm). At the highest dose level, quantifiable residues of isoxaflutole or RPA 202248 were not observed in eggs, meat, fat or muscle.

Based on the estimated maximum dietary burden of 0.2 ppm, the dietary feeding levels in this study were 0.9X, 2.7X and 9X. The results of this feeding study indicate that appropriate tolerances are: Poultry, Liver - 0.20 ppm. Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are now required for meat, eggs and fat of poultry. The required tolerances for these commodities, 0.20 ppm for meat and fat and 0.01 ppm for eggs, are based on the LOQ of the proposed analytical enforcement method.

The tolerance expression proposed by the petitioner includes RPA 203328. However, this metabolite is not found in animals nor is it measured in the proposed enforcement method for animal tissues. The poultry liver tolerance should be for: "the combined residues of the herbicide isoxaflutole and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione, calculated as the parent compound, in/on poultry liver.

x. Confined Accumulation in Rotational Crops

An accumulation study (MRID 43904839) on confined rotational crops was submitted. [Phenyl(U)-^{14}C]-isoxaflutole (18.4 mCi/mmol) was applied to outdoor plots at a rate of 200 g

ai/ha (0.18 lbs. ai/A, 0.9X) using preplant incorporation (PPI) or preemergence (PRE) application to separate plots. Test plots were established in NC (sandy loam soil, pH 6.3). Lettuce, sorghum and radishes were planted 34 days after treatment (DAT); mustard, radishes and wheat were planted 123 DAT; and lettuce, sorghum and radishes were planted 365 DAT. All crops were harvested when mature. Immature samples of wheat and sorghum forage, radish roots and foliage and mustard or lettuce were also taken.

The highest residue levels were seen in 34 DAT sorghum forage (0.13-0.24 ppm). Plant samples containing less than 0.01 ppm were extracted sequentially in hexane:ethyl acetate (9:1), acetonitrile, water and acetonitrile:0.2N HCl (1:1). Aqueous extracts were partitioned with ethyl acetate. The total extractability of residues was generally greater than 80% of the TRR.

RPA 203328 accounted for 59-63% of the TRR and unknown #1 accounted for another 27-32% of the TRR in lettuce. RPA 203328 accounted for 9-37% of the TRR; RPA 202248, 26-27% in 34-DAT radish leaf. In 34-DAT sorghum RPA 203328 was observed in forage, stover and grain, accounting for 24-100% of the TRR. RPA 202248 was observed in sorghum grain, accounting for 1-5% of the TRR and unknown #1 accounted for another 10-42% of the TRR in stover and grain. In 123-DAT wheat RPA 203328 was observed in forage, straw and grain, accounting for 56-100% of the TRR and unknown #1 accounted for up to 33% of the TRR in forage. RPA 203328 accounted for up to 20% of the TRR and unknown #1 accounted for another 90-100% of the TRR in 365-DAT radish leaf. RPA 203328 was observed in forage and stover, accounting for 7-66% of the TRR and unknown #1 accounted for another 33-76% of the TRR in stover and forage in 365-DAT sorghum.

The registrant submitted a supplemental report on confined rotational crops (MRID 44169002). Samples of each crop matrices were spiked with a mixture of ^{14}C-isoxaflutole, ^{14}C-RPA 202248, and ^{14}C-RPA 203328. The total concentration was approximately 2 ppm (49% isoxaflutole, 33% RPA 202248, and 18% RPA 203328). The samples were analyzed on day 0 and day 700 using methodology described in the initial submission. The results indicate that isoxaflutole is not stable in storage as shown by the decrease from ca. 49% (at 0-DAT) to 10% (at 700-DAT) of the total peak area. These results confirmed those reported in the corn metabolism report (MRID 43573249) where a decrease in isoxaflutole of up to 27% during a ca. 7-month storage period was reported. In contrast to the corn metabolism study, however, RPA 202248 was found to be somewhat susceptible to degradation over the longer storage period in this study. Although an average of ≈9% increase was realized (from 33.3 to 42.0%), a 30% increase in RPA 203328 was also demonstrated suggesting that degradation from isoxaflutole to RPA 202248 and subsequently from RPA 202248 to RPA 203328 had occurred.

The petitioner has provided stability data only for the parent and 2 metabolites instead of investigating the stability of the metabolite profile present in the samples at harvest. Further, the data submitted indicate that isoxaflutole was extensively metabolized to RPA 202248 and RPA 203328 during storage. As RPA 202248 and RPA 203328 were the only metabolites identified and these metabolites are determined in the proposed enforcement method, the petitioner will not be required to repeat the confined rotational crop study. Due to uncertainties in the composition of the samples at harvest, HED will base its conclusions from this study on the TRR. The results of this study show that residues are 0.01 ppm or greater in all crops at the 12-month plantback interval. Field accumulation studies in rotational crops are required to determine the appropriate plantback intervals and/or the need for rotational crop tolerances. These studies should be performed in accordance with OPPTS Test Guidelines 860.1900.

Until limited field trial data are submitted, reviewed and found acceptable, crop rotation restrictions are required. The end-use product label should contain a statement limiting the planting of rotational crops to 6 months after application.

xii. Anticipated Residues

HED reviewed a total of 32 corn residue trials (MRIDs 43588003 & 43904837). Isoxaflutole was applied prior to emergence at a rate of 0.223 lbs. ai/A (1.2X). For samples with residue levels below the LOQ pf 0.01 ppm, a value of ½ LOQ was used in calculating average residues. The average level of isoxaflutole and its metabolites in grain was 0.015 ppm; in silage, 0.11 ppm; in forage, 0.087 ppm; and in stover, 0.057 ppm. Corn was treated with isoxaflutole at a rate of 4X and the grain processed after harvest. The following concentration factors were observed: grits, 0.9X; meal, 0.9X; and oil, less than 0.3X. Data were not provided for corn sugar.

Anticipated Residues

Table 5. Summary of Isoxaflutole Anticipated Residues for Dietary Risk Assessment (Acute Endpoints).

Commodity	Required Tolerance (ppm)	Total Toxic Residues (ppm)
Corn Grain	0.20	0.015
Corn grits	-	0.014
Corn oil	-	0.005
Corn sugar	-	0.022
Liver, ruminant	0.50	0.85[1]
Meat	0.20	0.26[1]
Fat	0.20	0.48[1]
Meat by-products (except liver)	0.20	0.23[1]
Milk[2]	0.02	0.0014
Eggs[3]	0.01	0.021
Poultry meat	0.20	2.1
Poultry fat	0.20	0.35
Poultry meat by-products	0.30	0.30

[1] These anticipated residues should be used for beef, horses, hogs, goats and sheep in the DRES run.

[2] Based on the results of the feeding studies and the chemical nature of isoxaflutole and its metabolites, concentration of residues in milk fat is not expected.

[3] Based on the results of the feeding study, residues in egg whites are not expected.

Table 6. Summary of Isoxaflutole Anticipated Residues for Dietary Risk Assessment (Chronic Endpoints).

Commodity	Value for TMRC Calculation (ppm)	Anticipated Residue for DRES Run (ppm)
Corn Grain	0.20	0.015
Corn grits	0.20	0.014
Corn oil	0.20	0.005
Corn sugar	0.20	0.022
Liver, ruminant	0.85[1]	0.041[1]
Meat	0.26[1]	0.0017[1]
Fat	0.48[1]	0.00048[1]
Meat by-products (except liver)	0.23[1]	0.0056[1]
Milk[2]	0.036	0.00022
Eggs[3]	0.021	0.000089
Poultry meat	2.1	0.000023
Poultry fat	0.36	0.000017
Poultry meat by-products	0.30	0.015

[1] These anticipated residues should be used for beef, horses, hogs, goats and sheep in the DRES run.

[2] Based on the results of the feeding studies and the chemical nature of isoxaflutole and its metabolites, concentration of residues in milk fat is not expected.

[3] Based on the results of the feeding study, residues in egg whites are not expected.

In order to adjust the ARs for the presence of the isoxaflutole metabolites RPA 207048 and RPA 205834, the percentage of the total toxic residue (TTR) occupied by these metabolites had to be determined. The tolerance values were based on the combined residues of isoxaflutole and its metabolite RPA 202248. The adjustment factor is determined by dividing the TTR by the sum of isoxaflutole and RPA 202248:

[isoxaflutole + RPA 202248 +RPA 207048 + RPA 205834] ÷ [isoxaflutole + RPA 202248]

Table 7. Adjustment factors for animal commodities.

Animal	Commodity	% of TTR Comprised of Isoxaflutole + RPA 202248	Adjustment Factor
Ruminant	Liver	59	1.7
	Kidney	88	1.1
	Muscle	77	1.3
	Fat	42	2.4
	Milk	56	1.8
Poultry	Liver	100	1.0
	Muscle	9.5	10.5
	Fat	57	1.8
	Egg Yolk	49	2.1

Ideally, the results of the animal feeding studies should be used to calculate the adjustment factors. However, in the isoxaflutole feeding studies, ruminant liver was the only commodity which contained quantifiable residues of RPA 207048 and RPA 205834. The results of the animal metabolism studies were thus used to calculate adjustment factors for all other commodities.

Ruminant Commodities

The acute ARs (Table 5) are determined by multiplication of the required tolerances by the adjustment factors, except for milk which is considered to be a blended commodity. For milk, the acute AR is based on a diet (0.76 ppm) comprised of corn grain with average residues (0.015 ppm, blended commodity) and corn silage with the highest average field trial value (0.75 ppm, non-blended commodity).

The dosing levels used in the ruminant feeding study (MRID 43904835) correspond to 38X, 115X, and 380X the anticipated dietary burden for beef cattle and 31X, 92X and 310X the anticipated dietary burden for dairy cattle. Based on this information, and based on the residues found in meat, meat by-products, fat and milk in the ruminant feeding study anticipated residues in livestock commodities are expected to be liver, 0.024 ppm; meat by-product (except liver), 0.0049 ppm and milk, 0.00012 ppm. These ARs were multiplied by the adjustment factors shown above (Table 7). The tolerance values also must be adjusted for calculation of the TMRC.

Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are required for ruminant meat and fat. The required tolerance for these commodities, 0.20 ppm, is based on the LOQ of the proposed analytical enforcement method. The anticipated residues for the chronic dietary risk assessment were calculated by adjusting the residues of isoxaflutole + RPA 202248 + RPA 207048 + RPA 205834 found in the ruminant metabolism study at a 10 ppm feeding level for the anticipated dietary burden of 0.12 ppm.

Poultry Commodities

The dosing levels used in the poultry feeding study (MRID 43904836) correspond to 15X, 45X and 150X the anticipated dietary burden for poultry. Based on information, and based on the residues found in meat, liver, eggs, and fat in the poultry feeding study, the anticipated residues in poultry commodities to be used is 0.015 ppm.

Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are required for poultry meat, eggs and fat. The required tolerances for these commodities, 0.20 ppm for meat and fat and 0.01 ppm for eggs, are based on the LOQ of the proposed analytical enforcement method. The anticipated residues for the chronic dietary risk assessment were calculated by adjusting the residues of isoxaflutole + RPA 202248 + RPA 207048 + RPA 205834 found in the poultry metabolism study at a 10 ppm feeding level for the anticipated dietary burden of 0.012 ppm. The acute ARs for poultry meat, eggs and fat (Table 1) are determined by multiplication of the required tolerances by the adjustment factors.

xii. Codex Considerations

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of isoxaflutole and its metabolites in corn. Therefore, a compatibility issue is not relevant to the proposed tolerance.

b. Dietary Exposure - Drinking Water Source

Parent isoxaflutole is not expected to persist in surface water or to reach ground water. However, the metabolites RPA 202248 and RPA 203328 are expected to reach both ground and surface water, where they are expected to persist and accumulate.

The Environmental Fate and Effects Division (EFED) provided HED with estimates of exposure for isoxaflutole and its metabolites RPA 202248 and RPA 203328 for both surface and ground water based on available modeling. Since there are no registered uses for isoxaflutole in the U.S., there are no monitoring data to compare against the modeling. Table 8 presents the estimated environmental concentrations (EECs) for surface water using Tier 2 modeling from PRZM/EXAMS. Table 9 presents the acute and chronic ground water concentrations using the SCI-GROW model. For surface water, the maximum concentrations should be used for acute risk calculations. The annual means (1-10 years) are available for chronic risk calculations. For ground water, the SCI-GROW numbers for each compound should be used for acute, chronic, and cancer risk assessment.

If residues of isoxaflutole reach water resources, they will be primarily associated with the aqueous phase with minimal adsorption to sediment because of their low adsorption coefficients. Standard coagulation-flocculation and sedimentation processes used in water treatment are not expected to be effective in removing isoxaflutole residues, based on their adsorption coefficients. The use of GAC (Granular Activated Carbon) is also not expected to be effective in removing isoxaflutole residues because of low binding affinity to organic carbon.

Table 8.Tier II upper tenth percentile EEC's for Parent Isoxaflutole, RPA 202248, and RPA 203328 for simulated corn using PRZM 2.3 and EXAMS 2.94.

Compound	Maximum ($\mu g \cdot L^{-1}$)	Annual Mean ($\mu g \cdot L^{-1}$) 1-10 years
Parent Isoxaflutole	0.4	0.01
RPA 202248	2.0	1.7
RPA 203328	10.0	9.3

* Upper 90% confidence bound on the 36 year mean with the variance calculated from the annual means.

Table 9. Acute and Chronic Concentrations of Parent Isoxaflutole and Metabolites in Ground Water Using SCI-GROW.

Compound	Acute ($\mu g \cdot L^{-1}$)	Chronic ($\mu g \cdot L^{-1}$	Cancer ($\mu g \cdot L^{-1}$)
Parent Isoxaflutole	0.00025	0.00025	0.00025
RPA 202248	0.23	0.23	0.23
RPA 203328	6.1	6.1	6.1

Tier II EECs for surface water for parent isoxaflutole and its primary metabolites applied to corn in Pottawattamie County, Iowa were calculated to generate aquatic exposure estimates for use in the aquatic risk and human health risk assessments. The PRZM 2-3 and EXAMS 2.94 programs were dated 4/30/97 and 1/26/92, respectively. The Tier II upper tenth percentile EECs are listed in Table 8.

For PRZM-EXAMS modeling, for parent isoxaflutole, EFED used the maximum rate on the most recent proposed label (0.14 lbs ai/A) applied using ground equipment. For soil K_{oc}, the mean value of 122 ml/g was used (MRID 43588009). For soil metabolism in the field, an aerobic soil metabolism value of 3.5 days was used. This value was the upper 90th percentile bound of the 1.3 and 2.4 day half-lives in MRID 43588006. For degradation in the pond (EXAMS), EFED used an aerobic aquatic metabolism half-life of six hours, calculated by multiplying the 2-hour half-life (MRID 43588007) times three to account for the uncertainty of having only one half-life for this study. EFED has not formally reviewed the aerobic aquatic metabolism study submitted by Rhone Poulenc. Therefore, EFED multiplied the 3.5-day aerobic soil half-life used in the model by an uncertainty factor of 2 to account for a change in media. Hydrolysis was not included as a model input since both the aerobic and anaerobic aquatic metabolism inputs include the contribution to degradation from hydrolysis. An aqueous photolysis half-life of 6.7 days was used as an input into EXAMS (MRID 43588004). The water solubility of parent isoxaflutole was reported to be 3.5 mg/l (MRID 42275501)

For RPA 202248, a phytotoxic metabolite of isoxaflutole, surface water EEC's were calculated using an application rate of 0.15 lbs ai/A, and corrected by adjusting for the new maximum application rate of parent isoxaflutole (0.14 lbs ai/A). In the aerobic soil metabolism study, RPA 202248 was observed at 80 % of parent isoxaflutole on a mass basis. However, the registrant has not demonstrated that there are additional dissipation pathways for isoxaflutole dissipation in the environment. Therefore, EFED is assuming 100 % conversion from parent isoxaflutole to RPA 202248 in soil and water. For soil K_{oc}, the mean value of 93 ml/g was used (MRID 44065801). For soil metabolism in the field, an aerobic soil metabolism value of 106 days was used. This value was the upper 90th percentile bound of the 17 and 61 day half-lives (EFED-calculated) in MRID 43588006. For degradation in the pond (EXAMS), EFED used an aerobic aquatic metabolism half-life of 1155 days, which is the upper 90th percentile bound of the extrapolated half-lives of 250 and 700 days in the aerobic aquatic metabolism study that has not been formally reviewed. The quality of this data is uncertain, since the study has not been formally reviewed. The registrant has not shown that RPA 202248 actually degrades at a significant rate in aquatic environments. RPA 202248 was observed to be stable to hydrolysis (MRID 43573254)and to aqueous photolysis (MRID 43588004). Based on this persistence,

EFED expects that continued use of parent isoxaflutole will lead to accumulation of RPA 202248 in water resources.

For RPA 203328, another metabolite of isoxaflutole, surface water EEC's were calculated using an application rate of 0.15 lbs ai/A, and corrected by adjusting for the new maximum application rate of parent isoxaflutole (0.14 lbs ai/A). In the aerobic soil metabolism study, RPA 203328 was observed at 60 % of parent isoxaflutole on a mass basis. The registrant has not demonstrated that there are additional dissipation pathways for isoxaflutole dissipation in the environment. Therefore, EFED is assuming 100 % conversion from RPA 202248 to RPA 203328 in soil and water. For soil K_{oc}, the mean value of 69 ml/g was used (MRID 44291503). The quality of this data is uncertain, since the study has not been formally reviewed. For soil metabolism in the field, an aerobic soil metabolism value of 977 days was used. This value was the maximum registrant-calculated half-life in the aerobic soil metabolism study in MRID 43588006. The registrant has not shown that RPA 203328 degrades due to hydrolysis (MRID 43573254), aqueous photolysis (MRID 43588004), or aquatic metabolism. Therefore, no degradation rates were put into EXAMS. Based on this persistence, EFED expects that continued use of parent isoxaflutole will lead to accumulation of RPA 203328 in water resources. The water solubility of RPA 2003328 was reported to be 8,000 mg/l (Rhone Poulenc Fax).

There are certain limitations imposed when Tier II EEC's are used for drinking water exposure estimates. Obviously, a single 10 hectare field with a 1 hectare pond does not accurately reflect the dynamics in a watershed large enough to support a drinking water facility. A basin of this size would certainly not be planted completely to a single crop nor be completely treated with a pesticide. Additionally, treatment with the pesticide would likely occur over several days or weeks, rather than all on a single day. This would reduce the magnitude of the concentration peaks, but also make them broader, reducing the acute exposure but perhaps increasing the chronic exposure. The fact that the simulated pond has no outlet is also a limitation as water bodies in this size range would have at least some flow through (rivers) or turnover (reservoirs). In spite of these limitations, a Tier II EEC can provide a reasonable upper bound on the concentration found in drinking water if not an accurate assessment of the real concentration. The EECs have been calculated so that in any given year, there is a 10% probability that the maximum average concentration of that duration in that year will equal or exceed the EEC at the site. Risk assessment using Tier II values can capably be used as refined screens to demonstrate that the risk is below the level of concern.

A Tier II EEC uses a single site which represents a high exposure scenario for the use of the pesticide on a particular crop or non-crop use site. The weather and agricultural practices are simulated at the site over multiple (in all cases, 36) years so that the probability of an EEC occurring at that site can be estimated.

The SCI-GROW model (Screening Concentrations in Ground Water) is a model for estimating concentrations of pesticides in ground water under "worst case" conditions. SCI-GROW provides a screening concentration, an estimate of likely ground water concentrations if the pesticide is used at the maximum allowed label rate in areas with ground water exceptionally vulnerable to contamination. In most cases, a majority of the use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimate.

The SCI-GROW model is based on scaled ground water concentration from ground water monitoring studies, environmental fate properties (aerobic soil half-lives and organic carbon partitioning coefficients-Koc's) and application rates. The model is based on permeable soils that are vulnerable to leaching and on shallow ground water (10-30 feet).

Results from the SCI-GROW screening model predict that the maximum chronic concentration of parent isoxaflutole in shallow ground water is not expected to exceed ~~the~~ 2.5 x 10^{-4} ug/L for the proposed use on corn at 0.14 lbs ai/A. The concentrations of the metabolites RPA 202248 and RPA 203328 are estimated to reach 0.23 and 6.1 ug/L, respectively. These concentrations are expected to persist and accumulate, since there is no apparent means of degradation in the environment for these metabolites. This modeling of the metabolites using the proposed maximum labeled rate of 0.14 lb ai/acre/season assumed 100 % conversion to each of these sequentially-formed metabolites since they are both persistent, mobile, and are expected to persist and accumulate in water. SCI-GROW is a model that provides an upper bound of EEC's in shallow ground water.

c. Dietary Risk

i. Chronic (Non-cancer) Risk (TMRC, ARC)

A Dietary Risk Evaluation System (DRES) chronic exposure analysis was performed using a RfD of 0.002 mg/kg/day, tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC), and anticipated residues to estimate the Anticipated Residue Contribution (ARC) for the general population and 22 subgroups. Using tolerance level residues and assuming 100 percent crop treated, non-nursing infants (< 1 year old) is the subgroup that utilized the greatest percentage of the RfD at 81%. By refining the chronic dietary risk assessment assuming 34 percent of the corn crop treated and incorporating ARs for corn, animal RACs and processed commodities, less than 1 percent of the RfD is utilized for the general population and 1 percent of the RfD for nursing infants, the subgroup that accounts for the greatest percentage of the RfD.

The refined chronic dietary risk assessment is considered a reasonable estimate of risk since ARs and percent crop treated estimates were incorporated. Based on the risk estimates calculated in this analysis, the chronic (non-cancer) dietary risk from use of isoxaflutole on corn does not exceed HED's level of concern.

ii. Carcinogenic Risk (TMRC, ARC)

A prior analysis of the potential dietary cancer risk (See memo, B. Steinwand, 7/24/96) using tolerance level residues resulted in a cancer risk of 3 X 10^{-6} which exceeded HED's level of concern. Thus, ARs for isoxaflutole were requested and supplied by G. Kramer, 9/18/97. The aggregate (food and water) cancer risk exceeded HED's level of concern when a refined dietary risk assessment was conducted using the ARs. Therefore, more refined dietary risk assessments for cancer were conducted using ARs for isoxaflutole in corn and animal RACs and processed commodities including the metabolites RPA 207048 and RPA 205834 as well as information provided by Neil Anderson of the Biological and Economic Analysis Division (BEAD) stating that 34 percent crop treated information is appropriate. The results of these risk assessments are reported below.

As discussed in the Dose-Response section above the CPRC recommended that a non-linear (MOE) methodology be applied for the estimation of human cancer risk. The NOEL of 2 mg/kg/day in males from a 104 week combined chronic toxicity/carcinogenicity study in rats (MRID 43904806) is the endpoint to be used for the non-linear (MOE) cancer risk assessment. Cancer MOEs are estimated by dividing the carcinogenic NOEL by the chronic exposure. The assessment was conducted for the Total U.S. Population only.

Using this approach, the upper bound cancer risk was calculated as follows:

Exposure = ARC
= 0.000008 mg/kg/day

MOE = NOEL ÷ Exposure
= 2 mg/kg/day ÷ 0.000008 mg/kg/day = 250,000

This non-linear cancer risk assessment was done using the NOEL of 2 mg/kg/day from a 104 week combined chronic toxicity/carcinogenicity study in rats (MRID 43904806). The next dose tested, 20 mg/kg/day, was the LOEL for the study based on thyroid hyperplasia. A statistical significant increase of tumors was not seen until the next dose level of 500 mg/kg/day.

The CPRC also recommended that a linear low-dose extrapolation (Q_1^*) be applied for the tumors of the rat liver. It later was decided that there was no reason not to include the results from the 78-week feeding/carcinogenicity study in mice (MRID 3904807) when determining the Q_1^* to be used for risk assessment. The unit risk, Q_1^* $(mg/kg/day)^{-1}$ of isoxaflutole, based upon male mouse liver (adenomas and or carcinomas) tumors is 1.14×10^{-2} in human equivalents.

Using the linear approach and a Q_1^* of 0.0114 resulted in an upper bound cancer risk of 9.3×10^{-8}. This linear risk estimate, for use of isoxaflutole on corn is below HED's level of concern for life time cancer risk.

iii. Acute Dietary Risk (tiered assessment)

As discussed in the Dose-Response section of this document, an acute dietary endpoint of concern was identified for use in risk assessment for females 13+. The endpoint to be used in risk assessment is the LOEL of 5 mg/kg/day from the developmental toxicity study (MRID 43904808) in rabbits. An UF of 3x should be applied to account for the lack of a NOEL in the developmental rabbit study, 10x to account for increased sensitivity to fetuses following *in utero* exposure as well as 100 to account for inter- & intra-species variation. The appropriate MOE for acute dietary risk assessment is 3000.

An acute dietary endpoint was also identified for the general population including infants and children. The endpoint to be used in risk assessment is the NOEL of 125 mg/kg/day from the acute neurotoxicity study (MRID 43904804). An UF of 10x should be applied to account for enhanced sensitivity to infants and children as well as 100 to account for inter- & intra-species variation. The appropriate MOE for acute dietary risk assessment is 1000.

The Dietary Risk Evaluation System (DRES) detailed acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The

analysis evaluates individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of isoxaflutole in the commodity supply.

The MOE is a measure of how close the high end exposure comes to the NOEL (LOEL for females 13+) and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). For these acute dietary risk assessments, use of isoxaflutole on corn, anticipated residues were used since corn is a blended commodity. The high end MOE for the subgroup of Females, 13+ was 500, and is cause for concern given the need for a MOE of 3000. The high end MOEs for the general population, infants and children all exceed 3000, and demonstrate no acute dietary concern.

4. Occupational and Residential Exposure and Risk Characterization

Isoxaflutole is a new chemical, proposed for use on corn. Therefore, there are no residential uses associated with the use of this chemical at this time.

a. Occupational Exposure

Isoxaflutole is formulated as Balance WDG Herbicide (264-LAT), a water-dispersible granule containing 76.5% a.i. Balance is proposed for a single early preplant or preemergence broadcast application to field corn. The maximum use rate is 0.14 lbs. ai/A. Only one application may be made per season. Based on the proposed agricultural use and the recommendations of the HIARC, HED assessed short and intermediate term dermal exposure, short and intermediate term inhalation exposure and the potential cancer (linear) risk to workers resulting from exposure to isoxaflutole. HED did **not** assess chronic non-cancer and cancer (MOE approach) risk because no chronic exposure is expected to occur from the proposed agricultural use of isoxaflutole on corn.

The mechanism used for evaluating dermal and inhalation unit exposure was the Pesticide Handler Exposure Database (PHED), version 1.1. Based on label requirements, PHED estimated worker exposure under a long sleeve shirt, long pants, waterproof glove, shoes and socks protective clothing scenario. The label also mandates the use of protective eyewear, however PHED is unable to estimate the protection afforded by this item. Estimates of exposure and cancer risk have been made both for the farmer and the commercial mixer/loader or applicator. It is common practice for farmers to perform both the mixing/loading and application of a pesticide, thus exposure and risk have been estimated for those functions individually and combined. Commercial handlers do not usually perform both functions and so estimates have been made for mixing/loading and application separately.

Isoxaflutole is formulated as a water dispersible granule herbicide. PHED estimated mixer/loader (M/L) unit exposure using a water dispersible granule, open pour M/L scenario. The method of application is groundboom. The label does not specify the use of a closed mixing/loading system or a closed cab for the groundboom tractor, therefore open M/L and open cab scenarios were selected for analysis.

HED estimated that a farmer could treat 105 acres/day and a commercial applicator could treat 200 acres/day. These estimates were based on a program by Dr. Yuen-Shaun Ng,

of BEAD. The differences in acres treated/day by the farmer and commercial applicator are primarily due to swath width and tank capacity. Farm size was estimated as 249 acres based on the 1992 Ag Census for Monona County, Iowa. Iowa had the largest number of corn acres cropped in the United States and thus potentially the state most effected by isoxaflutole registration. Monona County was selected because of it's high typical farm size. This should not be judged as excessively conservative as there were other states (e.g. Nebraska) which had counties with larger average farm sizes than Monona County. Finally, BEAD has estimated that a commercial applicator would potentially treat 6 farms per year with isoxaflutole under the proposed use pattern (Keitt, George W Jr. BEAD, Personal Communication with Tracy Lynn Keigwin, October, 1997).

Tables 10, 11 and 12 summarize the use information and formulae which were used to estimate occupational exposure and risk.

Table 10. PHED Unit Exposure Estimates

Handler	Dermal Unit Exposure* (µg/lb ai handled)	Inhalation Unit Exposure (µg/lb ai handled)	Data quality
Mixer/Loader	63.3733	0.7686	Medium confidence dermal High confidence inhalation
Applicator	14.0180	0.7398	Medium confidence dermal High confidence inhalation
Mixer/Loader/ Applicator	77.3913	1.5084	Medium confidence dermal High confidence inhalation

(*Long Sleeve shirt, Long Pants, Glove clothing scenario)

Table 11. Occupational Exposure Assumptions

Parameter	Assumption
Percent Absorption	Dermal - 3.5% Inhalation - 100% (default value)
Endpoints	LOEL of 5 mg/kg/day to be used in short and intermediate term exposure estimates $Q^* = 1.14 \times 10^{-2}$ mg/kg/day
Application Type	Groundboom
Minimum Finish Spray (according to proposed label)	10 gallons/acre
Maximum Application Rate	0.2 lbs ai/acre
Farm Size (1992 Census of Agriculture)	249 acres, based on Monona county, Iowa
Acres Treated/Day (Y. NG, BEAD)	105 - farmer , 200 - PCO

Worker Weight	60 kg for short term and intermediate term exposure estimates 70 kg for cancer estimates
Number of farms treated by PCO per year	6

Table 12. FORMULAE

Average Daily Dose (ADD) = PHED Unit Exposure (µg/lb ai handled) x % absorption x application rate (lb ai/acre) x acres treated/day x 1 mg/1000 µg ÷ 60 kg body weight*

Combined ADD = Dermal ADD + Inhalation ADD

Lifetime Average Daily Dose (LADD) =
[PHED Unit Exposure (µg/lb ai handled) x % absorption x application rate (lb ai/acre) x acres treated/day x 1 mg/1000 µg ÷ 70 kg body weight*] x # of days to treat average field x number applications/year x # of farms treated by commercial handler ÷ 365 days/year x 35/70**

Short and Intermediate Term MOE = LOEL/ADD (where LOEL = 5 mg/kg/day)

Cancer Risk = Q* x LADD (where Q* = 1.14×10^{-2} mg/kg/day)

* A body weight of 60kg was assumed when estimating ADD due to developmental concerns. A body weight of 70 kg was assumed when estimating cancer risk.

** This is assuming that a grower or commercial applicator will be working with or exposed to a pesticide for 35 of a 70 year lifespan.

b. Occupational Risk

i. Risk from Dermal and Inhalation Exposures

As discussed previously in the Dose-Response section, residential and occupational risk assessments are required for short term (1 to 7 days) and intermediate term (1 week to several months) exposure to isoxaflutole. An endpoint of 5 mg/kg/day was identified for use in risk assessment for these exposure scenarios. A MOE of 3000 is required. Additionally, a cancer risk assessment using a linear low dose extrapolation with a Q* of 1.14×10^{-2} is required. Since the proposed use of isoxaflutole on corn is for one application per season, chronic exposure is not expected. Therefore, HED will **not** assess chronic non-cancer and cancer (non-linear) risk because no chronic exposure is expected to occur.

Tables 13 and 14 summarize the estimated short term, intermediate term and cancer risk associated with the use of isoxaflutole as a preplant or preemergent herbicide treatment to field corn.

Table 15 - Farmer Occupational Exposure and Risk Estimates

Function	Combined Dermal and Inhalation ADD mg/kg/day	Combined Dermal and Inhalation LADD mg/kg/day	Short and Intermediate Term MOE	Cancer Risk
Mixer/Loader	1.1×10^{-3}	3.1×10^{-6}	4500	3.5×10^{-8}
Applicator	4.3×10^{-4}	1.3×10^{-6}	12000	1.5×10^{-8}
Mixer/Loader/ applicator	1.5×10^{-3}	4.4×10^{-6}	3300	5.0×10^{-8}

Short and Intermediate Term MOE = LOEL/Combined Dermal and Inhalation ADD (where LOEL = 5 mg/kg/day)
Cancer Risk = Q* x Combined Dermal and Inhalation LADD (where Q* = 1.14×10^{-2} mg/kg/day)

Table 16 - Commercial Mixer/Loader or Applicator Occupational Exposure and Risk Estimates

Function	Combined Dermal and Inhalation ADD mg/kg/day	Combined Dermal and Inhalation LADD mg/kg/day	Short and Intermediate Term MOE	Cancer Risk
Mixer/Loader	2.0×10^{-3}	1.8×10^{-5}	2500	2.0×10^{-7}
Applicator	8.2×10^{-4}	7.2×10^{-6}	6100	8.2×10^{-8}

Short and Intermediate Term MOE = LOEL/Combined Dermal and Inhalation ADD (where LOEL = 5 mg/kg/day)
Cancer Risk = Q* x Combined Dermal and Inhalation LADD (where Q* = 1.14×10^{-2} mg/kg/day)

The only short-term and intermediate-term exposure scenario with an unacceptable MOE is the commercial mixer/loader. Exposure can be reduced to acceptable levels with the addition of a chemical resistant apron when mixing/loading and cleaning equipment. It should be noted that "acceptable" is strictly for this use scenario only. Should the registrant propose other methods of application (e.g. - aerial application) projected exposures and risk will need to be reassessed.

HED also assessed the potential cancer (linear) risk to workers resulting from exposure to isoxaflutole. Cancer risk for workers ranged from 2.0×10^{-7} to 8.2×10^{-8}. These risk estimates, all greater than 1×10^{-6}, do not exceed HED's level of concern and are considered protective of adult workers.

ii. Risk From Post-Application Exposures

With the present labeled use pattern, a great degree of post application exposure is not expected from isoxaflutole since this is a preplant/preemergent treatment and worker contact should be minimal.

iii. Restricted Entry Interval (REI)

A 12 hour REI based on the toxicity categories III and IV appears acceptable. Early reentry PPE should be coveralls, waterproof gloves, shoes, socks and protective eyewear. It

should be noted that isoxaflutole is not a candidate for the reduced 4 hour REI due to its carcinogenic concerns.

5. Aggregate Risk

FQPA requires that "aggregate exposure levels of consumers to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources" be considered. For the proposed use, of isoxaflutole on corn, HED only anticipates aggregate exposure from dietary - food and water sources since there are no residential uses.

a. Acute Aggregate Exposure and Risk

HED did not calculate drinking water levels of concern (DWLOC) for acute exposures to isoxaflutole in surface and ground water for females 13+ since the acute dietary risk from food sources alone exceeds HED's level of concern. To calculate the DWLOC for acute exposures for the general population and children (1-6 years) relative to an acute toxicity endpoint, the acute dietary food exposure (from the DRES analysis) was subtracted from the ratio of the acute NOEL of 125 mg/kg/day (used for dietary assessments) to the MOE of 1000 to obtain the acceptable acute exposure to isoxaflutole in drinking water. DWLOCs were then calculated from this acceptable exposure using default body weights (70 kg for general population & 10 kg for children) and drinking water consumption figures (2 liters general population & 1 liter for children). Based on this calculation HED's DWLOC for acute dietary risk is 4025 ppb for the general population and 366 ppb for children.

For acute dietary risk estimated maximum concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 were used. In surface water isoxaflutole and its metabolites RPA 202248 and RPA 203328 are estimated to be 0.4 ppb, 2.0 ppb, and 10.0 ppb, respectively. Estimated maximum concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in ground water are 0.00025 ppb, 0.23 ppb and 6.1 ppb, respectively.

The maximum estimated concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface and ground water were less than HED's levels of concern for acute exposure in drinking water for the general population and children. Therefore, HED concludes with reasonable certainty that residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in drinking water do not contribute significantly to the aggregate acute human health risk for the general population and children at the present time considering the present uses and uses proposed in this action for registration. HED does have concern for the aggregate acute human health risk for females 13+ since the acute risk from food sources alone exceeds HED's level of concern.

b. Short-term & Intermediate-term Aggregate Risk

Since there are no residential exposures expected with this proposed use, short and intermediate aggregate risk assessments will not be conducted.

c. Chronic Aggregate Exposure Risk

HED has calculated DWLOC for chronic (non-cancer) exposures to isoxaflutole in surface and ground water. To calculate the DWLOC for chronic exposures relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD (0.002 mg/kg/day) to obtain the acceptable chronic (non-cancer) exposure to isoxaflutole in drinking water. DWLOCs were then calculated from this acceptable exposure using default body weights (70 kg for males, 60 kg for females & 10 kg for children) and drinking water consumption figures (2 liters males & females & 1 liter children). Based on this calculation HED's DWLOC for chronic (non-cancer) risk is 70 ppb for males, 60 ppb for females and 19 ppb for children.

Estimated annual average concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface are 0.01 ppb, 1.7 ppb and 9.3 ppb, respectively. Estimated annual average concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in ground water are 0.00025 ppb, 0.23 ppb and 6.1 ppb, respectively. [Note: For the purposes of the screening level assessment, the maximum and average annual concentrations in ground water are not believed to vary significantly.]

The estimated annual average concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface and ground water were less than HED's levels of concern for chronic (non-cancer) exposure in drinking water. Therefore, HED concludes with reasonable certainty that residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in drinking water do not contribute significantly to the aggregate chronic (non-cancer) human health risk at the present time considering the present uses and uses proposed in this action for registration.

d. Carcinogenic Aggregate Risk

A non-linear cancer aggregate risk assessment has not been conducted since the point of departure for non-linear cancer risk assessment (2 mg/kg/day) is the same endpoint as the RfD and the aggregate cancer linear risk assessment using the Q* is considered more restrictive unless a MOE of greater than 20,000 is warranted. HED has calculated DWLOC for chronic (cancer, linear) exposures to isoxaflutole in surface and ground water. To calculate the DWLOC for chronic exposures relative to a carcinogenic toxicity endpoint, the chronic (cancer) dietary food exposure (from the DRES analysis) was subtracted from the ratio of the negligible cancer risk (1×10^{-6}) to the recommended that a linear low-dose extrapolation (Q_1^*, 1.14×10^{-2}) to obtain the acceptable chronic (cancer) exposure to isoxaflutole in drinking water. DWLOCs were then calculated from this acceptable exposure using default body weights (70 kg) and drinking water consumption figures (2 liters). Based on this calculation HED's DWLOC for carcinogenic risk is 3.1 ppb.

Estimated annual mean concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in surface water are 0.01 ppb, 1.7 ppb and 9.3 ppb, respectively. Estimated annual average concentrations of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in ground water are 0.00025 ppb, 0.23 ppb and 6.1 ppb, respectively.

The estimated concentrations of isoxaflutole and its metabolite RPA 202248 in ground and surface water were less than HED's levels of concern. However, the estimated concentrations of metabolite RPA 203328 in surface water (9.3 ppb) and in ground water (6.1 ppb) were greater than HED's levels of concern for chronic (cancer, linear) exposure in drinking water. Therefore, HED concludes that residues of metabolites RPA 203328 in surface water and ground water used as drinking water may contribute significantly to the aggregate human health risk at the present time considering the proposed corn use.

HED bases this determination on a comparison of estimated concentrations of metabolite RPA 203328 in surface waters and ground waters to levels of concern in drinking water. Although the estimates of RPA 203328 are derived from water quality models that use conservative assumptions regarding the pesticide transformation and transport from the point of application to surface and ground water, HED believes the potential exposure and risk associated with isoxaflutole's use cannot be dismissed for the following reasons:

- RPA 203328 is expected to reach both ground and surface water, where it is expected to persist. Based on this persistence, EFED expects that continued use of parent isoxaflutole will lead to accumulation of RPA 203328 in water resources. The water solubility of RPA 203328 was reported to be 8,000 mg/l (Rhone Poulenc Fax).

- If residues of isoxaflutole reach water resources, they will be primarily associated with the aqueous phase with minimal adsorption to sediment because of their low adsorption coefficients. Standard coagulation-flocculation and sedimentation processes used in water treatment are not expected to be effective in removing isoxaflutole residues, based on their adsorption coefficients. The use of GAC (Granular Activated Carbon) is also not expected to be effective in removing isoxaflutole residues because of low binding affinity to organic carbon.

- The HED Metabolism Committee determined that there was no conclusive evidence to suggest that metabolite 203328 is any less toxic than the parent and is consider toxicology equivalent to the parent.

- Corn, the proposed use, is grown in large geographical area in the United States so exposure to water could be wide spread.

Because there are no available, appropriate, and reliable monitoring data to use in a more-refined quantitative exposure and risk assessment, and because HED has concerns regarding the impacts of metabolite RPA 203328 on drinking water, mitigation measures and monitoring requirements should be imposed as a condition of registration.

Since HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of isoxaflutole on drinking water as a part of the aggregate risk assessment process.

6. Other Food Quality Protection Act Considerations

a. Cumulative Risk

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity". The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

HED does not have, at this time, available data to determine whether isoxafluotle has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, HED has not assumed that isoxaflutole has a common mechanism of toxicity with other substances.

b. Endocrine disruption

The Agency is required to develop a screening program to determine whether certain substances (including all pesticides and inerts)"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disruptor effects.

7. Data requirements - all disciplines

- A developmental neurotoxicity study in rats is required based on the evidence of neurotoxicity as well as the lack of assessment of susceptibility of the offspring in functional/neurological development in the standard developmental/reproduction toxicity studies.

- Field accumulation studies in rotational crops are required to determine the appropriate plantback intervals and/or the need for rotational crop tolerances. These studies should be performed in accordance with OPPTS Test Guidelines 860.1900.

- Revised version of the analytical enforcement method for plants.

- Revised version of the analytical enforcement method for animals.

- Revised Section F.

- Because there are no available, appropriate, and reliable monitoring data to use in a more-refined quantitative exposure and risk assessment, and because HED has serious concerns regarding the impacts of metabolite RPA 203328 on drinking water, the following mitigation measures and monitoring requirements should be imposed as a condition of registration. RD, HED and EFED should meet to discuss these requirements.

8. Labeling Requirements

- Until limited field trial data are submitted, reviewed and found acceptable, crop rotation restrictions are required. The end-use product label should contain a statement limiting the planting of rotational crops to 6 months after application.

References

Anderson, N. 1997. Evaluation of Public Interest Documentation for the Conditional Registration of Isoxaflutole Herbicide on Corn. Memo to Dan Kenny/Don Stubbs. December 31, 1997.

Breithaupt, J. 1997. Drinking Water Assessment for Isoxaflutole. Memo to Barbara Madden. November, 1997.

Breithaupt, J. 1997. 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. Memo to Joanne Miller, PM 23. May 2, 1997.

Diwan, S. and E.Rinde. 1997. Carcinogenicity Peer Review of Isoxaflutole. Memo to Joanne Miller/Daniel Kenny. August 6, 1997.

Diwan, S. 1997. TOXICOLOGY ENDPOINT SELECTION DOCUMENT, Chemical Name: ISOXAFLUTOLE (RPA 201772), PC Code:123000. June 18, 1997.

Diwan, S. 1997. **RPA 201772** ***(ISOXAFLUTOLE)*** **Herbicide:** Review of Toxicity Studies Submitted to Support Registration and Permanent Tolerance Petition. Memo to Joanne Miller/Daniel Kenny Product Manager (23). June 11, 1997.

Errico, P.V. 1995. 264-EUP-00/PP#5G4484. Proposed Temporary Tolerance Request For Isoxaflutole in/on Field Corn Grain. Evaluation of Analytical Method and Residue Data. D214199 & D214212. CBTS#'s 15430 & 15431. Memo to Daniel Kenny/Joanne Miller, PM 23. December 7, 1995.

Ghali, G.Z. 1997. RfD/Peer Review Report of Isoxaflutole [4-(2-methylsulphonyl-4-trifluotopmethyl-benzoyl)-5-cyclopropyl isoxazole]. Memo to Philip Errico. July, 16, 1997.

Johnson, S. 1997. OPP's Interim Approach for Addressing Drinking Water Exposure. Memo to OPP Division Directors. November 17, 1997.

Keigwin, T.L. 1997. **Revised** Occupational Exposure Assessment for the Use of Isoxaflutole (Balance) on Corn. Memo to Barbara Madden. January 27, 1997 (actual date should be 1998).

Keigwin, T.L. 1997. **Correction** to Occupational Exposure Assessment for the Use of Isoxaflutole (Balance) on Corn. Memo to Barbara Madden. November 25, 1997

Keigwin, T.L. 1997. Occupational Exposure Assessment for the Use of Isoxaflutole (Balance) on Corn. Memo to Barbara Madden. October 21, 1997.

Kramer, G.F. 1997. HED Metabolism Assessment Review Committee Meeting of 9/4/97. **Isoxaflutole**. PP#6F04664. Chemical 123000. Barcode D238728. Memo to HED Metabolism Committee Members. September 25, 1997.

Kramer, G.F. PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. **Request for Revised Anticipated Residues.** Barcode D238727. Chemical 123000. Case 287353. Memo to Barbara Madden. September 18, 1997.

Kramer, G.F. 1997. PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. **Request for Anticipated Residues.** Barcode D237699. Chemical 123000. Case 287353. Memo to Barbara Madden. August 20, 1997.

Kramer, G.F. 1997. Isoxaflutole. Issues to be Presented to the HED Metabolism Assessment Review Committee 7/29/97. Memo to HED Metabolism Committee Members. August 15, 1997.

Kramer, G.F. PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. Amendment of 12/2/96. Revised Sections B & F, New Analytical Method for Animal Tissues and Storage Stability Data. MRID#s 441690-01 thru -07. Barcode D232139. Chemical 123000. Case 287353. Memo to Barbara Madden. July 14,1997.

Kramer, G.F. 1996 PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. **Results of Petition Method Validation (PMV) Pre-Review**. MRID#s 439048-32 and -33. Chemical 123000. Barcode D230247. Memo to C. Eiden/D. McCall. October 4, 1996.

Kramer, G.F. 1996. PP#6F04664. Isoxaflutole in/on Field Corn. **Results of Petition Method Validation (PMV)**. MRID# 435732-51. Barcode D228481. Chemical No 123000. CBTS# 17413. Memo to C. Eiden/D. McCall. August 20, 1996.

Kramer, G.F. 1996. PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. **Evaluation of Residue Data and Analytical Methods**. MRID#s 439048-01, -02, -27 thru -37 and -39. Chemical 123000. Barcode D224213. CBTS# 17015. Case 287353. Memo to C. Eiden/D. McCall. August 14, 1996.

Law, M.W. 1997. PP# 6F04664. Tolerance Method Validation of Isoxaflutole in/on Field Corn and Animal RACs. Memo to E.Zager, Chief. November 4, 1997.

Madden, B.A. 1997. Meeting to Discuss Issues Regarding Cancer Peer Review Document for the New Chemical Isoxaflutole (123000). Memo to Daniel Kenny. September 30, 1997.

Pettigrew, H.M. 1997. Isoxaflutole, Quantitative Risk Assessment Based on CD-1 Mouse and CD(SD)BR VAF Plus Rat Dietary Studies. Memo to Sanjivani B. Diawn. October 6, 1997.

Rowland, J. 1997. ISOXAFLUTOLE-REASSESSMENT OF THE FQPA REQUIREMENT - Report of the Hazard Identification Assessment Review Committee. Memo to Barbara Madden. December 22, 1997

Steinwand, B. 1998. Dietary Exposure Analysis for Isoxaflutole (PC Code 123000) Using Revised Toxic End Points and Percent Crop Treated Data. January 21, 1998.

Steinwand, B. 1997. Dietary Exposure Analysis for Isoxaflutole on Field Corn, PP#6F04664. Memo to Karen Whitby, Chief. November 19, 1997.