



Pesticide Fact Sheet

Name of Chemical: Isoxaflutole
Reason for Issuance: Conditional Registration
Date Issued: September 15, 1998

1. Description of Chemical

Generic Name: 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl) isoxazole

Common Name: Isoxaflutole

Trade Name: Balance Herbicide

EPA Shaughnessy Code: 123000

Chemical Abstracts
Service (CAS) Number: 141112-29-0

Year of Initial
Registration: 1998

Pesticide Type: Herbicide

Chemical Family: Isoxazole

U.S. Producer: Rhone-Poulenc Ag Company

2. Use Patterns and Formulations

Application Sites: Isoxaflutole is registered for use on field corn.

Types of Formulations: 98% technical product
75% water dispersible granule end-use product

Types and Methods
of Application: Ground application using standard commercial sprayers.

Application Rates: Application rates 1 to 3 ounces of formulated product (0.046875 to 0.140625 pounds active ingredient) per acre. One application is allowed per season.

Carrier: Water and/or liquid fertilizer

3. Science Findings

Summary Science Statements

Based upon a battery of acute toxicity studies, Balance Herbicide is classified as Toxicity Category III. Isoxaflutole demonstrates developmental toxicity and has been classified as a Group B2 carcinogen (probable human carcinogen). The data available at this time indicate that isoxaflutole is very phytotoxic. Isoxaflutole is persistent and mobile, and may leach and accumulate in groundwater and through surface water.

Chemical Characteristics

| PROPERTY | TECHNICAL | END-USE |
|-------------------------------------|--|----------------|
| Physical State | Granular powder | Granular solid |
| Color | Yellow | Tan |
| Odor | Slight acetic acid-like odor | None |
| Melting Point | 135 to 136°C ($\pm 1^\circ\text{C}$) | N/A |
| Density | 1.416 g/mL @ 20°C | 43 lb./cu. ft. |
| Solubility (Water) | 6.2×10^{-4} mg/100L @ pH 5.5 | N/A |
| Vapor Pressure | 1.0×10^{-6} Pa @ 25°C | N/A |
| Octanol/Water Partition Coefficient | Log P = 2.34 @ 20°C | N/A |
| pH | 4.6 @ 25°C | 4.6 @ 25°C |

Toxicology CharacteristicsAcute Toxicity (Isoxaflutole Technical)

- Acute Oral Toxicity in Rats - $\text{LD}_{50} > 5000$ mg/kg in males and females; Toxicity Category IV
- Acute Dermal Toxicity in Rats - $\text{LD}_{50} > 2000$ mg/kg in males and females; Toxicity Category III
- Acute Inhalation Toxicity in Rats - $\text{LC}_{50} > 5.23$ mg/L in males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Non-irritating; Toxicity Category III
- Primary Dermal Irritation in Rabbits - Non-irritating; Toxicity Category IV
- Primary Dermal Sensitization in Guinea-Pigs - Did not exhibit any sensitization potential.

Acute Toxicity (Balance Herbicide)

- Acute Oral Toxicity in Rats - $\text{LD}_{50} = 5000$ mg/kg in males and females; Toxicity Category IV

- Acute Dermal Toxicity in Rats - LD₅₀ > 2000 mg/kg in males and females; Toxicity Category III
- Acute Inhalation Toxicity in Rats - LC₅₀ = 5.26 mg/l for males and females; Toxicity Category IV
- Primary Eye Irritation in Rabbits - Mild irritation cleared in 72 hours; Toxicity Category III
- Primary Dermal Irritation in Rabbits - Very slight irritation cleared in 7 days; Toxicity Category IV
- Primary Dermal Sensitization in Guinea-Pigs - Did not exhibit any sensitization potential.

Subchronic Toxicity

- In a 21-day dermal toxicity study in rats, 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 (LOAEL) 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 LOAEL 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, RPA 203328 (a metabolite of isoxaflutole) was administered in the diet to male and female rats. There were no compound related adverse effects on survival, clinical signs, body weight, food consumption, clinical chemistry, hematology, and gross or microscopic pathology. The LOAEL is greater than 1,117.79 mg/kg/day in males and 1,268.73 mg/kg/day in females. The NOEL for both sexes is 1,117.79 mg/kg/day in males and 1,268.73 mg/kg/day in females.

Chronic Toxicity/Carcinogenicity

- In a chronic toxicity study with dogs, a LOAEL was established 453 mg/kg/day for males and 498 mg/kg/day for females, 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 and 45.33 mg/kg/day for females.
- In a combined chronic toxicity/carcinogenicity study in rats, evidence of systemic toxicity was observed at 500 mg/kg/day and 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 LOAEL 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 and hepatocellular carcinomas. Combined incidences of liver adenoma/carcinoma in males and females showed animals bearing carcinomas in the majority. Thyroid follicular adenomas occurred with increased frequency in 500 mg/kg/day males. The tumor incidences exceeded the historical incidence of these tumors for this strain in the 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 measured in this study. However, in a separate special study investigating the mechanism of action of isoxaflutole on the thyroid, 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, 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 52% of the males and 29% of the females, and carcinomas in 33% of the males and 8% of the females (non-significant). The incidences of these tumors exceeded the corresponding historical incidence with this species in the 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 LOAEL 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.

Developmental Toxicity

- In a developmental toxicity study in rats, maternal toxicity was observed at 500 mg/kg/day, manifested as an increased incidence of salivation, decreased body weight, weight gain, and food consumption during the dosing period. The maternal LOAEL 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 sternbrae, 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 LOAEL 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 in rabbits, maternal toxicity was observed at 100 mg/kg/day, 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 LOAEL 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 LOAEL 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.

Reproductive Toxicity

- In a 2-generation reproduction study in rats, 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 pre-mating and gestation, and increased incidence of subacute inflammation of the cornea of the eye in F₀ adults as well as keratitis in F₁ 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 F₁ and F₂ offspring: at 20 and 500 mg/kg/day, reduction in pup survival was noted; at 500 mg/kg/day, decrease in body weights of F₁ and F₂ pups throughout lactation, increased incidence of chronic keratitis, low incidence of inflammation of the iris, as well as retinal and vitreous bleeding in F₂ pups and weanlings were observed. Necropsy of F₁ and F₂ pups culled on Day 4 revealed an increased number of pups with no milk in the stomach and underdeveloped renal papillae. The Systemic LOAEL 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 LOAEL 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.

Mutagenicity

- For parent isoxaflutole, in a *Salmonella typhimurium* reverse gene mutation assay, independently performed tests were negative in *S. typhimurium* strains up to insoluble doses ($\geq 500 \mu\text{g}/\text{plate}$ +/- S9) and was non-cytotoxic. In a mouse lymphoma L5178Y forward gene mutation assay, independently performed tests were negative up to insoluble ($\geq 150 \mu\text{g}/\text{mL}$ +/-S9) or soluble ($\leq 75 \mu\text{g}/\text{mL}$ +/-S9) doses. An in vitro cytogenetic assay in cultured human lymphocytes tested negative up to insoluble concentrations ($\geq 300 \mu\text{g}/\text{mL}$ -S9; $600 \mu\text{g}/\text{mL}$ +S9) and was non-cytotoxic. A mouse micronucleus assay tested 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.

- For the major metabolite RPA 202248, in a *Salmonella typhimurium* reverse gene mutation assay, independently performed plate incorporation or preincubation modification to the standard plate incorporation tests were negative in *S. typhimurium* strains up to the highest dose assayed (5000 µg/plate +/- S9).

- For the minor metabolite RPA 203328, in a *Salmonella typhimurium* reverse gene mutation assay, independently performed plate incorporation tests were negative in *S. typhimurium* strains up to cytotoxic doses (≥ 2500 µg/plate +/- S9). In an in vivo mouse micronucleus assay, there was no indication of a clastogenic and/or aneugenic effect associated with administration of RPA 203328. In a CHO/HGPRT forward mutation assay with duplicate cultures and a confirmatory assay, there was no indication of cytotoxicity \pm S9 at the highest dose level of 2700 µg/mL. Overall, there was no evidence of any increase in mutation frequency resulting from exposure to RPA 203328. In an in vitro cytogenetics assay in cultured Chinese hamster ovary cells (CHO), no effect on mitotic indices was observed at the highest dose level. The positive controls induced the expected high yield of cells with chromosome aberrations. There was, however, no evidence that RPA 203328 induced a clastogenic response at any dose or harvest time.

Metabolism

- In a metabolism study, ^{14}C -isoxaflutole was rapidly and extensively absorbed and metabolized. RPA 202248, a major metabolite, a diketone nitrile derivative, represented 70% or more of the radioactivity excreted in the urine and feces from the two lowest dose groups. The other minor metabolite, RPA 203328, was more polar. Elimination was rapid and dose-dependent. The mean total recovery was 99.21%. Urinary elimination was predominant in the two low dose groups while the major portion of radiolabel was excreted via the feces 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 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.

Neurotoxicity

- In an acute neurotoxicity study in rats, 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 functional observational battery (FOB) tests indicating impairment of neuromuscular function. At 500 mg/kg, males exhibited significant decreases in landing foot splay measurements on day 15. The LOAEL 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 in rats, treatment-related effects observed in high-dose males consisted of decreases in body weight and body weight gain. The LOAEL 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.

Exposures and Risks

Dietary exposure was calculated by using an Anticipated Residue Concentration (ARC) and by assuming 34% field corn crops treated. The resulting margins of exposure (MOE) and drinking water levels of concern (DWLOC) for the general population and most vulnerable subgroup(s) are summarized below:

| ACUTE RISK | | | | |
|----------------------------------|----------------|------------------------|-------------|----------|
| SUB-POPULATION | ACCEPTABLE MOE | ESTIMATED MOE | DWLOC (ppb) | |
| U.S. Population | 1,000 | 125,000 | 4,200 | |
| Females (13+ years) | 3,000 | 10,000 | 36 | |
| Children (1-6 years) | 1,000 | 125,000 | 1,200 | |
| CHRONIC (NON-CANCER) RISK | | | | |
| SUB-POPULATION | % RfD UTILIZED | DWLOC (ppb) | | |
| U.S. Population | 1% | MALES | FEMALES | CHILDREN |
| Non-Nursing Infants | <1% | 70 | 60 | 19 |
| CARCINOGENIC RISK | | | | |
| ACCEPTABLE CANCER RISK | | ESTIMATED CANCER RISK | | |
| 1 X 10 ⁻⁶ | | 9.8 X 10 ⁻⁸ | | |

Environmental Characteristics

| PARENT ISOXAFLUTOLE | |
|-------------------------------|--|
| STUDY TYPE | HALF LIFE/OTHER |
| Hydrolysis | 11.1 hours at pH 5; 20.1 hours at pH 7; 3.2 hours at pH 9 |
| Photolysis in Water | 6.7 days |
| Photolysis on Soil | 23 hours |
| Aerobic Soil Metabolism | 2.4 days |
| Anaerobic Aquatic Metabolism | Less than 2 hours |
| Mobility-Unaged Leaching | Very mobile in sand and sandy loam soils; Moderately mobile in sandy loam soil; Essentially immobile in silty clay soil and loam sediment |
| Mobility-Aged Leaching | Generally not found below 6 cm of soil depth |
| Terrestrial Field Dissipation | 1.4 to 3.0 days |

| PRIMARY METABOLITE RPA 202248 | |
|--------------------------------------|-------------------------|
| STUDY TYPE | HALF LIFE/OTHER |
| Hydrolysis | Stable at pH 7 |
| Photolysis in Water | Stable |
| Aerobic Soil Metabolism | 61 days |
| Mobility | Potentially very mobile |

| TERMINAL METABOLITE RPA 203328 | |
|---------------------------------------|-------------------------|
| STUDY TYPE | HALF LIFE/OTHER |
| Hydrolysis | Stable at pH 7 |
| Photolysis in Water | Stable |
| Aerobic Soil Metabolism | 977 days |
| Mobility | Potentially very mobile |

Mechanism of Pesticidal Action

Isoxaflutole is a pigment inhibitor. It works by preventing the biosynthesis of carotenoid pigments, which protect chlorophyll from decomposition by sunlight. Without carotenoid pigments, chlorophyll pigments are photo-oxidized and chloroplasts break down. Without the energy-collecting action of the chlorophyll, the whole plant eventually dies.

Potential to Contaminate Groundwater

Isoxaflutole is mobile and is expected to persist and accumulate in surface water and groundwater.

Modeling data show that parent isoxaflutole and its primary metabolite RPA 202248 may accumulate to concentrations that would result in harm to non-target plants. Isoxaflutole's terminal metabolite RPA 203328 is expected to persist and accumulate, but does not demonstrate phytotoxicity. Additional studies, including prospective groundwater studies and surface water monitoring, will be conducted to determine whether isoxaflutole and its primary metabolite RPA 202248 do or do not exceed concentrations deemed potentially harmful to the environment.

Ecological Characteristics

Terrestrial

Isoxaflutole is practically non-toxic to the mallard duck and the bobwhite quail on an acute basis ($LD_{50} > 2,150$ mg/kg) and slightly toxic to the mallard duck and the bobwhite quail on a sub-acute basis (5-day $LD_{50} > 4,255$ ppm). It is practically non-toxic to rats ($LD_{50} > 5,000$ mg/kg) and honey bees ($LD_{50} > 100$ μ g/bee).

Aquatic - Freshwater

Isoxaflutole is moderately toxic to the rainbow trout (96-hour $LC_{50} > 1.7$ ppm) and to the bluegill sunfish (96-hour $LC_{50} > 4.5$ ppm). It is also moderately toxic to *Daphnia magna* (48-hour $EC_{50} > 1.5$ ppm).

Aquatic - Estuarine/Marine

Isoxaflutole is highly toxic to the mysid shrimp (96-hour $LC_{50}/EC_{50} = 0.018$ ppm) and moderately toxic to the eastern oyster (96-hour $LC_{50}/EC_{50} = 3.3$ ppm). It is moderately toxic to the sheepshead minnow (96-hour $LC_{50} > 6.4$ ppm)

Plants

Isoxaflutole is highly toxic terrestrial plants ($EC_{25} = 1 \times 10^{-5}$ pounds active ingredient./Acre). Due to the low vapor pressure of this herbicide, and due to the fact that it is only to be applied using ground equipment, risk to nontarget plant species is not expected from the parent compound. The primary metabolite RPA 202248, however, is mobile and is expected to move off-site. Additional studies, including prospective groundwater studies and surface water monitoring, will be conducted to determine whether isoxaflutole and its primary metabolite RPA 202248 do or do not exceed concentrations deemed potentially harmful to the environment.

4. Summary of Regulatory Position and Rationale

Available data provide adequate information to support the conditional, time-limited, geographically-limited registrations of Technical Isoxaflutole and Balance Herbicide for use on field corn. The registrations will expire November 1, 2001. The registrations are limited to the states of Arkansas, Indiana, Illinois, Iowa, Kansas, Kentucky, Missouri, Montana, Nebraska, North Dakota, South Dakota, Tennessee, Ohio, Oklahoma, Texas (north of I-20), and Wyoming.

Use, Formulation, Manufacturing Process or Geographic Restrictions:

Restricted Use

May injure (phytotoxic) susceptible non-target plants. For retail to and use only be certified applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification. Commercial and certified applicators must ensure that all persons involved in these activities are informed of the precautionary statements.

Geographic Restrictions

For use in the states of: Arkansas, Indiana, Illinois, Iowa, Kansas, Kentucky, Missouri, Montana, Nebraska, North Dakota, South Dakota, Tennessee, Ohio, Oklahoma, Texas (north of I-20), and Wyoming.

Environmental Hazards

Drift or runoff may adversely affect non-target plants. Drift and runoff may be hazardous to aquatic organisms in neighboring areas. Keep out of lakes, ponds or streams. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwaters or rinsate.

Do not apply when weather conditions favor drift from treated areas. Do not use the same spray equipment for other purposes unless thoroughly cleaned. Do not contaminate water used for irrigation or domestic purposes.

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

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

In fields having sands, loamy sands and sandy loam soils, special care should be taken not to over-irrigate since substantial over-irrigation promotes the leaching of chemicals.

This pesticide is toxic to some plants at very low concentrations. Non-target plants may be adversely affected if the pesticide is allowed to drift from areas of application. Exposure to isoxaflutole residues may injure or kill susceptible plants. To prevent damage to crops and other desirable plants, read and follow all directions and precautions on this label before using.

This product may not be mixed or loaded within 50 feet of any wells (including abandoned wells and drainage wells), sink holes, perennial or intermittent streams and rivers, and natural or impounded lakes and reservoirs. This setback does not apply to properly capped or plugged abandoned wells and does not apply to impervious pad or properly diked mixing/loading areas.

Operations that involve mixing, loading, rinsing or washing of this product into or from pesticide handling or application equipment or containers within 50 feet of any well are prohibited unless conducted on an impervious pad constructed to withstand the weight of the

heaviest load that may be positioned on or moved across the pad. Such a pad shall be designed and maintained to contain any product spills or equipment leaks, container or equipment rinse or washwater and rainwater that may fall on the pad. Surface water shall not be allowed to either flow over or from the pad, which means the pad must be self-contained. The pad shall be sloped to facilitate material removal. An unroofed pad shall be of sufficient capacity to contain at a minimum 110% of the capacity of the largest pesticide container or application equipment on the pad. A pad that is covered by a roof of sufficient size to

exclude completely precipitation from contact shall be of sufficient capacity to contain at a minimum 100% of the capacity of the largest pesticide container or application equipment on the pad. Containment capacities as described above shall be maintained at all times. The above specific minimum containment capacities do not apply to vehicles when delivering pesticide shipments to the mixing/loading site. States may have in effect additional requirements regarding wellhead setbacks and operational containment.

Product shall be used in a manner which will prevent back siphoning in wells, spills or improper disposal of excess pesticide, spray mixtures or rinsate.

Use Directions

Do not apply this product using aerial application equipment.

Do not apply this product through any type of irrigation system.

Do not use flood irrigation to apply or incorporate this product.

Do not apply more than 3 ounces of product per acre in one season.

Do not rotate to other crops within 6 months after application.

In the states of Kansas, Kentucky, Missouri, and Tennessee, if the water table (i.e., level of saturation) is less than 25 feet below the ground surface, do not use on loamy sand or sand surface soils and subsoils with an average organic matter (in the upper 12 inches) of less than 2% by weight.

In the states of Iowa, Illinois, Indiana, Montana, North Dakota, Nebraska, Ohio, South Dakota, and Wyoming, if the water table (i.e., level of saturation) is less than 25 feet below the ground surface, do not use on sandy loam, loamy sand or sand surface soils and subsoils with an average organic matter (in the upper 12 inches) of less than 2% by weight.

5. Summary of Data Gaps

Toxicology Data:

- Developmental Neurotoxicity Study in Rats

Environmental Fate Data:

- Prospective Groundwater Studies
- Surface Water Monitoring

Ecological Effects Data:

- Avian Reproduction Study with Major Metabolite
- Acute Toxicity Study to Shrimp with Major Metabolite
- Acute Toxicity Study to Estuarine Fish with Major Metabolite

6. Contact Person at EPA

Joanne I. Miller
Product Manager 23
Herbicide Branch
Registration Division (7505C)
Office of Pesticide Programs
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Office Location and Telephone Number

Room 237, Crystal Mall Building #2
1921 Jefferson Davis Highway
Arlington, VA 22202
(703) 305-7830

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