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8

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 17-JULY-2003

SUBJECT: PP#: PP 0F6166. **Imazapyr in/on Rangeland and Aquatic Sites. Health Effects Division (HED) Risk Assessment.** PC Code: 128821. DP Barcode: D291393. Case Nos: 293089. Submissions: S598694.

FROM: Dana Vogel, Chemist
Registration Action Branch 1 (RAB1)/HED (7509C)

THRU: Karen Whitby, Chief
RAB1/HED (7509C) 7/17/03

TO: Donald Stubbs/Jim Tompkins, PM Team 25
Herbicides Branch (HB)/Registration Division (RD) (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of imazapyr on rangeland and aquatic sites.

A summary of the findings and an assessment of human risk resulting from the registered and proposed tolerances for imazapyr is provided in this document. The risk assessment was provided by Dana Vogel (RAB1), the residue chemistry data review, and the dietary exposure and risk assessment were provided by William Donovan (RRB3), the hazard characterization by Karen Whitby (RAB1), the occupational/residential exposure assessment by Troy Swackhammer (RAB1), and the drinking water assessment by Alex Clem of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration
Provided revised Sections B and F are submitted and that successful Agency validation of the analytical method is reported, the toxicological and residue chemistry databases, as well as the aggregate risk assessments, support conditional registration of the requested new uses and establishment of the following permanent tolerances for residues of imazapyr *per se*:

Grass, forage ..... 100 ppm
Grass, hay ..... 30 ppm

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Grass, forage . . . . . 100 ppm
Grass, hay . . . . . 30 ppm

Fish	1.0 ppm
Shellfish	0.10 ppm
Fat of cattle, sheep, goats, and horses	0.05 ppm
Kidney of cattle, sheep, goats, and horses	0.20 ppm
Meat byproducts (except kidney) of cattle, sheep, goats, and horses	0.05 ppm
Meat of cattle, sheep, goats, and horses	0.05 ppm
Milk	0.01 ppm

The following data gaps have been identified and should be addressed prior to granting unconditional registration:

Chemistry

- Fish metabolism study.
- Corn or grass storage stability information or study.
- Additional spray additive information supporting the grass field trials.

Table of Contents

1.0 EXECUTIVE SUMMARY

BASF has submitted a petition proposing uses for imazapyr (2 lbs acid equivalent (ae)/gallon) on pasture and rangeland grasses for the control of undesirable vegetation and on aquatic freshwater sites for the control of floating or emergent vegetation. The registrant, BASF is requesting registration of imazapyr, the active ingredient in Arsenal® (EPA Reg. No. 241-346) for control of invasive aquatic weeds at aquatic sites, including ponds, lakes, reservoirs and estuarine waterbodies and for spot treatment on pasture and rangeland. Arsenal® is an aqueous solution (liquid formulation) containing 28.7% imazapyr (equivalent to 22.6% imazapyr ae or 2 lb. acid equivalent [ae] per U.S. gallon). Imazapyr is a systemic herbicide used to control most annual and perennial grasses, broadleaf weeds, and many brush and vine species. Imazapyr is readily absorbed though the leaves, stems, and roots and is translocated rapidly throughout the plant. Noticeable herbicidal activity may take up to several weeks. Imazapyr is currently registered for use on rights-of-way, non-irrigation ditches, fence rows, storage areas, forestry sites, and recreational sites, including golf courses and fairgrounds.

Hazard Assessment

Imazapyr has low toxicity via the oral, dermal and inhalation routes of exposure. It is not irritating to the skin and is negative for dermal sensitization. However, imazapyr is corrosive to the eye (toxicity category I). In a 21-day dermal toxicity study in rabbits the No Observable Adverse Effect Level (NOAEL) was determined to be 400 mg/kg/day, which was the highest dose tested (HDT). The Hazard Identification Assessment Review Committee (HIARC) concluded that there is no concern for acute or chronic neurotoxicity resulting from exposure to imazapyr. No developmental toxicity was observed in the rabbit or in the rat; however maternal toxicity (based on salivation), was observed in rats at the mid-dose of 300 mg/kg/day. Neither study showed an increased susceptibility of the fetus to imazapyr *in utero*. No parental systemic, reproductive or offspring effects were observed in the 2-generation reproduction study in the rat. There were no compound-related adverse effects in a one-year dietary toxicity study in beagle dogs. No significant tumor response was observed in female rats. No tumors were noted in male or female mice after long-term dietary administration of imazapyr. Imazapyr was negative for mutagenic potential in the Salmonella assay, CHO HGPRT gene mutation assay, and *in vitro* chromosomal aberration assay in CHO cells. Imazapyr was classified as group E - Evidence of Non-Carcinogenicity for Humans. There is no repeated dose inhalation toxicity study or dermal absorption study and there are no acute or subchronic neurotoxicity studies available in the database. The HIARC determined that no additional studies are required at this time based on current and proposed uses.

In a 1-year dog study *imazapic*, a closely related structural analog of imazapyr, was administered in the diet to beagle dogs at doses up to 40,000 ppm (TXR No. 0014560). With *imazapic*, there was minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both male and, to a lesser extent, female dogs seen at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females).

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision
The HED HIARC met on February 06, 2003 to evaluate the hazard database and select endpoints for risk assessment, and to evaluate the potential for increased susceptibility of infants and children from exposure to imazapyr according to the February 2002 10X guidance document. The special FQPA Safety Factor (SF) was reduced to 1x based on toxicological considerations by HIARC (no concern for pre- and/or postnatal toxicity and no residual uncertainties), the conservative residue assumptions used in the chronic dietary and residential exposure assessments, and the completeness of the residue chemistry, and environmental fate databases.

An acute reference dose (aRfD) was not established, as there was no endpoint of concern identified in the hazard database that was attributable to a single dose, including the developmental toxicity studies.

The HIARC selected the 1-year dog feeding study with a NOAEL of 250 mg/kg/day for all durations, based on the skeletal muscle effects observed in the dog with a very closely related structural analog, *imazapic*. In a 1-year dog feeding study with *imazapic*, (TXR No. 0014560) at doses up to 40,000 ppm, there was minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both male and, to a lesser extent, female dogs seen at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females). Although there were no skeletal muscle effects or any other adverse effects seen with imazapyr up to 250 mg/kg/day (HDT), the HIARC noted that one cannot say that effects with imazapyr would not have occurred had dosing been higher. The 1-year dog study for imazapyr, with analogy to *imazapic*, was also applied to short-, and intermediate-term incidental oral exposures, and to short-, intermediate- and long-term dermal and inhalation exposures. The chronic RfD is 2.5 mg/kg/day and the chronic population adjusted dose (cPAD) is also 2.5 mg/kg/day (FQPA Safety Factor =1). Since an oral study was selected for all durations for dermal and inhalation exposure, and there is no information on dermal penetration for imazapyr, a 100% dermal absorption factor (oral equivalent) should be used for route-to-route extrapolation.

Imazapyr was negative for mutagenic potential in the Salmonella assay, CHO HGPRT gene mutation assay, and in vitro chromosomal aberration assay in CHO cells. Imazapyr was classified by the Cancer Peer Review Committee (CPRC) in October 1995 as a "Group E chemical", no evidence of carcinogenicity in at least 2 adequate animal tests in different species.." (TXR # 0050019). This decision was reaffirmed in June 2003 (TXR # 0051943). A quantitative cancer risk assessment is not required for imazapyr.

Risk assessments were conducted for the following specific exposure scenarios listed below. The chronic reference dose (cRfD) was calculated by dividing the NOAEL by 100 (10X for interspecies extrapolation and 10X for intraspecies variation). Since the special FQPA SF has been reduced to 1X, the chronic population adjusted dose (cPAD) is equal to the cRfD. The level of concern for occupational inhalation exposures are for margins of exposure (MOEs) <100.

Exposure Scenario	Dose	Endpoint	Study/Effect
Chronic Dietary	NOAEL= 250 mg/kg/day	**cPAD** == 2.5 mg/kg/day	No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC assumed this dose as an endpoint for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic* at 137 mg/kg/day in males and 180 mg/kg/day in females.
Short, and Intermediate-Term Incidental Oral	NOAEL= 250 mg/kg/day	Target MOE = 100 (occupational and residential)	No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC assumed this dose as an endpoint for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic* at 137 mg/kg/day in males and 180 mg/kg/day in females.
Dermal and Inhalation, All Durations	NOAEL= 250 mg/kg/day	Target MOE = 100 (occupational and residential)	No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic*.

Non-Occupational Exposure Estimates

RD has confirmed that there is one imazapyr formulation registered for residential use. The label for the product (EPA Reg. No. 239-2657) specifies that it is to be used on driveways, brick patios, walkways, and bare ground. Application is by sprinkler can. It is not labeled to be used on lawns. Residential handlers are anticipated to have short-term dermal and inhalation exposures; the combined MOE for dermal and inhalation exposures is 85,000. Based on the labeled use pattern, HED anticipates that the post-application residential dermal exposures experienced by adults and children would not be more than those experienced at recreational sites as discussed below. However, HED anticipates that, for the home turf use, the soil ingestion scenario (non-dietary) is also possible due to toddler hand-to-mouth behavior and treated bare ground. The MOE for toddler soil ingestion is greater than 1×10^6. All residential exposures assessed do not exceed HED's level of concern (MOEs <100, residential).

Imazapyr formulations are registered for use at recreational sites, including golf courses and fairgrounds. Although the registered labels indicate that imazapyr is not intended for intense wear areas, adults and children could potentially experience short-term, post-application dermal exposures, and toddlers could also experience non-dietary oral exposures (from hand-to-mouth behavior) at fairground sites. MOEs for dermal exposures by adults and children (toddlers) at recreational sites are 260,000 and 160,000, respectively. The combined non-dietary MOE for incidental ingestion by toddlers (for all hand-to-mouth behaviors) at fairground sites is greater than 1×10^6. The combined MOE for dermal and non-dietary oral exposures by toddlers is 150,000. MOEs for dermal exposures by child and adult golfers were both greater than 1×10^6.

Additionally, although the proposed aquatic use is most likely intended for remote or inaccessible aquatic sites, adults and children swimming in treated areas could potentially experience short-term

post-application incidental ingestion and dermal exposures. MOEs for incidental ingestion by toddler and adult swimmers range from 68,000 to 320,000, respectively; MOEs for dermal exposures by swimmers are all greater than 1 x 10^6. All recreational exposures assessed (Tier 1 screening level assessment) do not exceed HED's level of concern (MOEs <100, recreational).

Dietary Exposure Estimates
Chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™; ver. 1.30) program which incorporates consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996/1998. For chronic dietary risk estimates, HED's level of concern is for estimates that exceed 100% of the acute population adjusted dose (aPAD) or cPAD, respectively. An acute-dietary exposure assessment was not performed because there were no toxic effects attributable to a single dose.

The Tier 1 [deterministic assessment using tolerance-level residues, 100% crop treated assumptions, and DEEM default processing factors] chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at <1% of the cPAD.

Drinking Water Exposure Estimates
Per the recommendations of the HED Metabolism Assessment Review Committee (MARC), EFED provided drinking water estimated environmental concentration (EECs) for imazapyr parent only. The Tier 1, FQPA Index Reservoir Screening Tool (FIRST) and Screening Concentration in Ground Water (SCI-GROW) models were used to derive the surface and ground water EECs, respectively. Application to aquatic sites (1.5 lbs ae/Acre) provided the highest exposure scenario; and, therefore, the drinking water EECs were derived for this use. For surface water, the acute (peak) and chronic (annual average) EECs are 137 ppb and 81 ppb, respectively. The acute and chronic ground water EEC is 1,700 ppb.

Aggregate Exposure Scenarios and Risk Conclusions
For the proposed uses, human health aggregate risk assessments have been conducted for the following exposure scenarios: short-term aggregate exposure (food + drinking water + residential), and chronic aggregate exposure (food + drinking water). An acute-dietary exposure assessment was not performed because there were no toxic effects attributable to a single dose. Thus, an endpoint of concern was not identified to quantitate acute-dietary risk to the general population or to any population subgroup. Intermediate- and long-term aggregate risk assessments were not performed because, based on the current use patterns, HED does not expect exposure durations that would result in intermediate- or long-term exposures. A cancer aggregate risk assessment was not performed because imazapyr is classified as a Group E, "no evidence of carcinogenicity. All potential exposure pathways were assessed in the aggregate risk assessment. Dietary (food and drinking water), handler and post-application residential exposures were considered, as necessary, because there is a potential for individuals to be exposed concurrently

through these routes. All EEC values are less than the lowest drinking water level of comparison (DWLOC) value of 25,000 ppb (specifically for the "children 1-2 years old" population subgroup) determined for the short-term, and chronic scenarios. **Therefore, all aggregate exposure and risk estimates do not exceed HED's level of concern for the scenarios listed above.**

Occupational Exposure Estimates

Imazapyr is currently registered for use on non-cropland sites such as utility rights-of-ways, utility plant sites, petroleum tank farms, forestry (conifer release), golf courses and ornamental turf (commercial and recreational sites). The registrant, BASF, is requesting registration of imazapyr to control invasive aquatic weeds on wetlands within forestry or non-crop sites and for immersed weed control at aquatic sites, including ponds, lakes, reservoirs, rivers and estuarine areas. Ground, boat and aerial applications are permitted per the proposed label. Note that the proposed label specifies that pesticide handlers wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, and shoes with socks.

Commercial aquatic handlers are anticipated to have short-term dermal and inhalation exposures based on discussions with aquatic weed control professionals. However, since the short-, intermediate-, and long-term dermal and inhalation endpoints are the same, the short-term assessment is considered to be conservative for all durations of occupational exposures. Combined MOEs (dermal and inhalation exposures) for mixer/loaders supporting aerial, boat, and ground-based applications range from **10** to 890, when handlers wear PPE specified on the proposed label. The MOE for mixer/loaders supporting aerial applications (MOE = 10) is of concern to HED (MOE < 100, occupational); however, with the addition of waterproof gloves to mixers/loaders, all combined MOEs range from 130 to 48,000 and do not exceed HED's level of concern.

Workers entering treated sites could potentially have short-term dermal exposures. However, since the short-, intermediate-, and long-term dermal and inhalation endpoints are the same, the short-term assessment is considered to be conservative for all durations of occupational exposures. The MOE for workers entering treated wetland (aquatic) sites the day of application is 430 and does not exceed HED's level of concern. The restricted entry interval (REI) on the parent label is 12 hours, however, imazapyr is Toxicity Category I for primary eye irritation. Under the Worker Protection Standard (WPS; 40 CFR Part 170), an interim 48-hour REI is required for an active ingredient that has an acute toxicity of Category I.

Recommendation for Tolerances and Registration
Provided revised Sections B and F are submitted and that successful Agency validation of the analytical method is reported, the toxicological and residue chemistry databases, as well as the aggregate risk assessments, support conditional registration of the requested new uses and establishment of the following permanent tolerances for residues of imazapyr *per se*:

Grass, forage	100 ppm
Grass, hay	30 ppm
Fish	1.0 ppm
Shellfish	0.10 ppm
Fat of cattle, sheep, goats, and horses	0.05 ppm
Kidney of cattle, sheep, goats, and horses	0.20 ppm
Meat byproducts (except kidney) of cattle, sheep, goats, and horses	0.05 ppm
Meat of cattle, sheep, goats, and horses	0.05 ppm
Milk	0.01 ppm

The following data gaps have been identified and should be addressed prior to granting unconditional registration:

Chemistry

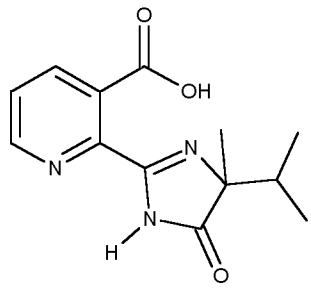
- Fish metabolism study
- Corn or grass storage stability information or study
- Additional spray additive information supporting the grass field trials

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredient

Chemical Name:	2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-3-pyridinecarboxylic acid
Common Name:	Imazapyr
Chemical Type:	Herbicide
PC Code Number:	128821
CAS Registry No.:	81334-34-1
Empirical Formula:	$C_{13}H_{15}N_3O_3$
Molecular Weight:	261.3

2.2 Structural Formula



Imazapyr

2.3 Physical and Chemical Properties

The following data for imazapyr were taken from product chemistry data supplied by BASF:

Vapor Pressure:	$<2 \times 10^{-7}$ mm Hg at 20°C
Water Solubility:	1.11 g/100 mL at 25°C
Octanol/Water Partition Coefficient:	1.3 at 22°C
Melting Point:	169-173°C
Density:	0.35 g/mL

Imazapyr is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for imazapyr supports the establishment of permanent tolerances for residues of imazapyr from the proposed uses (HIARC, Report, E.Rinde, TXR No. 0051689).

3.1 Hazard Profile

The toxicology database for imazapyr is complete. Imazapyr has low toxicity via the oral, dermal and inhalation routes of exposure. It is not irritating to the skin and is negative for dermal sensitization. However, imazapyr is corrosive to the eye (toxicity category I).

There is no concern for acute or chronic neurotoxicity resulting from exposure to imazapyr.

No developmental toxicity was observed in rabbits up to 400 mg/kg/day (HDT) or in the rat up to 1,000 mg/kg/day (the limit dose and HDT); however maternal toxicity, based on salivation, was

observed in rats at the mid-dose of 300 mg/kg/day. This was not considered to be evidence of neurotoxicity, since it occurred at the limit dose and there is no evidence of neurotoxicity in any other studies. Neither the rat nor the rabbit study showed an increased susceptibility of the fetus to imazapyr *in utero*. A 2-generation reproduction rat study did not show increased susceptibility to offspring at doses up to 10,000 ppm (HDT) (738 mg/kg/day males, 933.3 mg/kg/day females). There were no compound-related effects in clinical signs, mortality, body weight, food consumption, hematology, clinical chemistry, urinalyses, gross pathology, organ weights, and non-neoplastic and neoplastic lesions in a one-year dietary toxicity study in beagle dogs up to 250 mg/kg/day (HDT).

Imazapyr was classified by the CPRC in October 1995 as a "Group E chemical", no evidence of carcinogenicity in at least 2 adequate animal tests in different species.." (TXR # 0050019). This decision was reaffirmed in June 2003 (TXR # 0051943). A quantitative cancer risk assessment is not required for imazapyr. Imazapyr was negative for mutagenic potential in the Salmonella assay, CHO HGPRT gene mutation assay, and *in vitro* chromosomal aberration assay in CHO cells.

In a metabolism study imazapyr, (unlabeled 99.5% a.i. or C^{14}-labeled at the 6-carbon on the pyridine ring, 93.4% a.i.) was administered to Sprague Dawley rats (5/sex/dose) as a single gavage dose of approximately 9.5 mg/kg or 924 mg/kg or as 14-daily doses of unlabeled imazapyr, followed by a single labeled dose of 9.26 mg/kg imazapyr. Excretion via expired air was examined in a pilot study where two male and two female rats were given a single gavage dose of 10 mg/kg labeled imazapyr. Corn oil was used as the vehicle for all oral treatments. There was also an additional study in which 9.94 mg/kg imazapyr was administered by intravenous injection to five male and five female rats.

No sex-related differences in absorption were apparent. Within 48 hours of treatment, > 90% of the administered dose was recovered in the excreta suggesting that elimination of the labeled test material was rapid. No specific sequestering tissues or organs were identified. Seven days after treatment, essentially all the test material had been eliminated. The overall recovery of administered radioactivity for the single low-dose, multiple low-dose, and intravenous dose groups was similar and ranged from 92.1-107.7%, indicating acceptable mass balance. For the oral treatment groups, 68-81% of the administered test material was recovered in the urine and cage wash samples collected within 4 hours of treatment. Essentially all of the remainder was recovered in the feces with <0.2% of the administered dose remaining in the carcass/tissues. Rats that received the test material by intravenous injection excreted 87-95% of the administered dose in the urine and approximately 6% into the feces. This suggests that 15-28% of the administered dose recovered in the feces represents unabsorbed material.

Metabolite characterization studies show that essentially all of the test material was excreted unchanged. Two minor metabolites CL 252,974 and CL 60,032 were detected in the urine or feces of treated rats; however, their contribution combined was $\leq$ 0.5% of the administered dose. Up to 12 additional unidentified metabolites were isolated, but they constituted < 3% of the administered dose. Based on the results, the study author suggests that what limited metabolism of CL 243,997

occurs, proceeds through hydrolysis to form the 2-carbonyl derivatives: CL 252,974 and CL 60,032.

There is no repeated dose inhalation toxicity study or dermal absorption study and there are no acute or subchronic neurotoxicity studies available in the database for imazapyr, however these studies are not being requested at this time.

Table 1. Acute Toxicity of Imazapyr Technical Grade Active Ingredient (TGAI).

Guideline No/Study Type	MRIDs	Results	Toxicity Category
870.1100 Acute Oral	41551002	LD_{50} = > 5000 mg/kg	IV
870.1200 Acute Dermal	41551003	LD_{50} = >2000 mg/kg	III
870.1300 Acute Inhalation	00252004	LC_{50} = >1.3 mg/L (gravimetric) > 5.1 mg/L (nominal)	III
870.2400 Primary Eye Irritation	41551001	Corneal Opacity; Conjuctivae: redness, Chemosis & Discharge; Vascularization of Cornea; Corrosive: Irreversible Eye Damage	I
870.2500 Primary Skin Irritation	41551005	non-irritating to slight erythema and edema	IV
870.2600 Dermal Sensitization	00252004	Negative	-

Table 2. Toxicity Profile of Imazapyr Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	42774401 (1992) Acceptable/guideline 0, 15,000, or 20,000 ppm (equivalent to 0, 1248, or 1695 mg/kg bw/day in males and 0, 1423 or 1784 mg/kg bw/day in females).	**Dermal and Systemic** NOAEL =1,695 mg/kg/day for males and =1,784 mg/kg/day for females (HDT). This was the HDT; therefore, there is no LOAEL.

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.3200 21/28-Day dermal toxicity (rabbit)	00131609 (1983) Acceptable/guideline 0, 100, 200 or 400 mg/kg/day, 6 hrs/day for 5 d/week during a 21-day period.	**Dermal and Systemic** NOAEL =400 mg/kg/day. This was the HDT; therefore, there is no LOAEL.
870.3700a Prenatal developmental toxicity in rodents (rat)	00131611 (1983) Acceptable/guideline 0, 0, 100, 300 or 1,000 mg/kg/day from days 6 through 15 of gestation.	**Maternal** NOAEL = 300 mg/kg bw/day. LOAEL =1,000 mg/kg bw/day, based on salivation. **Developmental** NOAEL =1,000 mg/kg/day. This was the HDT; therefore, there is no LOAEL.
870.3700b Prenatal developmental toxicity in nonrodents (rabbit)	00131613 (1983) Acceptable/guideline 0, 25, 100, or 400 mg/kg /day from days 6 through 18 of gestation.	**Maternal** NOAEL =400 mg/kg bw/day This was the HDT; therefore, there is no LOAEL. **Developmental** NOAEL =400 mg/kg bw/day. This was the HDT; therefore, there is no LOAEL.
870.3800 Reproduction and fertility effects (rat)	41039505 (1987) Acceptable/guideline 0, 1,000, 5,000 and 10,000 ppm in the diet (equivalent to 0, 74.2, 380.5, or 738 mg/kg bw/day for males and 0, 94.3, 471.2, or 933.3 mg/kg bw/day for females).	**Parental systemic, reproductive and offspring** NOAEL =10,000 ppm (738 mg/kg bw/day in males 933.3 mg/kg bw/day in females). This was the HDT; therefore, there is no LOAEL.
870.4100a Chronic toxicity (rodent)	NA; see 870.4300	NA
870.4100b Chronic toxicity (dog)	41039502 (1987) Acceptable/guideline 0, 1,000, 5,000 or 10,000 ppm (equivalent to 0, 25, 125 or 250 mg/kg/day) for 1 year.	NOAEL is =10,000 ppm (250 mg/kg/day). This was the HDT; therefore, there is no LOAEL.
870.4200a Carcinogenicity (rat)	NA; see 870.4300	

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.4200b Carcinogenicity (mouse)	42774401 (1992) Acceptable/guideline 0, 1,000, 5,000 or 10,000 ppm (equivalent to 0, 126, 674 or 1,301 mg/kg /day in males and 0, 151,776 or 1,639 mg/kg /day in females) for 18 months.	NOAEL =10,000 ppm (1,301 mg/kg/day in males and 1,639 mg/kg/day in females). This was the HDT; therefore, there is no LOAEL.
870.4300 Combined Chronic/carcinogenicity (rat)	41039503 (1988) Acceptable guideline 0, 1,000, 5,000 or 10,000 ppm (equivalent to 0, 49.9, 252.6 or 503 mg/kg bw/day in males; 0, 64.2, 317.6 or 638.6 mg/kg bw/day in females) for 2 years. An additional 10 rats/sex/dose/group were sacrificed at 1 year.	Increase in brain astrocytomas in male rats for which there was a statistically significant positive trend, but which was not statistically significant in pairwise comparison to controls. The CPRC considered the astrocytomas in the male rats unrelated to treatment because there was no statistically significant pairwise increase. Dosing was considered to be adequate based on the HDT of 10,000 ppm which exceeds the limit dose of 7000 ppm for mice.
870.5100 Bacterial reverse mutation (Ames Assay)	00131615 (1983) Acceptable	Negative up to 5,000 µg/plate.
870.5300 *In vitro* mammalian cell gene mutation	00151641 (1984) Acceptable	Negative up to toxic doses (5,000 µg/ml) with and without activation.
870.5375 *In vitro* mammalian chromosome aberration (CHO)	00151640 (1984) Acceptable	Negative up to toxic doses (5,000 µg/ml) with and without activation.
870.5450 Rodent Dominant Lethal	00151638 (1985) Unacceptable	Reported as negative (though unacceptable).

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.5550 Unscheduled DNA synthesis (RPH)	00151639 (1984) Unacceptable	Reported as negative (though unacceptable).
870.7485 Metabolism and pharmacokinetics (rat)	43861501 (1994) Acceptable M&F: unlabeled or labeled imazapyr ~ 9.5 mg/kg or 924 mg/kg single gavage dose or as 14-daily doses of unlabeled imazapyr followed by single labeled dose of 9.26 mg/kg. M&F: 10 mg/kg labeled imazapyr single gavage dose to measure excretion via expired air (pilot study). M&F: 9.94 mg/kg labeled imazapyr by intravenous injection.	No sex-related differences in absorption were apparent. Within 48 hours of treatment, >90% of the administered dose was recovered in the excreta suggesting that elimination of the labeled test material was rapid. No specific sequestering tissues or organs were identified. Seven days after treatment, essentially all the test material had been eliminated. Rats that received the test material by intravenous injection excreted 87-95% of the administered dose in the urine and approximately 6% into the feces. This suggests that 15-28% if the administered dose recovered in the feces represents unabsorbed material. Metabolite characterization studies show that essentially all of the test material was excreted unchanged. Two minor metabolites CL 252,974 and CL 60,032 were detected in the urine or feces of treated rats; however, their contribution combined was ≤0.5% of the administered dose. Up to 12 additional unidentified metabolites were isolated, but they constituted <3% of the administered dose. Based on the results, the study author suggests that what limited metabolism of CL 243,997 occurs, proceeds through hydrolysis to form the 2-carbonyl derivatives: CL 252,974 and CL 60,032.
870.7600 Dermal penetration	NA	NA

3.2 FQPA Considerations

On February 06, 2003, the HED HIARC evaluated the potential for increased susceptibility of infants and children to exposure to imazapyr according to the February 2002 OPP 10X guidance document. The HIARC concluded that the toxicology database for imazapyr was complete for FQPA purposes and that there was no concern for pre-and/or postnatal toxicity (Memo, E.Rinde, March 25, 2003; TXR # 0051689). The HIARC recommended that the 10X FQPA factor be reduced to 1X, based on the following:

- Lack of concern for pre- and post-natal toxicity.
- No qualitative/quantitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure was reported in the developmental studies at doses up to 1000 mg/kg/day (Limit Dose) in the rat and 400 mg/kg/day (HDT) in the rabbit.
- There is no concern for developmental neurotoxicity resulting from exposure to imazapyr. While there are were no neurotoxicity studies available from the published literature, there was no evidence of neurotoxicity/neuropathology in adult animals in the available studies.
- The toxicological database is complete based on the developmental studies in the rat and rabbit and the 2-generation reproduction study in the rat.
- No developmental neurotoxicity (DNT) study is required.

Additionally, the team evaluated the exposure data for imazapyr and recommended that the special FQPA factor be reduced to 1X based on the following rationale:

- No residual uncertainties were identified in the exposure database.
- The chronic dietary food exposure assessment utilizes tolerance level residues and 100%CT information for all commodities. By using these screening level assumptions, actual exposures/risks will not be underestimated.
- The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations which will not likely be exceeded.
- Residential exposure and risk were assessed using standard assumptions from Science Advisory Council on Exposure(Expo SAC) Standard Operating Procedure (SOP). These assumptions are not expected to underestimate risk.

3.3 Dose-Response Assessment

Acute Dietary Endpoint: An acute-dietary exposure assessment was not performed because there were no toxic effects of concern attributable to a single dose. Thus, an endpoint of concern was not identified to quantitate acute-dietary risk to the general population or to any population subgroup.

Chronic Dietary Endpoint: The 1-year dog feeding chronic toxicity study was used to select the endpoint for establishing the chronic RfD of 2.5 mg/kg/day, based on the skeletal muscle effects observed in the dog with a closely-related structural analog, *imazapic*. The HIARC selected the 1-year dog feeding study with a NOAEL of 250 mg/kg/day because it was the lowest NOAEL in the imazapyr data base. While there were skeletal muscle effects in dogs at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females) with *imazapic,* a structural analog of imazapyr, **there were no skeletal muscle effects or any other adverse effects seen with imazapyr** up to 250 mg/kg/day (HDT). The HIARC noted that one cannot say that effects with Imazapyr would not have occurred had dosing been higher, and chose the dose of 250 mg/kg/day and skeletal muscle effects as an endpoint for risk assessment of imazapyr, based on analogy to *imazapic*.

Carcinogenicity: Imazapyr was classified by the CPRC in October 1995 as a "Group E chemical", no evidence of carcinogenicity in at least 2 adequate animal tests in different species.." (TXR # 0050019). This decision was reaffirmed in June 2003 (TXR # 0051943). A quantitative cancer risk assessment is not required for imazapyr.

Short- and Intermediate Term Incidental Oral Endpoint: The HIARC selected the 1-year dog feeding study with a NOAEL of 250 mg/kg/day (HDT), based on the skeletal muscle effects observed in the dog with a structural analog, imazapic. With *imazapic* there were skeletal muscle effects in dogs at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females). Although there were no skeletal muscle effects or any other adverse effects seen with imazapyr up to 250 mg/kg/day (HDT) the HIARC noted that one cannot say that effects with imazapyr would not have occurred had dosing been higher.

Dermal Absorption Factor: No dermal absorption study was submitted. A dermal absorption factor can not be extrapolated due to the absence of an endpoint at the HTD in the developmental and dermal studies. Therefore, HIARC selected a 100 % default absorption factor (oral equivalent).

Dermal Endpoint (all durations): The HIARC selected the 1-year dog feeding study with a NOAEL of 250 mg/kg/day, based on the skeletal muscle effects observed in the dog with a structural analog, *imazapic*. With *imazapic* there were skeletal muscle effects in dogs at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females). Although there were no skeletal muscle effects or any other adverse effects seen with imazapyr up to 250 mg/kg/day (HDT) the HIARC noted that one cannot say that effects with imazapyr would not have occurred had dosing been higher. Since an oral dose was selected, and there is no information on dermal penetration for imazapyr, a 100% default dermal absorption factor (oral equivalent) was used for route-to-route extrapolation.

Inhalation Endpoint (all durations): The HIARC selected the 1-year dog feeding study with a NOAEL of 250 mg/kg/day, based on the skeletal muscle effects observed in the dog with a structural analog, *imazapic*. With *imazapic* there were skeletal muscle effects in dogs at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females). Although there were no skeletal muscle effects or any other adverse effects seen with imazapyr up to 250 mg/kg/day (HDT) the HIARC noted that one cannot say that effects with imazapyr would not have occurred had dosing been higher. Absorption via the inhalation route is presumed to be equivalent to oral absorption (100%).

Margin of Exposure (MOE) for Occupational/Residential Risk Assessments: A MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for inhalation routes of exposure. This MOE is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation). There are currently no residential uses for imazapyr.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for Imazapyr for Use in Human Health Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age and General population including infants and children)	none	none	An acute dietary endpoint was not selected based on the absence of an appropriate endpoint attributable to a single dose.
Chronic Dietary (All populations)	Oral Study NOAEL= 250 mg/kg/day UF = 100 **Chronic RfD**= 2.5 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 2.5 mg/kg/day	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic*.
Short- and Intermediate- Term Incidental Oral (1-30 days and 1-6 months)	Oral Study NOAEL= 250 mg/kg/day	**LOC for MOE**= NA (Occupational) **LOC for MOE** =100 (Residential, includes the FQPA SF - At present time no residential uses)	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic*.
Short- and Intermediate- and Long-Term Dermal (1 to 30 days, 1 to 6 months, >6 months)	Oral study NOAEL= 250 mg/kg/day (dermal absorption rate = 100 %)	**LOC for MOE** =100 (Occupational) **LOC for MOE** =100 (Residential, includes the FQPA SF - At present time no residential uses)	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog *imazapic*.
Short- and Intermediate- and Long-Term Inhalation (1 to 30 days, 1 to 6 months, >6 months)	Oral study NOAEL= 250 mg/kg/day (inhalation absorption rate = 100%	**LOC for MOE** =100 (Occupational) **LOC for MOE** =100 (Residential, includes the FQPA SF - At present time no residential uses)	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog imazapic.

Table 3. Summary of Toxicological Dose and Endpoints for Imazapyr for Use in Human Health Risk Assessment[1].			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer Risk	A quantitative cancer risk assessment is not required for imazapyr	N/A	**2-Year Chronic** [feeding] **Toxicity/Carcinogenicity Study in Rats**: Group E - "no evidence of carcinogenicity in at least 2 adequate animal tests in different species.."

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable, RA = Risk Assessment, CPRC = Carcinogenicity Peer Review Committee.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, imazapyr may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

A review of information pertaining to residue chemistry data requirements for aquatic and grass pasture and rangeland uses of imazapyr is available in a separate memo (Memo, W. Donovan, D275561, 20-MAR-2003).

4.1 Summary of Proposed Uses

Table 4 summarizes the use directions for the new uses of imazapyr proposed by BASF.

Table 4. Summary of Proposed Directions for Use of Imazapyr.

Application Timing, Type, and Equip.	Formulation [a] [EPA Reg. No.]	Maximum Applic. Rate (lb ae/A) [b]	Max. No. Applic/ Season	PHI (days)	Use Directions and Limitations [c]
Grass Pasture and Rangeland					
Spot treatment ground application (Ground equipment)	2 lb ae/gal EC [241-346]	0.75 lb ae/ acre	NS	7	Applications may not exceed more than 1/10 of a given acre, therefore the maximum rate per acre is 0.075 lb ae/A. Do not cut forage for hay for 7 days after application. Rotational crops: 12 months after application, a successful field bioassay must be completed. If no crop injury is evident in the bioassay, then the intended rotational crop may be planted the following year. Post-emergence applications require the addition of a spray adjuvant (nonionic surfactant or methylated seed oils or vegetable oil concentrates).
Aquatic (fresh water) [d]					
Broadcast application to aquatic areas or draw down area (Surface or aerial equipment)	2 lb ae/gal EC [241-346]	1.5	NS	NA	Do not apply to marine or estuarine areas. Do not apply within ½ mile (standing water) or within ½ mile upstream (flowing water) of an active irrigation or potable water intake. For application, within ½ mile of a water intake, the water intake must be turned off for a minimum of 48 hours after the application. Allow 1 hour after treatment before refilling draw down area. Apply in a minimum of volume of 5 gal/A.

NS = Not specified.
PHI = pre-harvest interval.

Label Deficiencies

Provided that the petitioner 1) adds a statement prohibiting more than one application of imazapyr per season and 2) submits residue data for irrigated crops or adds a label restriction that prohibits the use of treated water for irrigation purposes for 120 days following application or demonstrates non-detectable residue levels of imazapyr in irrigation water by laboratory analysis prior to use, the proposed use directions adequately reflect the use pattern for imazapyr application to aquatic

systems and grass pastures and rangeland. **A revised Section B should be submitted.**

4.2 Dietary Exposure/Risk Pathway

The residue chemistry data submitted in support of proposed petitions were reviewed in the following HED-memorandum dated 3/20/03 (Memo, W. Donovan, D275561). The drinking water assessment was completed by EFED on 2/10/03 (Memo, A.Clem, D278110). The chronic dietary exposure assessment was completed in a HED-memorandum dated 3/26/03 (Memo, W.Donovan, D288806). A residential exposure assessment for imazapyr was prepared in an HED memorandum dated 4/15/03 (Memo, J.T.Swackhammer; D289502).

4.2.1 Residue Profile

Background

BASF has submitted a petition proposing uses for imazapyr (2 lb ae/gallon aqueous solution (AS)) on pasture and rangeland grasses for the control of undesirable vegetation and on aquatic freshwater sites for the control of floating or emergent vegetation. In conjunction with these uses, BASF is proposing the establishment of permanent tolerances for residues of imazapyr applied as the isopropylamine salt, in/on the following plant and animal commodities:

Grass, forage	125.0 ppm
Grass, hay	35.0 ppm
Fish, freshwater finfish	1.0 ppm
Shellfish	0.1 ppm
Fat of cattle, sheep, goats, and horses	0.05 ppm
Kidney of cattle, sheep, goats, and horses	0.5 ppm
Meat byproducts (except kidney) of cattle, sheep, goats, and horses	0.05 ppm
Meat of cattle, sheep, goats, and horses	0.05 ppm
Milk	0.01 ppm

Imazapyr is a broad-spectrum, imidazolinone herbicide used for pre- and post-emergence control of annual and perennial grass and broadleaf weeds, brush, vines, and deciduous trees. Imazapyr is currently registered to BASF Corporation for use on non-cropland areas and on imidazolinone-resistant field corn. End-use products currently registered to BASF include AS and ready-to-use (RTU) formulations of imazapyr, formulated as a isopropylamine salt.

For the use on field corn, the HED MARC concluded (N. Dodd, 2/26/97) that the residues of concern in field corn and animal commodities included only the parent compound. Tolerances for residues of imazapyr in or on plant and animal commodities are currently expressed as parent imazapyr. Permanent tolerances have been established for residues in/on field corn forage, grain and stover each at 0.05 ppm [40 CFR §180.500].

Nature of the Residue

Plants: The qualitative nature of imazapyr residues in plants is understood based upon the adequate corn and grass metabolism studies. An acceptable corn metabolism study was submitted in conjunction with the earlier petition for use on corn (D222027, N. Dodd, 6/26/96), and an adequate bermuda grass metabolism study was submitted with the grass/aquatic use petition. In both the corn and grass metabolism studies, imazapyr was the principal residue identified in each commodity. Based on the minor metabolites identified, the metabolism of imazapyr in plants primarily involves esterification of the carboxylic acid of the parent molecule to form CL 240000 and/or CL 247087 (cyclization product), and hydrolysis of the imidazolinyl ring to form pyridine dicarboxylic acid (CL 9140).

In a meeting of the HED MARC held 26-FEB-2003, the residue of concern in plants (primary and rotational crops) was determined to be imazapyr *per se* (TXR# 0051641, W. Donovan and E. Rinde, 13-MAR-2003).

Livestock: The qualitative nature of imazapyr residues in livestock is understood based upon one adequate poultry and two adequate goat metabolism studies. In the poultry metabolism study, two groups of hens were dosed orally for 7 days with [6-pyridine-^{14}C]imazapyr at levels equivalent to 1.98 ppm or 9.72 ppm (~50x and 240x the maximum theoretical dietary burden (MTDB)). The total radioactive residue (TRR) were <0.01 ppm (< limit of detection (LOD)) in eggs, liver, kidneys, muscle, and skin with adhering fat from both dose groups. Imazapyr *per se* was the sole radioactive component identified in the excreta of treated hens.

In the first goat metabolism study, two goats were dosed orally for 7 days with [6-pyridine-^{14}C]imazapyr at levels equivalent to 17.7 ppm or 42.5 ppm in the diet (0.7x or 1.8x the MTDB). The TRR ranged from <0.01 ppm-0.02 ppm in milk and were 0.08 ppm and 0.11 ppm, respectively, in the kidneys of the low and high dose goats. The TRR in the remaining tissues (fat, liver, and leg and loin muscle) were nondetectable (<0.05 ppm) and were not further characterized. The study sufficiently characterized and identified detectable residues in extracts of milk and kidney by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). Imazapyr *per se* was the sole radioactive component identified, comprising ~50% of TRR in milk and ~95% of TRR in kidney.

The petitioner conducted a second goat metabolism study to generate ^{14}C-labeled samples for radiovalidation of the proposed enforcement method. In this study, a single goat was dosed orally for 7 days with [imidazole-5-^{14}C]imazapyr at a level equivalent to 46.9 ppm in the diet (2x) and only milk and kidney samples were collected for analysis. TRR were 0.014-0.016 ppm in milk and 0.074 ppm in kidneys, and parent compound accounted for 65.6% of the TRR in milk and 81.9% of the TRR in kidney. This study was also adequate and confirmed the finding of the earlier goat metabolism study.

The HED MARC concluded (N. Dodd, 2/26/97) that the residues of concern in animal commodities included only the parent compound. In a meeting of the HED MARC held 26-FEB-2003, the residue of concern in livestock (ruminants) was confirmed to be imazapyr *per se* (TXR#

0051641, W. Donovan and E. Rinde, 13-MAR-2003).

Fish and Shellfish: No fish metabolism studies are available for imazapyr. Shellfish bioaccumulation studies are available for imazapyr. No bioaccumulation was observed in these studies and the residue levels were close to the limit of quantitation (LOQ) of the analytical method. The HED MARC concluded it is appropriate to translate the metabolism data for livestock to fish and shellfish, provided the submission of a fish metabolism study is made a condition of the registration of imazapyr for use on aquatic areas. The MARC tentatively concluded the residue of concern in fish and shellfish is the parent compound, imazapyr, for both risk assessment and tolerance setting purposes. This conclusion should be reconsidered upon receipt and evaluation of an acceptable fish metabolism study (TXR# 0051641, W. Donovan and E. Rinde, 13-MAR-2003). **A fish metabolism study should be submitted.**

Residue Analytical Methods

Two methods are currently listed in the Pesticide Analytical Manual (PAM) Vol. II for enforcing tolerances of imazapyr in/on corn commodities. Method M 2468 is a gas chromatography/mass spectrometry (GC/MS) method with a limit of quantitation (LOQ) of ~0.01 ppm for imazapyr in/on corn grain, forage and fodder, and Method M 2657 is a capillary electrophoresis (CE) method with ultraviolet (UV) detection that has a LOQ of 0.05 ppm for imazapyr in/on corn grain, forage and fodder.

The petitioner is proposing a series of CE/UV Methods as enforcement methods for determining imazapyr in/on grass forage and hay (Method M 3023), in livestock tissues (Method M 3184), in milk and milk fat (Methods M 3075 and M 3223), and in fish and shellfish tissues (Method M 3066). These methods are similar to the current enforcement method M 2657, and each of these methods also include directions for a confirmatory analysis using liquid chromatography/mass spectrometry (LC/MS).

Based on concurrent method recovery data submitted with the grass field trials, the cattle feeding study, and the bioaccumulation studies for fish and shellfish, the above CE/UV methods are adequate for collecting data on residues of imazapyr in grass forage and hay, cattle tissues and milk, and fish and shellfish. The validated LOQs for imazapyr in the respective CE/UV methods are 0.5 ppm in/on grass forage and hay, 0.05 ppm in cattle tissues, fish and shellfish, and 0.01 ppm in milk and milk fat.

All of the proposed CE/UV methods have undergone successful independent laboratory validation (ILV) trials. Adequate radiovalidation data were also submitted for CE/UV methods M 3066, M 3075, and M 3185, demonstrating the efficiency of these methods in extracting residues from aged samples.

The CE/UV Methods M 3023, M 3184, M 3075, and M 3066 have been forwarded to the Analytical Chemistry (ACB) for petition method validation (PMV) trials (D288863, W. Donovan,

14-MAR-2003). **Conclusions regarding the suitability of the proposed enforcement methods will be deferred until completion of the PMV trials.**

Multiresidue Method (MRM)

Federal Drug Administration (FDA) MRMs do not exhibit sufficient sensitivity to other imidazolinone herbicides, and thus there is no reasonable expectation that these methods would prove to be useful for determining residues of imazapyr.

Crop Field Trials

Grass

Supervised crop field trials were conducted in AR, CO, GA, ID, IN, MI, NE (2), OR (2), PA, TX (2), and WI in/on grass treated once at an application rate of 0.73-0.78 lb acid equivalents (ae)/A of imazapyr in 20-60 gallons of water per acre with a 0.25% (v/v) nonionic surfactant. Forage and hay samples of bermuda, tall fescue, bluegrass, and brome grass were harvested 0.1, 7, 14, and 28 days after application; the hay samples were allowed to field dry for 1-17 days after cutting. Samples were stored frozen for a maximum of 24 months and then analyzed for residues of imazapyr using CE/UV Method M 3023. The LOQ was established at 0.50 ppm for forage and hay.

Residues of imazapyr were 27-98 ppm in/on grass forage harvested immediately following application (0.1 day), which is the proposed PHI. Residues in/on forage declined steadily at subsequent sampling intervals to 0.59-12.2 ppm by 7 day after treatment (DAT), <0.5-10.6 ppm by 14 DAT, and <0.5-6.25 ppm by 28 DAT. Residues of imazapyr were 65-277 ppm in/on hay harvested immediately following application, and declined to 0.88-27.1 ppm in/on hay harvested at 7 DAT, which is the proposed PHI. Residues in/on hay continued to declined at later sampling intervals; 0.51-19.6 ppm by 14 DAT and <0.5-8.56 ppm by 28 DAT.

Fish and Shellfish

To support the proposed aquatic use of imazapyr for control of floating and emergent weeds, BASF submitted two field trials examining imazapyr residues in water, sediments, fish and shellfish following an application at the proposed use rate.

In aquatic field trials at two locations (FL and MO), imazapyr was applied at a broadcast rate of 1.6 lb ae/A to either the banks and water's edge of a pond (Treatment I) or to the banks and the entire pond surface (Treatment II). Ponds were stocked with fish (bluegill, bass, tilapia, and catfish) and crayfish prior to treatment. Samples of each animal and water were collected at various intervals up to 42 DAT and samples of pond sediments were collected at up to 180 DAT.

Residues of imazapyr were <0.05 ppm (<LOQ) in all samples of each non-target species from Treatment I at both test sites and from Treatment II at the MO test site. For Treatment II at the FL site, imazapyr residues were detected only in bluegill (0.636 ppm), tilapia (0.233 ppm), catfish

(0.068 ppm), crayfish (0.059 ppm) at 3 hours post-treatment.

Conclusions

The field trials on fish and shellfish are adequate to depict the maximum residue levels expected from imazapyr use according to the proposed label. **The grass field trial data will be complete once BASF provides the following support information: 1) corn or grass storage stability data demonstrating the stability of imazapyr residues for at least 24 months in frozen storage, and 2) spray additive identities and concentrations used in all the grass field trials (this information was not specified in seven of the fourteen trials).**

Based on the data now available, the following permanent tolerances for residues of imazapyr *per se* are appropriate:

Grass, forage	100 ppm
Grass, hay	30 ppm
Fish	1.0 ppm
Shellfish	0.10 ppm
Fat of cattle, sheep, goats, and horses	0.05 ppm
Kidney of cattle, sheep, goats, and horses	0.20 ppm
Meat byproducts (except kidney) of cattle, sheep, goats, and horses	0.05 ppm
Meat of cattle, sheep, goats, and horses	0.05 ppm
Milk	0.01 ppm

A revised Section F is required to lower the proposed tolerance levels for the following RACs: *grass, forage; grass, hay; and kidney of cattle, sheep, horses, and goats.* Also, the commodity term "Fish, freshwater finfish" should be changed to "Fish".

Meat, Milk, Poultry, Eggs (MMPE)

Registration requirements for magnitude of the residue in meat, milk, poultry, and eggs are fulfilled. An adequate ruminant feeding study is available for imazapyr, and a poultry feeding study is not required as detectable ^{14}C-residues were not found in eggs and tissues from a poultry metabolism study conducted at a dose level equivalent to 9.72 ppm (~240x) in the diet. In the cattle feeding study, four groups of dairy cows (3 cows/group) were dosed orally with imazapyr for 28 consecutive days at dose levels equivalent to 58, 157, 607, and 1680 ppm of imazapyr in the diet. These dose levels correspond to exaggerated rates of approximately 2.4x, 6.5x, 25x, and 70x the maximum theoretical dietary burden (MTDB) of cattle.

The MTDBs for livestock are calculated below in Table 5. Based on a diet including corn grain at 80% of the diet, the MTBD is 0.04 ppm for both for poultry and swine. For cattle the recommended tolerances on grass forage (100 ppm) and hay (30 ppm) have the major impact on the dietary burden for cattle. However, these tolerances are based on a broadcast application rate of 0.75 lb ae/A, and the label directions specify spot applications at 0.75 lb ae/treated acre, with no

more than 10% of an acre being treated. Accordingly, the calculation of the MTDB for cattle includes multiplication by a 10% correction factor to account for the label restriction limiting the spot treatment of grasses to a maximum of 10% of any given acre. This approach is consistent with a previous HED Chemistry Science Advisory Council (ChemSAC) decision to set the grass forage and hay tolerance levels on residue levels in the treated area alone, while calculating dietary burdens for livestock based on the average residue across the whole crop (i.e., the % area treated is multiplied by the residue in the treated spot) [Minutes of 1/20/99 ChemSAC meeting].

Table 5. Calculation of maximum theoretical dietary burdens of livestock animals for Imazapyr.

Feed Commodity	% Dry Matter [a]	% Diet [a]	Recommended or established Tolerances (ppm)	% Area treated/acre [b]	Potential Dietary Contribution (ppm) [c]
Beef and Dairy Cattle					
Grass forage	25	60	100	10	24.0
Grass hay	88	60	30	10	2.05
Corn grain	88	80	0.05	NA	0.05
Corn forage	40	50	0.05	NA	0.06
Corn stover	83	25	0.05	NA	0.02
TOTAL BURDEN					**24.0** [d]
Poultry					
Corn grain	NA	80	0.05	NA	0.04
TOTAL BURDEN					**0.04**
Swine					
Corn grain	NA	80	0.05	NA	0.04
TOTAL BURDEN					**0.04**

[a] Table 1 (August 1996).

[b] For the spot application to grasses, the label specifies that no more than 10% of any given acre is to be treated.

[c] Contribution = [tolerance / % DM (if cattle)] X % diet X % area treated (for grass).

[d] Based on a diet consisting of 60% grass forage and 40% corn grain.

NA = not applicable.

Based on a MTDB of 24.0 ppm and comparison with the maximum residue levels observed in the 58 ppm dose group in the cattle feeding study, the maximum expected imazapyr residues in cattle commodities are <0.010 ppm in milk, <0.050 ppm in muscle, fat, and liver; and 0.15 ppm in kidney. Accordingly, the appropriate tolerance levels for imazapyr residues in cattle tissues are as follows: milk 0.01 ppm; meat, fat, and meat byproduct (except kidney) 0.05 ppm; kidney 0.20 ppm.

Based upon a MTDB of 0.04 ppm for swine, the 58 ppm dose level in the ruminant feeding study is equivalent to 1450x the MTDB for swine. Based on the maximum residues detected in the 58 ppm dose group, there is no reasonable expectation of finding quantifiable residues of imazapyr in

hog tissues [40 CFR 180.6(a)(3)]. Thus, tolerances for imazapyr residues in hog commodities are not necessary.

As indicated above, total ^{14}C-residues were <0.01 ppm in eggs and poultry tissues from hens dosed in the poultry metabolism study at a level equivalent to 9.72 ppm (~240x) in the diet. Therefore, there is no reasonable expectation of finding quantifiable residues of imazapyr in poultry commodities [40 CFR 180.6(a)(3)] and tolerances are not required.

Confined and Field Accumulation in Rotational Crops

An adequate confined rotational crop field trial was previously submitted to support the use on field corn at 0.014 lb ae/A (D222027, N. Dodd, 6/26/96). This earlier study was conducted at an application rate of 0.025 lb ae/A. To support the currently purposed use on grass pastures and rangeland, the petitioner has submitted a new confined rotational crop field trial reflecting the higher proposed spot-treatment use rate on grass (0.75 lb ae/treated acre).

Although supporting storage stability data were not provided, and metabolite identities were not confirmed using a second analytical method, the submitted confined rotational crop study is adequate. Based on the low TRR levels observed (<0.02 ppm) in each crop at the ~12 and 18 month plant-back intervals, and the HPLC analyses of solvent extracted ^{14}C-residues, any residues of concern in rotational crops at the proposed 12-month plantback interval (PBI) would be <0.005 ppm. In addition, while the use rate in the current study (0.79 lb ae/A) approximates the maximum proposed rate for spot treatments, the total amount applied per full acre is limited to 0.075 lb ae/A, since the spot treatment is only permitted on a maximum of one tenth (1/10) of a given acre. Therefore, the maximum average exposure of rotational crops to imazapyr should reflect a rate of 0.075 lb ae/A, and the present study may be considered an exaggerated rate study conducted at 10x.

Accordingly, limited field rotational crop trials and rotational crop tolerances will not be required to support the proposed use on grasses.

International Harmonization of Tolerances

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) for residues of imazapyr in/on any of the crops involved in the proposed new uses. Therefore, international harmonization is not an issue at this time.

4.2.2 Dietary Exposure Analyses

A imazapyr chronic dietary exposure assessment (Memo, W. Donovan, D288806, 26-MAR-2003) was conducted using DEEM-FCID™, Version 1.3, which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-1996, and 1998 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as

consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

4.2.2.1 Chronic Dietary Exposure Analysis

The Tier 1 chronic dietary risk assessment for imazapyr shows that exposures for all population subgroups are below HED's level of concern. Total food exposure for all population subgroups was determined to occupy <1% cPAD.

Table 6 summarizes the chronic dietary exposure assessment of Imazapyr.

Table 6. Results of Chronic Dietary Exposure Analysis for Imazapyr.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	2.5	0.00034	<1
All Infants (< 1 year old)	2.5	0.000273	<1
Children 1-2 years old	2.5	0.000828	<1
Children 3-5 years old	2.5	0.00073	<1
Children 6-12 years old	2.5	0.000499	<1
Youth 13-19 years old	2.5	0.000309	<1
Adults 20-49 years old	2.5	0.000267	<1
Females 13-49 years old	2.5	0.000257	<1
Adults 50+ years old	2.5	0.000287	<1

The present dietary exposure analysis made use of tolerance-level residues, 100% crop treated assumptions, and DEEM default processing factors. All processing factors in the current analysis were 1.0 except for the "beef, meat, dried" factor where a value of 1.92 was used. Thus, the

exposure estimates provided here overestimate the actual risk. With the current low-level of risk from imazapyr, refinement was determined to be unnecessary. All dietary exposure estimates are below HED's level of concern (100% of the cPAD).

4.3 Water Exposure/Risk Pathway

In a meeting on 2/26/03, the HED MARC determined that the residues of concern for the imazapyr in drinking water is parent only (TXR# 0051641, W. Donovan and E. Rinde, 13-MAR-2003).

According to its physicochemical properties and collateral data, imazapyr is non-volatile. Laboratory bioconcentration studies with bluegill sunfish, eastern oyster and grass shrimp, and a supplemental aquatic field dissipation studies indicate that parent imazapyr is not subject to bioconcentration. Imazapyr's low n-octanol to water partitioning ratio is also consistent with little likelihood of bioconcentration.

Imazapyr is persistent in soil. Judging from the sorption coefficients, its intrinsic acidic (anionic) nature, and some evidence from terrestrial field data, imazapyr is prone to leach and runoff. The combination of low sorption and long residence time in soil offers increased opportunities for transport to ground and surface waters.

Within laboratory study conditions and durations, imazapyr was essentially stable (half-lives indeterminately long) to hydrolysis, photolysis in soil, anaerobic soil metabolism, and aerobic and anaerobic aquatic metabolism. Minor concentrations of identified and unidentified transformation products were detected in of some of the aforementioned processes. Slow production and accumulation of relatively low residual concentrations of identified or unidentified imazapyr byproducts could be responsible, at least in part, for the long rotational crop intervals and the need for bioassays before planting. Of course, even though bulk soil-sorption coefficients for parent imazapyr are low, preferential sorption in some soils by specific minor or trace soil components could also sequester enough imazapyr to contribute to the long residual soil bioactivity.

Based on laboratory tests and previous reviews, imazapyr is prone to leach and is relatively long-lived under field soil conditions. Photolysis in laboratory water was the only process that occurred fast enough for imazapyr to produce major degradates (> 10% of parent equivalents) during study periods. Photolysis half-lives in laboratory water of approximately three to five days (twelve hours of sun per day) translate into effective aquatic field half-lives of approximately 300 to 700 days under the more typical aquatic field conditions (water depth and clarity) used in current modeling scenarios. The major photolysis products were CL 119060 and CL 9140. CL 119060 and CL 9140 reached a maximum of approximately 32% and 23%, respectively, of chemical equivalents of parent.

The two major photodegradates were tested for aquatic metabolism under aerobic conditions. In a 14-day study for each, their aerobic aquatic metabolism half-lives were in the range of three to

eight days in two different sediment/water systems. Nicotinic acid was a metabolite of CL 119060, reaching a maximum equivalent of approximately 10% of parent; unexpectedly, CL 9140 apparently did not produce nicotinic acid. Mineralization, as evidenced carbon dioxide production, was significant for each photodegradate in both sediment/water systems, with a range of production amounting to approximately 20 to 50% of photodegradate equivalents.

A supplemental aquatic field dissipation study for imazapyr is inconclusive about routes of dissipation. Based on study limitations, it would not be meaningful to report a field "half-life." Four small, shallow pond water columns were analyzed for parent and for the two degradates, CL 119060 and CL 9140. Neither of the photodegradates were observed in three of the four pond waters, and only minor concentrations of each were found in the remaining pond. There was no analysis for other degradates/metabolites, including nicotinic acid. Pond sediments/soils were analyzed for parent only; minor sediment concentrations of imazapyr in two ponds were effectively persistent at approximately 4 to 18 parts per billion. Plant compartments were not sampled. No major routes of dissipation were identified in any pond.

As part of the aquatic field study, the bioconcentration of imazapyr in caged fish and crayfish species was also measured. However, the reported limit of quantitation for imazapyr in tissue was a relatively high 50 parts per billion (ppb). Within the 50 ppb limit, parent imazapyr did not bioconcentrate appreciably in the fish and crayfish species tested (three fish and one crayfish species at each site, total of seven different species). There were no tests for metabolites or degradates in any of the test species.

EFED provided Tier 1 EECs for ground water (using SCI-GROW) and surface water (using FIRST) for total residues of imazapyr (see Table 7).

Table 7. Estimated Tier 1 Concentrations of Imazapyr in Drinking Water.

Chemical	Surface Water (ug/L)		Groundwater (ug/L)
	Acute	Chronic	Acute and Chronic
Imazapyr total residues[1]	137	81	1700

1. Imazapyr.

4.4 Non-Occupational Exposure/Risk Pathway

4.4.1 Residential Exposure and Risk Assessment/Characterization

This section discusses the residential exposure scenarios associated with the registered uses of imazapyr. The representative registered product is Ortho GroundClear Triox Complete Vegetation Killer (EPA Reg. No. 239-2657). Label instructions state that the product is intended for use on driveways, parking areas, brick walls, gravel pathways, patios, along sidewalks and bare ground. Mixing instructions are provided for up to 600 ft^2 (use 1 gal. product/300 ft^2 = 0.0056 lb ae/300 ft^2, 2 gal. product would be used for up to 600 ft^2). Application is via sprinkling

can. The product is not intended for use on lawns per the registered label. The anticipated exposure scenarios are:

- Residential handler: Short-term dermal and inhalation exposures from mixing/loading and application via sprinkling can (per label instructions). Note that the registered label states that the product offers long-term weed control and prevents re-growth for up to one year with a single application; therefore only short-term handler exposures are anticipated.
- Post-application: Adults and children are anticipated to have short-term dermal exposures; however, given that the product is not intended for lawn use, dermal exposures by adults and children are considered to be negligible as compared to recreational post-application exposures (from treated turf) given that the application rate is higher for the golf course/fairground use pattern. However, toddlers could potentially ingest soil from treated bare ground (short-term soil ingestion from hand-to-mouth behavior) in the residential use scenario. Therefore, this exposure scenario *is* assessed below.

The following HED SOP were used to estimate residential exposure for this assessment:

- Residential handler: Summary of HED's Reviews of Outdoor Residential Exposure Task Force (ORETF) Chemical Handler Exposure Studies; MRID 449722-0. ORETF Study Number OMA004 (hose-end sprayer, [as surrogate for sprinkling can]), April 30, 2001.
- Post-application exposures: *Standard Operating Procedures (SOPs) For Residential Exposure Assessment*s, Draft, 17-DEC-1997 and ExpoSAC Policy No. 11, 22-FEB-2001: *Recommended Revisions to the SOPs for Residential Exposure*.

a. Residential Handler Exposure and Risk Assessment

Table 8 presents the exposure and risk assessment for homeowners performing spot treatments around the home.

Table 8. Residential Handler Exposure and Risk Assessment for Homeowner Use of Imazapyr

Exposure Scenario	Unit Exposure[1] (mg/lb ae handled)	AR[2]	Area treated per day[3]	Potential Dose Rate[4] (mg/kg bw/day)	Combined Short-term MOE[5]
Mixer/Loader/Applicator (MLAP), spot treatment, hose-end sprayer (as surrogate for sprinkling can, "mix your own"	dermal, short pants, short sleeves: 11 (HC)	0.0056 lbs ae/ 300 ft^2	1,000 ft^2	dermal: 0.00293	85,000
	inhalation: 0.016 (HC)			inhalation: 4.27×10^{-6}	

Notes:
1. Source: Summary of HED's Reviews of Outdoor Residential Exposure Task Force (ORETF) Chemical Handler

Exposure Studies; MRID 449722-0. ORETF Study Number OMA004 (hose-end sprayer), April 30, 2001. HC = high confidence data.
2. AR = Maximum application rate; Source: Ortho GroundClear label (EPA Reg. No. 239-2657).
3. Daily acres treated Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.
4. Potential Dose Rate (PDR) = Unit exposure(mg/lb ai) x AR x Area treated/day x 1/BW (70 kg) x %Absorption (100% dermal absorption and 100% inhalation absorption rate to convert to an equivalent oral equivalents per HIARC). Combined PDR = PDR_{dermal} + $PDR_{inhalation}$.
5. MOE = NOAEL/PDR; short-term dermal and inhalation NOAELs based on oral NOAEL = 250 mg/kg/day. HED's level of concern is for MOEs < 100 (residential).

The MOE for residential handler use of imazapyr for spot treatments around the home is greater than 100 and does not exceed HED's level of concern.

b. Residential Post-Application Toddler Exposure and Risk Assessment

As discussed above, only the treated soil ingestion scenario is the anticipated residential, non-dietary exposure pathway for toddlers, since available residues for dermal transfer from bare ground or rough, hard surfaces, such as driveways, gravel walkways, etc. are anticipated to be lower than the available residues for the recreational use pattern. However, since the short- and intermediate-term endpoints are the same, the short-term assessment is considered to be conservative for intermediate-term soil ingestion exposures. The following assumptions were used to assess the soil ingestion scenario:

- DAT 0 residues are assumed to be available for short-term exposure.
- Toddler body weight: 15 kg.
- 100% of application rate is available in the top 1 cm of soil for soil ingestion exposures.
- A toddler can possibly ingest 100 mg soil/day.

Table 9 presents the assumptions for incidental soil ingestion by toddlers.

Table 9. Exposure and Risk Assessment for Incidental Soil Ingestion (Non-Dietary) by Toddlers Following Application of Imazapyr to Bare Ground Around Homes[1]

Activity	AR[2]	Soil Residue Estimate[3]	PDR (mg/kg bw/day)[4]	Short-term Non-Dietary MOE[5]
Soil Ingestion	0.0056 lb ae/300 ft^2	6.11 µg/g soil	4.07 x 10^{-5}	> 1 x 10^{o}

Notes:
1. Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.
2. AR = maximum application rate on Ortho GroundClear label (EPA Reg. No. 239-2657).
3. Soil residue estimates based on the following protocol from the Residential SOPs: Soil Residue = 0.0056 lb ae/gal x 1 gal/300 ft^2 x 43,560 ft^2/A x fraction of residue in soil (100%)/cm x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) x 0.67 cm^3/g = 6.11 µg/g soil.

4. Potential Dose Rate (PDR; normalized to body weight of toddler) = (6.11µg/g soil x 100 mg soil/day x 10^{-6} g/µg)/15 kg =4.07 x 10^{-5} mg/kg bw/day.
5. MOE = NOAEL/PDR, where the short-term incidental oral NOAEL = 250 mg/kg/day; HED's level of concern is for MOEs < 100 (residential).

The MOEs calculated for incidental soil ingestion exposure by a toddler is greater than 100 and does not exceed HED's level of concern.

4.4.2 Recreational Exposure and Risk Assessment/Characterization

This section discusses the recreational exposure scenarios associated with the registered and proposed uses of imazapyr. These scenarios comprise:

- Registered uses: adult and child golfers, post-application dermal exposures at golf courses and fairgrounds.
- Proposed use: adult and child swimmers, post-application exposures following application to a lake or pond, incidental ingestion and dermal exposures.

Based on the proposed use pattern, it is possible, although unlikely (since swimmers are unlikely to swim in a waterbody where floating weeds are present), that the public may swim in a treated waterbody immediately following an application of Arsenal®. Based on discussions with U.S. Army Corps of Engineers (USACE), and the University of Florida, South Florida Water Management District (SFWMD), the majority of treatments may occur at remote sites. However, since there are no specific prohibitions on the proposed label restricting public access to treated sites, a post-application assessment is included for adults, toddlers, and children swimming in treated waters immediately after application. This is considered to be a conservative assessment.

a. Post-application Golfer Exposure and Risk Assessment

Golfer exposure assumptions are based on HED's ExpoSAC SOP for golfer exposure for adults and children. The exposure assumptions are:

- One round of golf (18 holes) takes 4 hours and average golfer plays 18 times per year, so short-term dermal exposures are anticipated. Inhalation exposures are considered to be negligible since the vapor pressure of imazapyr was reported by the registrant to be < 2 x 10^{-7} mm Hg (vs. HED ExpoSAC vapor pressure threshold of 1 x 10^{-5} mm Hg).
- 5% of the maximum application rate are available as turf transferrable residues (TTR) available on Day 0 (assumes no dissipation).
- TC for dermal exposure: 500 cm^2/hr based on golfers wearing short pants and short-sleeved shirts.
- The exposure estimate for child golfers is 1.7 times the adult exposure estimate to account for differences in body weight and surface area.
- Maximum labeled application rate: 0.0041 lb ae/A broadcast liquid formulation applications.

There are no chemical-specific, post-application exposure data available for imazapyr use on golf courses. In order to assess the potential post-application exposures, an estimate of TTR on Day 0 was used, and this TTR estimate is anticipated to represent the highest potential short-term post-application exposures for the registered use of imazapyr on golf courses (see Table 10 below).

Table 10. Post-Application Golfer Exposure and Risk Assessment for Registered Uses of Imazapyr at Golf Courses

Exposure Scenario	AR[1] (lb ae/A)	TC (cm^2/hr)	TTR[2] (ug/cm^2)	Potential Dermal Exposure (PDE; mg/kg/day)[3]	Short-term Dermal MOE[4]
Adult golfer	0.0041	500	0.00230	6.57×10^{-5}	$>1 \times 10^6$
Child golfer				1.12×10^{-4}	$>1 \times 10^6$

Notes

1. Maximum AR from Event™ (EPA Reg. No. 241-317) containing 0.6% imazapyr; total acid equivalent = 1.46 lb ae/gal. Imazapyr content = 10 fl. oz. product/A x gal/128 oz. x 1.46 lb ae/gal x 0.6/16.9 = 0.0041 lb ae/A.
2. TTR = application rate (lb a.i./A) x 5% available as dislodgeable residue x 4.54E+8 ug/lb x 2.47E-8 A/cm^2.
3. PDE = TTR (ug/cm^2) x TC (cm^2/hr) x 4 hrs/day x 0.001 mg/ug x 1/ BW x %dermal absorption; BW= 70kg for adult golfers; dermal absorption = 100%. DE for child golfers = Adult DE x 1.7 per ExpoSAC's Draft Golfer Policy.
4. MOE = NOAEL/ ADD; short-term dermal NOAEL = 250 mg/kg bw/day. HED's level of concern for recreational dermal exposures is for MOEs < 100.

The MOEs presented for golfer post-application exposures are greater than the 100, and therefore, do not exceed HED's level of concern.

b. Adult and Toddler Post-Application Exposure and Risk Assessment at Fairground Sites

This section presents the post-application exposures to adults and toddlers from use of imazapyr at recreational sites, namely fairgrounds (see registered label: Event™, EPA Reg. No. 241-317). For this scenario, HED assumed that a lawn care operator (LCO) performed a liquid broadcast application to turf at a fairground site at the maximum label rate of 0.0041 lb ae/A. The following paragraphs further summarize the assumptions used in the recreational post-application assessment.

Dermal Exposures (Adults and Toddlers)

The following assumptions were used to assess dermal exposures to adults and toddlers after contact with treated lawns:

- Adult and toddler body weights are 70 kg and 15 kg, respectively.
- 5% of the maximum application rate represents fraction of imazapyr available as dislodgeable foliar residue (DFR) on the day of treatment.

- Dermal TC for adults is 14,500 cm^2/hr and for toddlers, 5,200 cm^2/hr.
- Exposure duration is 2 hours.

Table 11 presents the post-application dermal exposure assumptions and risk estimates for adults and toddlers in the residential setting.

Table 11. Post-Application Dermal Exposure and Risk Assessment for Fairground Sites Treated with Imazapyr[1]

Exposure Scenario	AR (lbs ae/A)[2]	DFR on Day 0 (µg/cm^2)[3]	PDR (mg/kg bw/day)[4]	Short-term Dermal MOE[5]
Adult	0.0041	0.00230	9.53×10^{-4}	260,000
Toddler			1.60×10^{-3}	160,000

Notes:
1. Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.
2. AR = Maximum AR from Event™ (EPA Reg. No. 241-317) containing 0.6% imazapyr; total acid equivalent = 1.46 lb ae/gal. Imazapyr content = 10 fl. oz. product/A x gal/128 oz. x 1.46 lb ae/gal x 0.6/16.9 = 0.0041 lb ae/A.
3. DFR = 0.0041 lb ae/A x 0.05 x (4.54×10^8 µg/lb ai) x (2.47×10^{-8} A/cm^2) = 0.00230 µg/cm^2.
4. PDR = (0.00230 µg/cm^2 x 0.001 mg/µg x TC (cm^2/hr) x 2 hrs/day x % dermal absorption (100%)/BW (70 kg for adults and 15 kg for toddlers). Note: TC for adults, short-term = 14,500 cm^2/hr and TC for toddlers, short-term = 5,200 cm^2/hr.
5. MOE = NOAEL/PDR, where the short-term dermal NOAEL = 250 mg/kg/day. HED's level of concern is for MOEs <100.

All MOEs calculated for post-application dermal exposures are greater than 100 and do not exceed the HED's levels of concern for the respective exposure scenarios.

Hand-to-Mouth Exposure Assessment Assumptions (Toddlers)

Short-term incidental oral exposures by toddlers are anticipated to encompass hand-to-mouth behavior, object-to-mouth behavior (turf mouthing) and ingestion of treated soil. HED believes that incidental "ingestion" of residues on treated turf might occur on a repeated basis as a result of "normal" hand-to-mouth behavior, and thus, a toddler may possibly ingest herbicide that has been applied to the turf, including residues on soil. HED anticipates that toddlers will only experience short-term exposures, since the registered use is for fairgrounds, and infrequent contact is expected.

The following assumptions were used to assess exposures to toddlers after contact with treated turf:

- DAT 0 residues are assumed to be available for the short-term and intermediate-term

exposure durations.

- Toddler body weight: 15 kg.
- Toddler hand surface area is 20 cm^2, and a toddler performs 20 hand-to-mouth events per hour for short-term exposures.
- 5% of application rate represents fraction of imazapyr available for transfer to hands on the day of treatment with a 50% saliva extraction factor for hand-to-mouth exposures.
- For object-to-mouth exposures, 20% of application rate available as dislodgeable residues on the day of treatment, and the "object" area is approximately 25 cm^2.
- 100% of application rate is available in the top 1 cm of soil for soil ingestion exposures. Also, it is assumed that a toddler can ingest 100 mg soil/day.
- Exposure duration: 2 hours per day.

HED's ExpoSAC policy directs assessors to aggregate the risk estimates for incidental oral exposures ingestion exposures by a toddler, as it may be possible for a toddler to perform all of activities in a single day. Thus, Table 12 includes the combined exposure and risk estimates for incidental oral exposures by toddlers.

Table 12. Exposure and Risk Assessment for Incidental Ingestion (Non-Dietary) by Toddlers Following Application of Imazapyr at Fairground Sites[1]

Activity	AR (lbs ae/A)[2]	Residue Estimate[3]	PDR (mg/kg bw/day)[4]	Short-term, Non-Dietary MOE[5]
Hand-to-mouth	0.0041	DFR: 0.00230 µg/cm^2	6.13 x 10^{-5}	>1 x 10^6
Object-to-mouth		DFR: 0.00920 µg/cm^2	1.53 x 10^{-5}	>1 x 10^7
Soil Ingestion		Soil residue: 0.0308 µg/g soil	2.05 x 10^{-7}	>1 x 10^9
Combined incidental ingestion exposure	---	---	7.68 x 10^{-5}	>1 x 10^6

Notes:

1. Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for Residential Exposure.
2. AR = Maximum AR from Event™ (EPA Reg. No. 241-317) containing 0.6% imazapyr; total acid equivalent = 1.46 lb ae/gal. Imazapyr content = 10 fl. oz. product/A x gal/128 oz. x 1.46 lb ae/gal x 0.6/16.9 = 0.0041 lb ae/A.
3. Residue estimates based on the following protocol from the Residential SOPs:
   a. Hand-to-mouth DFR = 0.0041 lb ai/A x 0.05 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 0.00230µg/cm^2.
   b. Object-to-mouth DFR = 0.0041lb ai/A x 0.20 x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) = 0.00920 µg/cm^2.
   c. Soil Residue = 0.0041lb ai/A x fraction of residue in soil (100%)/cm x (4.54 x 10^8 µg/lb ai) x (2.47 x 10^{-8} A/cm^2) x 0.67 cm^3/g= 0.0308 µg/g soil.
4. Potential Dose Rate (PDR; normalized to body weight of toddler):

a. Short-term Hand-to-mouth PDR = (0.00230 µg/cm^2 x 0.50 x 20 cm^2/event x 20 events/hr x 10^{-3} mg/µg x 2 hrs/day)/15 kg = 6.13 x 10^{-5} mg/kg bw/day.
b. Object-to-mouth PDR = (0.00920 µg/cm^2 x 25 cm^2/day x 10^{-3} mg/µg)/15 kg = 1.53 x 10^{-5} mg/kg bw/day.
c. Soil Ingestion PDR = (0.0308µg/g soil x 100 mg soil/day x 10^{-6} g/µg)/15 kg = 2.05 x 10^{-7} mg/kg bw/day.

7. MOE = NOAEL/PDR, where the short-term incidental oral NOAEL = 250 mg/kg/day; HED's level of concern is for MOEs < 100 (residential).

The MOEs calculated for incidental ingestion exposures by a toddler are negligible and do not exceed HED's level of concern. The MOE for the combination of incidental ingestion exposures by toddlers is > 1 x 10^6 and does not exceed HED's level of concern.

Aggregate Recreational Toddler Exposure

HED's ExpoSAC policy directs assessors to aggregate the exposure estimates for the hand-to-mouth ingestion, object-to-mouth ingestion, soil ingestion and dermal exposures by a toddler, since it may be possible for a toddler to perform all of these incidental ingestion activities and receive dermal exposure from a treated lawn in a single day. Since the short-term incidental oral and dermal endpoints are based on the same toxicological study and effects, these exposures can be combined per HIARC to estimate aggregate risk. As such, Table 13 presents the aggregate risk of the combination of the short-term incidental ingestion and dermal exposures for toddlers at fairground sites.

Table 13. Aggregate Risk Estimate for Short-term Incidental Ingestion and Dermal Exposures by Toddlers following Application of Imazapyr at Fairground Sites

Exposure	PDR (mg/kg bw/day)	Short-term MOE
hand-to-mouth ingestion	6.13 x 10^{-5}	>1x 10^6
object-to-mouth ingestion	1.53 x 10^{-5}	>1 x 10^7
soil ingestion	2.05 x 10^{-7}	>1 x 10^9
dermal	1.60 x 10^{-3}	160,000
Combined short-term incidental oral and dermal exposures[1]	1.68 x 10^{-3}	150,000

Notes:
1. MOE for combined short-term incidental oral and dermal exposures = $1/(1/MOE^{hand\text{-}to\text{-}mouth} + 1/MOE^{object\ to\ mouth} + 1/MOE^{soil\ ingestion} + 1/MOE^{dermal})$.
2. HED's level of concern is for MOEs < 100 (residential).

The aggregate MOE for short-term post-application incidental ingestion and dermal exposures by toddlers is 150,000 and does not exceed the HED's levels of concern (for MOEs <100).

c. Post-application Swimmer Exposure and Risk Assessment

As discussed earlier, a post-application assessment is included for adults, toddlers, and children swimming in treated waters immediately after an application, since the proposed label does not prohibit swimming in treated waters. The registrant submitted a field dissipation study using Arsenal® (MRID: 45119707) applied at a rate of 1.6 lb ae/A. At four test sites (Florida and Missouri), the highest imazapyr concentration observed was approximately 196 ppb in Missouri; however, at the Florida sites, the EFED noted that the initial concentrations of imazapyr were only about one-third of the amount applied. Accounting for this observation, the highest imazapyr concentration could have approached 500 ppb. Therefore, HED estimated a worst-case concentration for imazapyr in the top one-foot of the water column in a treated waterbody; this peak estimate is 550 ppb and is anticipated to be conservative.

The exposure assumptions used in the swimmer assessment are based on HED's SOP for Residential Exposure Assessments, Draft, December 17, 1997 and HED's SWIMODEL V 1.0 (W. Dang and Versar, 27-MAR-1999) for swimming pools adapted for this assessment. It should be noted that the Residential SOP/SWIMODEL assumptions are considered to be conservative for use in assessing the lake/pond swimmer scenario as explained in Table 14.

Table 14. Comparison of Assumptions for Post-Application Swimmer Exposure Assessments for Imazapyr

Assumption	Residential SOP for Swimmers in Pools	Arsenal® Application: Post-Application at Aquatic Sites
Post-application concentration	100% available concentration post-application	Maximum imazapyr concentration in top one-foot of water column is approx. 550 ppb. Assuming 100% available is considered conservative.
Subsequent post-application	Assumed not to dissipate	Exposed foliage is the intended target of treatments. Any spray entering water column is anticipated to dissipate.
Duration of exposure	5 hours for competitive adult 2 hours for non-competitive child	2 hours assumed, since floating or emerged weeds will be present making competitive swimming (training) very difficult
Inhalation exposure	Assumed for pool swimmers	No significant inhalation exposure is anticipated. An inhalation assessment is not included.

Based on the above qualifiers, the assumptions used in the swimmer assessment are summarized below:

Incidental Ingestion by Swimmers

- The worst-case estimate of imazapyr in the top one-foot of the water column in a treated waterbody is 550 ppb. Assume that 100% of this concentration is available for ingestion.
- Ingestion rate: 0.05 L/hr.
- Exposure duration: 2 hrs/day for non-competitive adult and child swimmers.
- Body weight: 70 kg for adults, 29 kg for children (mean figure from SWIMODEL) and 15 kg for toddlers.

Dermal Exposure by Swimmers

- Same assumption on water concentration as above: 550 ppb.
- Body surface area: 20,670 cm^2 for adult and 14,580 cm^2 for toddler/child swimmers (mean figures from SWIMODEL).
- Exposure duration: 2 hrs/day for non-competitive adult and toddler/child swimmers.
- Permeability coefficient (K_p): 5.85 x 10^{-5} cm/hr (where K_{ow} = 1.3 {MRID 45119707}, molecular weight of imazapyr acid = 261.3).
- Body weight: 70 kg for adults, 29 kg for child swimmers (mean from SWIMODEL), 15 kg for toddlers.

Table 15 presents the risk estimates for post-application exposures by swimmers.

Table 15. Post-Application Swimmer Exposure and Risk Assessments for Proposed Use of Imazapyr at Aquatic Sites

Exposure Scenario	AR (lb ae/A)	Concentration in water (ppb)	Potential Dose Rate (PDR; oral) [1] or Absorbed Dose Rate (ADR; dermal) [2] (mg/kg/day)	Short-term MOE[3]
Incidental Ingestion, adult	1.5	550 (0.55 mg/L)	7.86×10^{-4}	320,000
Incidental Ingestion, child			1.90×10^{-3}	130,000
Incidental Ingestion, toddler			3.67×10^{-3}	68,000
Dermal, adult			1.90×10^{-5}	$> 1 \times 10^{7}$
Dermal, child			3.24×10^{-5}	$> 1 \times 10^{6}$
Dermal, toddler			6.26×10^{-5}	$> 1 \times 10^{6}$

Notes

1. PDR, incidental oral ingestion = concentration, C_w (mg/L) x ingestion rate, IgR (L/hr) x exposure time, ET (hrs/day) x 1/BW (adult=70 kg; child = 29 kg; toddler = 15 kg)
2. ADR= concentration, C_w (mg/L) x dermal surface area exposed, SA (cm^2) x ET x K_p (cm/hr) x 1/1000 cm^3 x %Dermal Absorption (correct to oral equivalent) x 1/BW, where K_p is estimated as follows: log K_p = -2.72 +0.71log K_{ow} - 0.0061MW; K_{ow} =1.3 , MW = 261.3, so $K_p = 5.85 \times 10^{-5}$ cm/hr.
3. MOE = NOAEL/PDR; short-term incidental oral NOAEL = 250 mg/kg/day short-term dermal NOAEL =250 mg/kg bw/day. The level of concern for short-term recreational exposures is for MOEs < 100.

The MOEs presented in Table 15 representing post-application exposure to imazapyr in aquatic weed control applications are greater than 100, and therefore, do not exceed HED's level of concern for short-term recreational exposures.

4.4.3 Non-occupational Off-Target Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce

off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following scenarios: short-term aggregate exposure (food + drinking water + residential), and chronic aggregate exposure (food + drinking water). An acute-dietary exposure assessment was not performed because there were no toxic effects of concern attributable to a single dose. Thus, an endpoint of concern was not identified to quantitate acute-dietary risk to the general population or to any population subgroup. Intermediate- and long-term aggregate risk assessments were not performed because, based on the current use patterns of imazapyr, HED does not expect exposure durations that would result in intermediate- or long-term exposures. A cancer aggregate risk assessment was not performed because imazapyr is classified as a Group E chemical , "not likely to be carcinogenic". All potential exposure pathways were assessed in the aggregate risk assessment. Dietary (food and drinking water), handler and post-application residential exposures were considered, as necessary, because there is a potential for individuals to be exposed concurrently through these routes.

Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID™) were subtracted from the PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (US Population, adult male), 60 kg/2L (adult female, and youth), and 10kg/1L (infants and children).

For acute and chronic dietary exposure, HED is concerned when estimated dietary risk exceeds 100% of the aPAD and cPAD, respectively. HED's level of concern for residential oral, dermal and inhalation exposures for imazapyr are for MOEs <100. For imazapyr, short-term oral, dermal and inhalation exposures estimates can be aggregated due to the use of oral equivalents and a common toxicity endpoint (skeletal muscle effects).

5.1 Short-Term Aggregate Risk Assessment

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to imazapyr residues from food, drinking water, and residential pesticide uses. High-end estimates of the non-occupational exposure are used in the short-term assessment, and average values are

used for food and drinking water exposures.

Short-term aggregate risk assessments are required for adults as there is potential for both dermal and inhalation handler exposure, and dermal post-application exposure from the residential and recreational uses of imazapyr on turf and swimmer exposure. In addition, short-term aggregate risk assessments are required for children and toddlers because there is a potential for oral and dermal, post-application exposure resulting from the residential uses of imazapyr on turf and from swimming.

The short-term residential handler scenario results in the highest exposure for adults. This scenario combines the exposure via the dermal and inhalation routes for homeowners mixing, and applying imazapyr to turf (see Table 8). Since the homeowner use of imazapyr is a spot treatment, no post-application exposure is expected for the spot applications and therefore was not combined with the handler exposures. HED's ExpoSAC directs that when combining non-occupational exposures, only those scenarios which have a high likelihood of co-occurrence should be aggregated. Since it is unlikely that an adult would apply imazapyr as a spot treatment, swim in imazapyr treated waters, and be dermally exposed to imazapyr treated golf courses or fairgrounds concurrently, these scenarios were not combined. Rather, for adults, the homeowner handler scenario was aggregated with the chronic dietary food exposure for the U.S. General population (highest estimated chronic dietary food exposure) (see Table 16).

The short-term non-occupational exposure potential from residential, recreational, and aquatic uses for children and toddlers can be found in Tables 9-15 The swimmer scenario resulted in the highest exposure for toddlers and children. The turf-treatment scenarios resulted in lower post-application exposures for both toddlers and children. Therefore, the swimmer scenario exposure estimates were aggregated with the chronic dietary (food) to provide a worst-case estimate of short-term aggregate risk for children 1-2 years old (the child population subgroup with the highest estimated chronic dietary food exposure)(see Table 16).

As the MOEs are greater than 100, the short-term aggregate risks are below HED's level of concern. For surface and ground water, the estimated average concentrations of imazapyr are less than HED's calculated DWLOCs for imazapyr in drinking water as a contribution to short-term aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of imazapyr in drinking water do not contribute significantly to the short-term aggregate human health risk at the present time.

Table 16. Short-Term Aggregate Risk Assessment for Imazapyr.

Population Subgroups	Short-Term Scenario									
	NOAEL (mg/kg/day)	Level of Concern[1]	Max Exposure[2] (mg/kg/day)	Average Food Exposure (mg/kg/day)	Residential Exposure [3] (mg/kg/day)	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] (mg/kg/day)	Ground Water EEC[6] (ug/L)	Surface Water EEC[6] (ug/L)	Short-Term DWLOC[7] (µg/L)
US Population	250	100	2.5	0.00034	0.00296	75000	2.496	1700	81	87000
Children 1-2 years old	250	100	2.5	0.000828	0.0037	55000	2.495	1700	81	25000

[1] The level of concern (target MOE) includes 10X for interspecies extrapolation and 10X for intraspecies variation (MOE < 100).
[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
[3] Adult Residential/Recreational Exposure = [Dermal Exposure + Inhalation Exposure] resulting from the residential homeowner handler scenario (see Table 8). Toddler and Child Residential/Recreational Exposure = [Oral Exposure + Dermal Exposure], resulting from the recreational swimmer scenario (see Table 15).
[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]
[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)
[6] The crop producing the highest level was used.
[7] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

5.2 Chronic Aggregate Risk Assessment

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of imazapyr (food and drinking water) and residential uses. However, due to the use patterns, no chronic non-occupational exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only.

The Tier 1 [deterministic assessment using tolerance-level residues, 100% crop treated assumptions, and DEEM default processing factors] chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at <1% of the cPAD. The Tier 1 EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to imazapyr in drinking water. Therefore, the chronic aggregate risk associated with the proposed uses of imazapyr do not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 17 summarizes the chronic aggregate exposure estimates to imazapyr residues.

Table 17. Chronic Aggregate Risk Assessment for Imazapyr.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Ground Water EEC[2] (µg/L)	Surface Water EEC[2] (µg/L)	Chronic DWLOC[3] (µg/L)
U.S. Population	2.5	0.00034	2.499	1700	81	87000
All infants (< 1 year old)	2.5	0.000273	2.499	1700	81	25000
Children (1-2 years old)	2.5	0.000828	2.499	1700	81	25000
Children (3-5 years old)	2.5	0.00073	2.499	1700	81	25000
Children (6-12 years old)	2.5	0.000499	2.499	1700	81	75000
Youth (13-19 years old)	2.5	0.000309	2.499	1700	81	75000
Adults (20-49 years old)	2.5	0.000267	2.499	1700	81	87000
Females (13-49 years old)	2.5	0.000257	2.499	1700	81	87000
Adults (50+ years old)	2.5	0.000287	2.499	1700	81	87000

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)
[2] The crop producing the highest level was used.
[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{\left(\text{maximium water exposure (mg / kg / day)}\right) * \left(\text{body weight (kg)}\right) * \left(1000\ \mu\text{g / mg}\right)}{\text{water consumption (liter / day)}}$$

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA 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."

EPA does not have, at this time, available data to determine whether imazapyr has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to imazapyr and any other substances and imazapyr does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that imazapyr has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE

Based on the proposed use patterns for this action, commercial handlers are anticipated to have short-term dermal and inhalation exposures. Additionally, workers entering treated sites could potentially have short-term dermal exposures. Short-term handler and worker exposures are anticipated based on information provided by the USACE and SFWMD, which indicate that most applications to be one-time applications. In cases where multiple applications are planned, USACE and SFWMD envision two split treatments at the 0.75 lb ae/A for a total of 1.5 lb ae/A/yr maximum rate (electronic communication from K. Getsinger, USACE to RD, 29-MAR-2003). However, since the short-, intermediate, and long-term dermal and inhalation endpoints are the same, the short-term assessment is considered to be conservative all durations of occupational exposures.

a. Overview of Proposed Uses

Aquatic Weed Control

The following information provides an overview of the proposed use patterns for imazapyr in aquatic weed control from the following sources:

- Informational meeting with U.S. Army Corps of Engineers (USACE), University of Florida, South Florida Water Management District (SFWMD), and USDA-Agricultural Research Service (CA) on Aquatic Weed Control, August 17, 2001.

The USACE, Univ. of Florida, and SFWMD are members of the Federal Aquatic Herbicide Working Group. Most weed control boat applications involve approximately 2 - 3 acres per day, where 10 acres per day is the upper range anticipated for boat applications for maintenance programs (see RAB1 memo for triclopyr use in aquatic weed control [22-JUL-2002, D269448] for more background on aquatic weed control discussed in this meeting).

- Informational meeting with BASF, USACE, University of Florida, SFWMD, and University of Washington on imazapyr proposed uses,
  January 29, 2003.

The SFWMD envisions imazapyr to be used in the Everglades Restoration, particularly in Lake Okeechobee for melaleuca and torpedograss control. (Please see the *Melaleuca Management Plan*, Florida Exotic Pest Plant Council, May 1999 for more details on melaleuca management in South Florida. Imazapyr use is discussed in this document.) Melaleuca control programs typically involve aerial applications via helicopter followed by frill and girdle treatments via machete and backpack sprayer. One aerial application per treatment area is envisioned by SFWMD. Crews also use chain saws to fell trees followed by stump and cut end treatment via hand-gunner from airboats. Aerial applicators could potentially treat up to 400 acres per day. Torpedograss control typically involves prescribed burns followed by aerial applications. The USACE discussed the use of imazapyr for phragmites control along the Atlantic and Gulf coasts as well as the Great Lakes. Anticipated

spray equipment includes all-terrain vehicles (ATV's) equipped with spraybooms applying up to 3 pints/A (0.75 lb ae/A) Arsenal® followed by a prescribed burn.

The University of Washington discussed the use of Arsenal® for spartina control in Willapa Bay, Puget Sound and San Francisco Bay using airboats, ATV's and backpack sprayers. Treatment via airboat is anticipated to reach upwards of 5 acres/day.

Spot Treatment on Pasture and Rangeland

The registrant also proposes to use imazapyr for control of undesirable vegetation in grass pasture and rangeland. The proposed label language indicates that spot treatment would involve 1/10 of an acre, although the registrant also proposed an application rate range from 2 to 48 fl. oz. per acre. The resulting maximum single application rate equates to 0.075 lb ae/0.1 A. Note that the registrant indicated to RD that they do not intend to exceed the 1.5 lb ae/A-yr (or 0.15 lb ae/0.1A/yr) maximum application rate. As such, the proposed application rate for spot treatment on pasture and rangeland would allow for 2 applications on a given 0.1 acre plot. However, this application information is not clearly stated on the proposed label.

Note to RD: HED recommends that the registrant clarify the single-application rate maximum and the maximum annual application rate for spot treatment on pasture/rangeland in the proposed label.

b. Occupational Handler Exposure Assumptions and Risk Assessment

No chemical-specific data were available to assess potential exposures to handlers from the proposed uses. However, application-specific data was available from a study conducted by G.A. Wojeck *et al.* (1983) regarding worker exposure to diquat dibromide used for aquatic weed control. The exposure data from this study were used in the re-registration eligibility document (RED) for diquat dibromide completed in July 1995. Although the boat-based application scenarios described in this study are very similar to the proposed uses of imazapyr, specific exposure data from the Wojeck study were not used in this assessment, because no inhalation exposure data were available from this study. However, qualitative exposure comparisons in this study are useful for characterizations as discussed below. In summary, this exposure assessment was conducted using dermal and inhalation unit exposure data available in the Pesticide Handler's Exposure Database (PHED) Surrogate Table (v1.1., 1998).

Based on the above background information, the following exposure scenarios are anticipated:

- Mixer/loader supporting aerial (helicopter), boat, and ground applications at aquatic sites.
- Aerial, boat or ground applicator.
- Boat driver.
- Backpack sprayer, mixer/loader/applicator (MLAP; see discussion below).

Flagger scenarios are not anticipated since it appears to be impractical to use flaggers in an aquatic

setting, and due to the widespread use of global positioning system (GPS) devices (per discussions with aquatic herbicide specialists). Specific acreage treated daily by aquatic field crews are based on discussions with USACE and SFWMD presented above, except for the backpack sprayer assessment, where default assumptions from HED's ExpoSAC SOP were used. Additionally, according to the Wojeck *et al.* study, applicators conducting surface weed control received approximately 9 times the estimated total body exposure as compared to boat drivers. Thus, for this assessment, only the boat-based applicator was included. The occupational handler scenarios included in this assessment are further characterized below:

- Mixer/loader supporting aerial applications.
  Explanation: Aerial applications are anticipated to treat higher acreage than ground or boat applications, based on discussions with the USACE and SFWMD. For this assessment, it is assumed that 400 acres could be treated per day, based on anticipated restoration treatments for melaleuca control.

- Mixer/loader and applicator supporting boat-based applications.
  Explanation: The proposed label specifies a maximum label rate of 1.5 lb ae/A for floating and immersed weed control. It is assumed that a boat applicator could treat up to approximately 10 acres/day based on discussions with the USACE and SFWMD. Acres treated via ATV are anticipated to be on-par or just below boat-based application.

- Boat- and truck-based handgun applicators conducting surface and wetland weed control.
  Explanation: Open boat applicators are expected to have to a higher exposure than aerial applicators in open cockpits. HED assumed that a handgun applicator could treat up to approximately 10 acres/day based on discussions with the USACE and SFWMD.

- MLAP, backpack sprayer conducting frill or girdle treatments for melaleuca control using concentrated solutions.
  Explanation: Note that applicators using backpack sprayers conducting frill or girdle treatments are anticipated to have higher exposures than applicators conducting spot treatment at pasture/rangeland sites, since the maximum application rate using concentrated solutions is higher than the rate proposed for pasture/rangeland sites.

Note on HED's ExpoSAC MLAP SOP: HED's policy concerning MLAPs performing ground applications directs that exposure and risk estimates for mixer/loaders and applicators for tractor-drawn equipment remain separate due to the conservative nature of the data in PHED, while the exposure and risk estimates for handheld equipment (e.g., backpack sprayers) be combined.

Table 18 presents the assumptions used in the handler assessments and corresponding risk estimates for proposed uses of imazapyr.

Table 18. Handler Exposure Assumptions and Risk Assessment for Proposed Uses of Imazapyr

Exposure Scenario	Unit Exposure[1] (mg/lb ae handled)	AR[2] (lbs ae/A, unless specified)	Acres/day[3] (unless specified)	Potential Daily Dose[4] (PDD; mg/kg bw/day)	Combined Short-term MOE[5]
Mixer/loader: liquid, open pour, supporting aerial application (by helicopter).	dermal: S/L w/o gloves[6]: 2.9 (HC) S/L w/gloves[6]: 0.023 (HC)	1.5	400	dermal: w/o gloves: 24.9 w/gloves: 0.197	w/o gloves: **10** w/gloves: 1,200
	inhalation: 0.0012 (HC)			inhalation: 0.0103	
Mixer/loader: liquid, open pour, supporting boat application	dermal: S/L w/o gloves: 2.9 (HC) S/L w/gloves[6]: 0.023 (HC)		10	dermal: w/o gloves: 0.621 w/gloves: 0.00493	w/o gloves: 400 w/gloves: 48,000
	inhalation: 0.0012 (HC)			inhalation: 2.57×10^{-4}	
Applicator: handwand from boat, truck or ATV	dermal: S/L w/o gloves: 1.3 (LC) S/L w/o gloves: 0.39 (LC)		10	dermal: w/o gloves: 0.279 w/gloves: 0.0836	w/o gloves: 890 w/gloves: 3,000
	inhalation: 0.0039 (HC)			inhalation: 8.36×10^{-4}	

Table 18. Handler Exposure Assumptions and Risk Assessment for Proposed Uses of Imazapyr

Exposure Scenario	Unit Exposure[1] (mg/lb ae handled)	AR[2] (lbs ae/A, unless specified)	Acres/day[3] (unless specified)	Potential Daily Dose[4] (PDD; mg/kg bw/day)	Combined Short-term MOE[5]
MLAP: backpack sprayer, girdle treatments, concentrated solution	dermal: S/L w/ gloves: 2.5 (LC); no w/o gloves data available	1.33 lb ae/gal conc. soln.	40 gal/day	dermal, w/gloves: 1.89	w/gloves: 130
	inhalation: 0.030 (LC)			inhalation: 0.0227	

Notes:

1. Source: PHED Surrogate Exposure Table (v1.1., 1998). SL = single layer of clothing, without or with waterproof gloves. (HC) = high confidence data; (LC) = low confidence data; unit exposures for boat-based handwand applicators adopted from high-pressure handwand scenario in PHED for use in this assessment.
2. AR = Maximum application rate. Note: For MLAP backpack sprayer, application rate was based on: 40 gal/day x 2 qt Arsenal/3 qt solution x 2 lb ae/gal Arsenal = 53.3 lb ae/day.
3. Daily acres treated based on discussions with USACE and SFWMD for aerial and boat-based applications. Daily amount handled for backpack sprayer from Exposure SAC Policy No. 9, July 5, 2000.
4. Potential Daily Dose (PDD) = Unit exposure(mg/lb ai) x AR x Acres/day x 1/BW (70 kg) x %Absorption (100% dermal absorption and 100% inhalation absorption rate to convert to oral equivalents per HIARC). Combined PDD = PDD_{dermal} + $PDD_{inhalation}$.
5. MOE = NOAEL/ADD; short-term dermal and inhalation NOAELs based on Oral NOAEL = 250 mg/kg/day. HED's level of concern is for MOEs < 100 (occupational), so MOE is expressed as combination of dermal and inhalation risk.
6. S/L w/o gloves: single layer of clothing without gloves; S/L w/ gloves: single layer of clothing with gloves.

As shown in Table 18, all MOEs are above 100 and do not exceed HED's level of concern when handlers wear gloves. (Note that HED does not have "no glove" unit exposure data in PHED for backpack sprayers, so the "with gloves scenario was assessed.) However, it should be noted that the dermal exposure estimates are based on a 100% dermal absorption rate. Therefore, this assessment is considered conservative.

Note to PM: HED recommends that the label required PPE for handlers include the addition of waterproof gloves.

c. Post-Application Occupational Exposures and Risk Assessment

As discussed previously, personnel entering wetland sites and pasture/rangeland following applications could potentially have short-term dermal exposures. No post-application exposure is anticipated from floating or immersed weed control treatments. Post-application inhalation exposures are anticipated to be negligible given that the vapor pressure of imazapyr technical is $< 2 \times 10^{-7}$ mm Hg.

No chemical-specific, post-application worker studies have been submitted by the registrant. As such, standard HED post-application assumptions were used to provide an estimate of post-application exposure risks to workers. Specifically, the residue transfer coefficients (TCs) used in this assessment are from an interim TC policy developed by HED's ExpoSAC using proprietary data from the Agricultural Re-entry Task Force (ARTF) database. It is the intention of HED's ExpoSAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. The assumptions for this assessment are as follows:

- Maximum application rate: 1.5 lb ae/A.
- 20% of the maximum application rate are available as dislodgeable foliar residues (DFR) available on Day 0 of treatment.
- Re-entry into treated wetland sites is anticipated to result in higher post-application dermal exposure than re-entry into treated pasture/rangeland. A TC of 1,500 cm^2/hour based on scouting in rice fields (Central value from ARF021) with full foliage development is used for this exposure assessment.
  Explanation: Note that there is no post-application data for post-application entry into treated wetland sites in ExpoSAC TC Policy, therefore, a surrogate scenario was selected from available data and adapted for this scenario (re-entry into treated wetland sites).
- Work day of 8 hours.

Table 19 presents the results of the post-application assessment for re-entry into treated wetland sites.

Table 19. Post-Application Worker Exposure and Risk Assessment for Proposed Use of Imazapyr in Wetlands

Exposure Scenario	AR (lb ae/A)	DFR[1] (ug/cm^2)	TC (cm^2/hr)	ADD[2] (mg/kg/day)	Short-term Dermal MOE[3]
Re-entry into treated areas	1.5 lb ae/A	3.36	1,500	0.576	430

Notes
1. Surrogate DFR on Day 0 (no dissipation) = application rate (lb ae/A) x 20% available as dislodgeable residue x 4.54E8 ug/lb x 2.47E-8 A/cm^2. Ex. calc = 1.5 lb ae/A x 0.20 x 4.54E8 ug/lb x 2.47E-8 A/cm^2 = 3.36 µg/cm^2.
2. ADD =DFR (3.36 ug/cm^2) x TC (1,500 cm^2/hr) x 8 hrs/day x 0.001 mg/ug x 1/ BW x %dermal absorption; BW= 70kg for adults; dermal absorption = 100%.
3. MOE = NOAEL/ ADD; short-term dermal NOAEL = 250 mg/kg bw/day. The level of concern is for MOEs < 100 (occupational).

The MOE for workers entering treated sites is 430 and does not exceed HED's level of concern for occupational exposures (MOEs <100).

d. REI

The REI on the parent label is 12 hours, however, imazapyr is Toxicity Category I for primary eye irritation. Under the WPS (40 CFR Part 170), a 48-hour interim REI is required for an active ingredient that has an acute toxicity of Category I.

Note to PM: HED recommends that RD amend the REI of 12 hours on the parent label to an REI of 48 hours, based on WPS requirements and for added protection against adverse eye effects.

7.3 Incidents

A review of all incident data available in REFS (13-MAR-2003) revealed approximately 3 records (for a total of 8 incidents) involving humans. Seven of the incidents (from Record Nos. I011766 and I013322) were related to imazapyr, but it was not clear if the symptoms were directly related to imazapyr exposure. The eighth incident (from Record No. I011801) related to alleged spray drift exposure; however, the product referenced was a multiple, active-ingredient product, so it is not apparent if the symptoms were related to imazapyr exposure *per se*. It should be noted that a search of the incident data under the "definite, probable, or possible" certainty categories in REFS did not reveal any incident records for imazapyr.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Revised Section B.
- Revised Section F.

- Successful Agency validation of the analytical method.
- Fish metabolism study.
- Corn or grass storage stability information or study.
- Additional spray additive information supporting the grass field trials.

8.2 Toxicology

- The HED HIARC requested a 28-day inhalation toxicity study as a condition of registration. However, based on the low volatility and low inhalation toxicity (Category IV) of imazapyr and inhalation MOEs >1000 for the proposed uses in this risk assessment, imazapyr qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses [SOP 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02]. **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

- According to the 1995 CPRC , a data gap for a test for other genotoxic effects was identified and was required to be filled (based on the pre-1991 guideline). If the registrant wants to fulfill the data gap based on the current (post-1991 guideline), an *in vivo* cytogenetics assay using rodent bone marrow would satisfy the requirement. **The HIARC had no comment on this and did not identify any other data gaps.**

8.3 Occupational/Residential

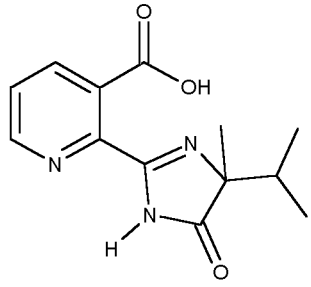
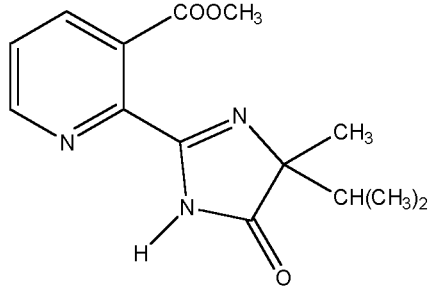
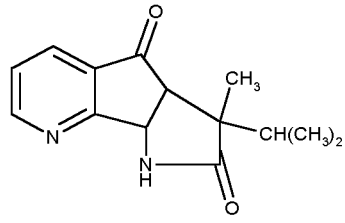
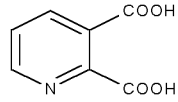
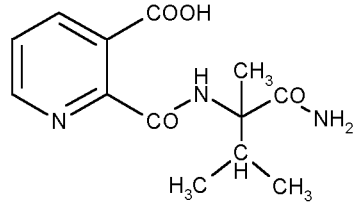
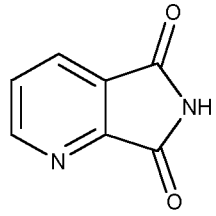
- Revised Section F (see *Note to PM* on pages 46, 50, and 51).

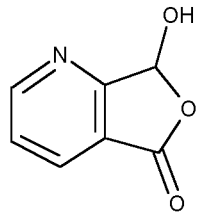
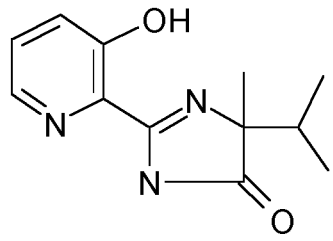
9.0 ATTACHMENTS

Attachment 1. Summary of Metabolites Discussed in Risk Assessment.

cc: D.Vogel and K.Whitby (RAB1).
RDI: RAB1 (7/9/03), K.Whitby (7/17/03).
D.Vogel 809B: CM#2: (703)305-0874: 7509C: RAB1

ATTACHMENT 1. Summary of Metabolites Discussed in Risk Assessment.

Metabolite Identifier	Chemical Name [matrix where found]	Structure
Imazapyr (AC 243997)	2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl) nicotinic acid [grass, fish, goat milk and kidney, rotational crops, rat, water; field corn forage, fodder, and grain |	
CL 240000	2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-methyl ester nicotinic acid [grass, water]	
CL 247087	5*H*-imidazol[1',2':1,2]pyrrolo [3,4-b]pyridine-2(3*H*), 5-dione, 1,9*b* α(&β)-dihydro-3α-isopropyl-3-methyl] [grass, rotational crops|	
CL 9140	2,3-pyridinedicarboxylic acid [grass, water; field corn forage, fodder, and grain|	
CL 252974	2-[(1-carbamoyl-1,2-dimethylpropyl)-carbamoyl]-nicotinic acid [rotational crops, rat, water; field corn forage, fodder, and grain]	
CL 17226	Quinolinimide [rotational crops]	

Metabolite Identifier	Chemical Name [matrix where found]	Structure
CL 119060	7-hydroxyfuro[3,4-*b*]pyridin-5(7*H*)-one [rotational crops, water]	
CL 60032	2-carbamoyl-nicotinic acid [rat; field corn forage, fodder, and grain]	
CL 288247	2-[4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl]-3-hydroxy pyridine [water]	
Nicotinic acid	Pyridine 3-carboxylic acid [water]