014653

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 01-AUG-2001

SUBJECT: PP# 9F05092. **IMAZAPIC IN/ON PASTURES AND RANGELAND. HED Risk Assessment.**
Barcode D267227. PC Codes 128943 & 129041. Case 290787. Submission S576934.

FROM: William G. Dykstra, Ph.D., Toxicologist
William H. Donovan, Ph.D., Chemist
Mark Dow, Ph.D., Biologist
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509C)

THROUGH: G. Jeffrey Herndon, Branch Senior Scientist
RAB1/HED (7509C)

TO: Jim Tompkins, PM Team 05
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate 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 imazapic in/on pastures and rangeland.

A summary of the findings and an assessment of human risk resulting from the proposed uses of imazapic is provided in this document. The risk assessment and hazard characterization were provided by William Dykstra of the Registration Action Branch 1 (RAB1), the residue chemistry data review and the dietary risk assessment by William Donovan, the occupational/residential exposure assessment by Mark Dow (RAB1), and the drinking water assessment by James Wolf of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that revised Sections B and F are submitted and that successful Agency validation of the analytical method is reported, the chemistry and toxicological databases support the following permanent tolerances for residues of imazapic [(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid] and its metabolite (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-hydroxymethyl-3-pyridinecarboxylic acid both free [CL 263284] and conjugated [CL 189215] in/on:

Grass, forage	30 ppm
Grass, hay	15 ppm

In addition, provided the conditions listed above are satisfied, the databases support the following permanent tolerances for residues of imazapic and its metabolite CL 263284 in/on the commodities listed below:

Milk	0.10 ppm
Meat*	0.10 ppm
Fat*	0.10 ppm
Meat byproducts (except kidney)*	0.10 ppm
Kidney*	1.0 ppm

* Of cattle, goats, horses, and sheep

However, registration of Plateau™ Herbicide for use on pastures and rangeland should be made conditional upon the submission of additional chemistry and toxicological data as specified below. Registration of Plateau™ DG Herbicide for use on pastures and rangeland should be delayed until the petitioner has submitted the requested field trial data supporting its use.

Chemistry

- Four additional grass field trials reflecting a single postemergence application of the 2 lb acid equivalence (ae)/gal ammonium salt SC formulation at 0.1875 lb ae/A, preferably in Regions 7 and 8.

- Additional rotational crop data or a revised Section B with updated rotational crop intervals for rye, wheat, and legume vegetables.

- Successful petition method validation (PMV) of the analytical enforcement method.

PLUS

- Nine grass field trials reflecting a single postemergence application of the 0.0625 lb ai/packet WDG acid formulation at 0.1875 lb ae/A.

OR

- Four side-by-side maximum rate grass field trials using the ammonium salt SC and WDG acid formulations.

Toxicology

- 28-day inhalation toxicity study (OPPTS Guideline No. 870.3465) [The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline No. 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.] This 28-day inhalation study will provide a basis from which to determine more reliable route-specific Margins of Exposure (MOEs) for worker inhalation risks rather than the less reliable route-to-route MOE calculations currently being used.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Imazapic is an imidazolinone herbicide which is currently registered for use on peanuts. The current petition is for use of imazapic on pasture grass and rangeland. There currently are no residential uses. The herbicidal activity of imazapic, as an imidazolinone, is due to the inhibition of acetohydroxyacid synthetase, which is a key plant enzyme in the biosynthesis of the amino acids leucine, isoleucine, and valine. Animals lack this biosynthetic pathway and must obtain these amino acids from their diet. The fact that the herbicidal mode of action of imazapic is through inhibition of a biosynthetic pathway not present in humans and livestock is one of the factors contributing to the low toxicity of imazapic to animals.

Hazard Assessment

The acute toxicity data for imazapic show that this chemical is not acutely toxic by the oral, inhalation, or dermal routes of exposure (Toxicity Categories IV). It is minimally irritating to the eye (Toxicity Category III) and non-irritating to the skin (Toxicity Category IV). Additionally, imazapic is not a dermal sensitizer.

There were no toxic effects up to the limit dose in the subchronic oral toxicity study in rats, the subchronic dermal toxicity study in rabbits, the developmental toxicity study in rats, the chronic toxicity/carcinogenicity feeding study in rats, the carcinogenicity feeding study in mice, and the 2-generation reproduction toxicity study in rats. The mutagenic potential was negative in a acceptable battery of studies. There was no evidence of carcinogenic potential in either the rat or mouse study up to the limit dose and imazapic has been classified as a "Group E" chemical - negative carcinogenic potential for humans by any relevant route of exposure. Both the rat and rabbits developmental and rat reproductive toxicity studies did not indicate fetal or offspring toxicity or increased susceptibility from *in utero* and post natal exposure to imazapic.

In the one-year dog feeding study, minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both sexes was seen at the lowest dose tested of 137 mg/kg/day in males and 180 mg/kg/day in females. At higher doses, additional effects were seen in the liver and hematopoietic system. The Lowest-Observed-Adverse-Effect-Level (LOAEL) of 137 mg/kg/day based on skeletal degeneration and/or necrosis was selected as the study/endpoint for the chronic Reference Dose (RfD).

The rat metabolism study demonstrated that only the unchanged parent compound was detected in the urine, which was the major route of excretion. There was no evidence of bioaccumulation of imazapic in tissues. Additionally, there were no sex- or dose-related differences following oral or intravenous administration.

Dose Response Assessment

On April 17, 2001 the HED Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of imazapic and re-assessed the Reference Dose (RfD) established in 1995, as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments. The HIARC also addressed the potential

enhanced sensitivity of infants and children from exposure to imazapic as required by the Food Quality Protection Act (FQPA) of 1996 (memo of W. Dykstra, J. Rowland and E. Doyle dated 03-05-01; HED Doc. No. 014560).

Food Quality Protection Act (FQPA) Decision
The HED FQPA Safety Factor Committee (SFC) met on June 11, 2001 to evaluate the hazard and exposure data for imazapic and recommended that the 10x FQPA safety factor (SF) be reduced to 1x in assessing the risk posed by this chemical, because there was no evidence of increased susceptibility in the developmental toxicity study in rats, the developmental toxicity study in rabbits and in the two-generation reproduction toxicity study in rats (memo of B. Tarplee dated 21-06-01; HED Doc. No. 014597). The acute and chronic Population Adjusted Doses (aPAD and cPAD, respectively) are modifications of the acute and chronic RfDs to include the FQPA SF. The acute or chronic PAD is equal to the acute or chronic RfD divided by the FQPA SF.

An acute reference dose (aRfD) was not established for any population subgroup, including females 13-50 years old or the general U.S. population (including infants and children) because there were no effects observed in any oral toxicology studies, including developmental or maternal toxicity in the developmental toxicity studies in rats and rabbits, that are attributable to a single exposure (dose).

The chronic reference dose (cRfD) of 0.5 mg/kg/day was determined on the basis of a one-year feeding study in dogs. The LOAEL of 137 mg/kg/day (Lowest-Dose-Tested (LDT)) was based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle. A No-Observed-Adverse-Effect-Level (NOAEL) was not established in this study. Due to the absence of a NOAEL in this study, an uncertainty factor of 300 (10x for interspecies extrapolation, 10x for intra species variation, and 3x for the lack of a NOAEL) was used to derive the chronic RfD. This RfD was originally established in the RfD document dated September 27, 1995. The FQPA SF of 10x was reduced to 1x for chronic dietary risk assessment. Thus, the cPAD is 0.5 mg/kg/day.

Carcinogenicity: Imazapic has been classified as a "Group E" chemical (evidence of non-carcinogenicity for humans) based upon lack of evidence of carcinogenicity in two adequate studies (rats and mice). Therefore, a carcinogenic risk assessment is not required.

Occupational/Residential Endpoint Selection: Short - and intermediate-term dermal dose/endpoints were not identified since no dermal or systemic toxicity was seen at the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits and there were no concerns for developmental effects in rats and rabbits. A long-term dermal endpoint was chosen from a one-year feeding study in dogs. The HIARC selected the LOAEL of 137 mg/kg/day based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle. The HIARC determined that since an oral LOAEL was selected for the long-term dermal scenario, a dermal absorption (DA) factor of 50%, obtained by comparing the oral maternal LOAEL in the rabbit developmental study (500 mg/kg/day) to the dermal NOAEL (1,000 mg/kg/day) in the 21-day

dermal toxicity study in rabbits, should be used for upper bound risk assessment purposes.

No appropriate inhalation studies were available for endpoint selection; therefore, HIARC selected oral NOAELs for inhalation exposure risk assessment. For margin of exposure (MOE) calculations, the short- and intermediate-term inhalation exposure NOAEL is 350 mg/kg/day (based on the maternal oral NOAEL of 350 mg/kg/day due to decreased body weight gain and food consumption at the LOAEL of 500 mg/kg/day in the developmental toxicity study in rabbits) and use of 100% inhalation absorption. A long-term inhalation endpoint was chosen from a one-year feeding study in dogs. The HIARC selected the LOAEL of 137 mg/kg/day based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle.

Dermal exposure can not be combined with inhalation, since a dose/endpoint (hazard) was not identified for short- and intermediate-term dermal exposure risk assessment. For long-term inhalation exposure risk assessments, the dermal and inhalation exposures can be combined (using 100% absorption for inhalation and 50% absorption for dermal), since the same study was used for both endpoints and the doses selected are oral equivalent doses and the same toxic effect was observed (minimal degeneration and/or necrosis of skeletal muscle).

An aggregate exposure risk assessment was performed for the following: chronic aggregate exposure (food + drinking water). An acute aggregate risk assessment was not performed because an acute dietary endpoint was not selected by the HIARC due to the absence of a toxicological hazard for a single oral dose. Short- and intermediate-term and cancer aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses and imazapic is not carcinogenic, respectively.

Occupational Exposure Estimates: Imazapic may be applied aerially, (fixed wing or helicopter), by ground equipment for broad area applications and by ground equipment or backpack for "spot treatments." The maximum rate of application is 0.19 lb acid equivalents (ae)/Acre. There is a 7 day Pre-Harvest Interval (PHI) for areas cut for hay. The Restricted Entry Interval (REI) is 12 hours (proposed amended labels). Based on the proposed use patterns, commercial growers, handlers, and harvesters are expected to have short (1-7 days) and intermediate-term (7 days-several months) dermal and inhalation exposure. Therer is no potential for long-term exposure. Short and intermediate-term dermal exposures were not calculated due to the absence of a toxicological concern for these scenarios. All MOE calculations for inhalation occupational exposure scenarios are greater than 100, and therefore, occupational risk estimates do not exceed HED's level of concern.

Dietary Exposure Estimates
A chronic dietary exposure analyses was conducted using the Dietary Exposure Evaluation Model (DEEM™, ver.7.075) and consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). The chronic analysis was based on very conservative assumptions (tolerance level residues and 100% crop treated). Imazapic will enter the human dietary pathway through a transfer of livestock feed to meat and milk. This

potential for human exposure is very low as indicated by the chronic dietary risk analysis. The chronic dietary food exposure estimates were less than HED's level of concern (<100% of cPAD) for the general population and all population subgroups. Specifically, the chronic dietary risk estimates occupied ≤ 0.1% of the cPAD for all population subgroups. Since no acute dietary endpoint was selected by the HIARC, an acute dietary risk assessment was not performed.

Drinking Water

Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of imazapic levels in surface and ground water were made using computer modeling which were provided by EFED. Except for rapid aqueous photolysis, imazapic appears to be extremely persistent, mobile and highly soluble. The major route of dissipation of imazapic appears to be transport with water. Therefore, contamination of ground water and surface water by imazapic appears possible. Once in ground water or surface water where light can not penetrate imazapic will be very persistent. This assessment is consistent with other imidazolinone chemicals.

The surface water EECs from FIRST are 16.8 µg/L for peak day (acute) concentration and 1.46 µg/L annual average (chronic) concentration. The EEC of imazapic in ground water for drinking water using the SCI-GROW model was 13.67 µg/L when the half-life was assumed to be equal to 1500 days (upper bound used for the model's development) and the median K_{oc} of 71 was used. Using the half-life of 2010 the estimated concentrations is 13.73 µg/L. All the EEC values are less than the lowest DWLOC value of 5,000 µg/L (ppb) determined for the chronic exposure scenarios.

Exposure Scenarios and Risk Conclusions

For the proposed use of imazapic on pasture grass, human health risk assessments have been conducted for the following scenario: chronic dietary exposure (food only); aggregate chronic exposure (food and water); and short- and intermediate-term occupational inhalation exposure. Other scenarios were not evaluated, since imazapic does not have an acute dietary endpoint, has not been classified as a carcinogen, no residential uses have been proposed at this time, and long-term occupational exposure is not expected. **All aggregate dietary and occupational exposures are below HED's level of concern.**

Recommendation for Tolerances and Registration

Provided that revised Sections B and F are submitted and that successful Agency validation of the analytical method is reported, the chemistry and toxicological databases support the following permanent tolerances for residues of imazapic [(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid] and its metabolite (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-hydroxymethyl-3-pyridinecarboxylic acid both free [CL 263284] and conjugated [CL 189215] in/on:

Grass, forage ..... 30 ppm

Grass, hay ..... 15 ppm

In addition, provided the conditions listed above are satisfied, the databases support the following permanent tolerances for residues of imazapic and its metabolite CL 263284 in/on the commodities listed below:

Milk ..... 0.10 ppm
Meat* ..... 0.10 ppm
Fat* ..... 0.10 ppm
Meat byproducts (except kidney)* ..... 0.10 ppm
Kidney* ..... 1.0 ppm

* Of cattle, goats, horses, and sheep

However, registration of Plateau™ Herbicide for use on pastures and rangeland should be made conditional upon the submission of additional chemistry and toxicological data as specified below. Registration of Plateau™ DG Herbicide for use on pastures and rangeland should be delayed until the petitioner has submitted the requested field trial data supporting its use.

Chemistry

- Four additional grass field trials reflecting a single postemergence application of the 2 lb ae/gal ammonium salt SC formulation at 0.1875 lb ae/A, preferably in Regions 7 and 8.

- Additional rotational crop data or a revised Section B with updated rotational crop intervals for rye, wheat, and legume vegetables.
- Successful petition method validation of the analytical enforcement method.

PLUS

- Nine field trials reflecting a single postemergence application of the 0.0625 lb ai/packet WDG acid formulation at 0.1875 lb ae/A.

OR

- Four side-by-side maximum rate grass field trials using the ammonium salt SC and WDG acid formulations.

Toxicology

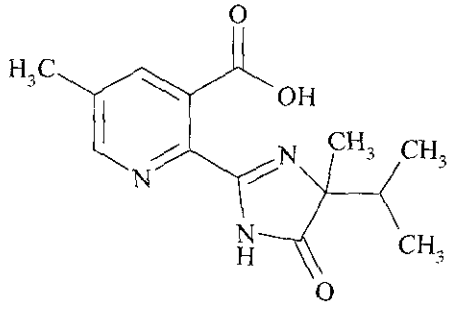
- 28-day inhalation toxicity study (OPPTS Guideline No. 870.3465) [The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline No. 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.] This 28-day inhalation study will provide a basis from which to determine more reliable route-specific MOEs for worker inhalation risks rather than the less reliable route-to-route MOE calculations currently being used.

2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

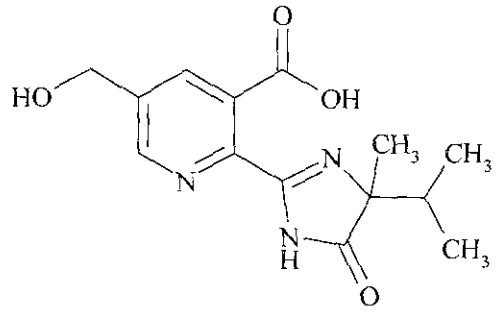
2.1. Identification of Inert Ingredient

CA Chemical Name:	(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid
Common Name:	Imazapic
Chemical Type:	Herbicide
PC Code Number:	129041
CAS Registry No.:	81334-60-3
Empirical Formula:	$C_{14}H_{17}N_3O_3$
Molecular Weight:	275

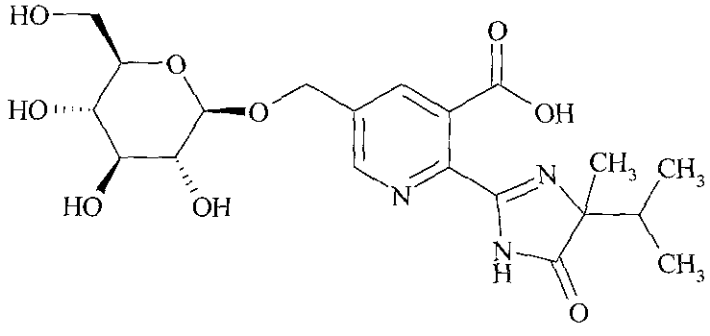
2.2. Structural Formulae



Imazapic



CL 263284



CL 189215

2.3. Physical and Chemical Properties

The product chemistry data review for imazapic was conducted in conjunction with the Experimental Use Permit (EUP) peanut petition (D195919, F. Griffith, 01-FEB-1994). Deficiencies noted in the initial review were satisfactorily resolved in the review for permanent tolerances (D207019, J. Garbus, 18-SEP-1995). The following data were taken from the studies reported in MRID# 427114-03 and refer to values obtained at 25 ± 1 °C, unless otherwise indicated.

Physical State:	Powdered solid
Vapor Pressure:	$< 1 \times 10^{-7}$ mmHg
Water Solubility:	0.215 g/100 mL in deionized water
Octanol/Water Partition Coefficient, K_{ow}:	4.83 between n-octanol and pH 4-6 buffers
Melting Point:	207-208 °C
Density:	0.38 g/mL
pKa:	2.0, 3.6, 11.1

Imazapic is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal. The relatively low K_{ow} value indicates that imazapic is not expected to bioconcentrate in fish.

3.0 HAZARD CHARACTERIZATION

3.1. Hazard Profile

Table 1. Acute Toxicity of IMAZAPIC Technical

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute Oral	42711407	$LD_{50} > 5{,}000$ mg/kg	IV
870.1200	Acute Dermal	42711408	$LD_{50} > 2000$ mg/kg	III
870.1300	Acute Inhalation	42711409	$LC_{50} > 5.52$ mg/L	IV
870.2400	Primary Eye Irritation	42711410	minimal irritation	III
870.2500	Primary Skin Irritation	42711411	non-irritating	IV
870.2600	Dermal Sensitization	42711412	not a dermal sensitizer	

Table 2. Toxicity Profile of Imazapic Technical

Guideline No.	Study Type (All Studies Acceptable)	Results
870.3100	90-Day oral toxicity rodents-rat	NOAEL = **1,552** mg/kg/day in males, 1,728 mg/kg/day in females (HDT). LOAEL = **not established**
870.3200	21-Day dermal toxicity- rabbit	NOAEL = **1,000** mg/kg/day (males and females). LOAEL = **not established**
870.3700a	Prenatal developmental in rodents- rat	**Maternal** NOAEL = **1,000** mg/kg/day (HDT). LOAEL = **not established** **Developmental** NOAEL = **1,000** mg/kg/day. LOAEL = **not established**
870.3700b	Prenatal developmental in nonrodents- rabbit	**Maternal** NOAEL = **350** mg/kg/day LOAEL = **500** mg/kg/day based on decreased body weight gain and food consumption. At 700 mg/kg/day (HDT), there was excessive mortality resulting in a total of only 7 surviving litters. **Developmental** NOAEL = **500** mg/kg/day LOAEL = **not established**. Due to excessive mortality at 700 mg/kg/day, only 47 fetuses were available for examination which precluded a meaningful evaluation of developmental findings at this dose level.
870.3800	Reproduction and fertility effects- rat	**Parental/Systemic** NOAEL = **1,205** mg/kg/day in males, 1,484 mg/kg/day in females (HDT). LOAEL = **not established** **Reproductive** NOAEL = **1,205** mg/kg/day in males, 1,484 mg/kg/day in females. LOAEL = **not established.** **Offspring** NOAEL = **1,205** mg/kg/day in males, 1,484 mg/kg/day in females. LOAEL = **not established**
870.4100b	Chronic toxicity dogs	NOAEL = **not established** LOAEL = **137** mg/kg/day in males, 180 mg/kg/day in females based on increased incidence of minimal degeneration and/or necrosis and lymphocyte and/or macrophage infiltration in skeletal muscle in both males and females and slightly decreased blood creatinine levels in females (LDT).
870.4300	Chronic/Carcino-genicity rats	NOAEL = **1,029** mg/kg/day in males, 1,237 mg/kg/day in females (HDT). LOAEL = **not established** **No evidence of carcinogenicity**
870.4300	Carcinogenicity mice	NOAEL = **1,134** mg/kg/day in males, 1,422 mg/kg/day in females (HDT). LOAEL = **not established** **No evidence of carcinogenicity**
870.5265	Gene Mutation	Non-mutagenic when tested up to 5000 ug/plate, in presence and absence of activation, in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E.coli* strain WP2uvra.

Table 2. Toxicity Profile of Imazapic Technical

Guideline No.	Study Type (All Studies Acceptable)	Results
870.5300	Gene Mutation	Non-mutagenic at the HGPRT locus in Chinese hamster ovary (CHO) cells tested up to cytotoxic concentrations or limit of solubility, in presence and absence of activation.
870.5375	Chromosome aberration	Did not induce structural chromosome aberration in CHO cell cultures in the presence and absence of activation.
870.5385	Chromosomal aberration	Non-mutagenic in rat bone marrow chromosomal aberrations assay up to 5000 mg/kg.
870.7485	Metabolism and pharmacokinetics - rat	Total recovery of the administered dose was 98-106% at 7 days. Urinary excretion was the major route of elimination (94-102% of the dose), with only unchanged parent detected. There was no evidence of bioaccumulation in the tissues. There were no sex- or dose-related differences following oral or intravenous administration.

Hazard Characterization

The existing toxicity database for imazapic is adequate according to the Subdivision F Guideline requirements for a food-use registration. There are no current residential uses. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

The acute toxicity data for imazapic show that this chemical is not acutely toxic by the oral, inhalation, or dermal routes of exposure (Toxicity Categories IV). It is minimally irritating to the eye (Toxicity Category III) and non-irritating to the skin (Toxicity Category IV). Additionally, imazapic is not a dermal sensitizer.

There were no toxic effects up to the limit dose (≥ 1,000 mg/kg/day) in the subchronic oral toxicity study in rats (1,522 mg/kg/day [M] and 1,728 mg/kg/day [F], the subchronic dermal toxicity study in rabbits (1,000 mg/kg/day), the developmental toxicity study in rats (1,000 mg/kg/day), the chronic toxicity/carcinogenicity feeding study in rats (1,029 mg/kg/day [M] and 1,237 mg/kg/day [F]), the carcinogenicity feeding study in mice (1,134 mg/kg/day [M] and 1,422 mg/kg/day [F]), and the 2-generation reproduction toxicity study in rats (1,205 mg/kg/day [M] and 1,484 mg/kg/day [F]. There was no evidence of neurotoxicity (clinical signs or neuropathology) in any of the toxicology studies conducted with imazapic, although guideline acute and subchronic neurotoxicity studies were not conducted.

In a acceptable battery of mutagenicity studies, imazapic was negative in forward and reverse gene mutation assays and was negative in both the in vitro and in vivo cytogenetic assays. Based on these results, it is concluded that the overall mutagenic potential of imazapic is negative.

Imazapic has been classified by the RfD/Peer Review Committee as **"Group E"** - not likely to be a human carcinogen by any relevant route of administration based on the absence of carcinogenicity in acceptable studies in mice and rats.

Only two studies in the data base had significant systemic toxicity, the one-year dog feeding study and the rabbit developmental study.

In the one-year dog feeding study, minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both sexes was seen at the lowest dose tested of 137 mg/kg/day in males and 180 mg/kg/day in females. At higher doses, additional effects were seen in the liver and hematopoietic system. The LOAEL of 137 mg/kg/day based on skeletal degeneration and/or necrosis was selected as the study/endpoint for the chronic RfD.

In the developmental toxicity study in rabbits, there was decreased weight gain and food consumption in the does at the LOAEL of 500 mg/kg/day, with the NOAEL being 350 mg/kg/day. There were no developmental effects in rabbit fetuses in the study up to 500 mg/kg/day. The significant increase in maternal deaths at the 700 mg/kg/day (HDT) precluded an meaningful evaluation of this dose level, since only 7 litters and 47 fetuses were available for examination.

3.2. FQPA Considerations

The FQPA SFC met on June 11, 2001 to evaluate the hazard and exposure data for imazapic (memo of Brenda Tarplee, 21-06-01; HED Doc. No. 014597). The toxicology database for imazapic is adequate according to the Subdivision F Guideline requirements for a food-use chemical. Acceptable developmental toxicity studies in the rat and rabbit are available, as is an acceptable 2-generation reproduction study in the rat. The HIARC concluded that a developmental neurotoxicity study with imazapic is not required.

Based on the available data, no evidence of increased susceptibility was seen in the rat and rabbit prenatal toxicity studies or following pre/post natal exposure in the 2-generation reproduction study.

The FQPA SFC concluded that the **FQPA safety factor** could be removed (reduced to 1x) for imazapic because:

- The toxicology data base is complete;
- A developmental neurotoxicity study is **not** required;
- The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children; and
- There are currently no residential uses.

3.3. Dose Response Assessment

On April 17, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) met to examine the hazard data base and identify the acute dietary endpoints for Females 13-50 years old, as well as the General Population, the chronic reference dose (RfD), and the toxicological endpoints selected for use as appropriate in occupational/residential exposure risk assessments for imazapic. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to imazapic as required by the Food Quality Protection Act (FQPA) of 1996. The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for IMAZAPIC Used in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary for general population and females 13-50 years old	None	An acute dietary endpoint was not selected based on the absence of an appropriate endpoint attributed to a single dose	None
Chronic Dietary all populations	LOAEL= 137 mg/kg/day UF = 300 **Chronic RfD** = 0.5 mg/kg/day	FQPA SF = 1X **cPAD** = cRfD / FQPA SF = **0.5 mg/kg/day**	LOAEL = 137 mg/kg/day based on increased incidence of minimal degeneration and/or necrosis of skeletal muscle in One Year Dog Feeding Study
Incidental Oral, Short Term (1-7 days)	Oral NOAEL = 350 mg/kg/day	LOC = 100	LOAEL = 500 mg/kg/day based on decreased body weight and food consumption during the dosing period in Rabbit Developmental Study
Incidental Oral, Intermediate Term (7 days - several months)	Oral NOAEL = 350 mg/kg/day	LOC = 100	LOAEL = 500 mg/kg/day based on decreased body weight and food consumption during the dosing period in Rabbit Developmental Study

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short- and Intermediate-Term Dermal (1-7 days and 1 week-several months) (Occupational)	None	No systemic toxicity was seen following repeated dermal application at 1,000 mg/kg/day over a 3-week period. Since no hazard was identified, quantification is not required.	None
Long-Term Dermal (several months-lifetime) (Occupational)	Oral LOAEL= 137 mg/kg/day (dermal absorption rate = 50%)	LOC for MOE = 300	LOAEL = 137 mg/kg/day based on increased incidence of minimal degeneration and/or necrosis of skeletal muscle in One Year Dog Feeding Study
Short- and Intermediate-Term Inhalation (1-7 days and 1 week-several months) (Occupational)	Oral study NOAEL= 350 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100	LOAEL = 500 mg/kg/day based on decreased body weight and food consumption during dosing in Rabbit Developmental Study
Long-Term Inhalation (several months-lifetime) (Occupational)	Oral study LOAEL= 137 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 300	LOAEL = 137 mg/kg/day based on increased incidence of minimal degeneration and/or necrosis of skeletal muscle in One Year Dog Feeding Study

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral, dermal, inhalation)	Cancer classification ("Group E")	Risk Assessment not required	No evidence of carcinogenicity

[1] UF = uncertainty factor, FQPA SF = 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, LOC = level of concern, MOE = margin of exposure

Acute Dietary Endpoint: An acute dietary RfD for the females 13-50 years of age and the general population, including infants and children, was not selected because an acute oral endpoint attributed to a single-dose exposure could not be identified in any of the studies in the toxicology data base, including developmental and maternal toxicity in the developmental toxicity studies.

Chronic Dietary Endpoint: The chronic reference dose (cRfD) of 0.5 mg/kg/day was determined on the basis of the one year dog toxicity study. Dogs are the most sensitive species tested with imazapic. A UF of 300 (10-fold for interspecies extrapolation, 10-fold for intra species variability, and 3-fold for the absence of a NOAEL) was applied to the LOAEL of 137 mg/kg/day to derive the cRfD. The LOAEL of 137 mg/kg/day is based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle. **The FQPA safety factor of 1X is applicable for chronic dietary risk assessment.** Therefore, the chronic population dose (cPAD) also equals 0.5 mg/kg/day.

Carcinogenicity: Imazapic has been classified as a "Group E" chemical (evidence of non-carcinogenicity for humans) based upon lack of evidence of carcinogenicity in rats and mice (Memorandum, G. Ghali, 9/27/95). Therefore, a cancer dietary exposure and risk assessment is not required.

Short-, Intermediate- and Long-Term Dermal Endpoint: A short- and intermediate-term dermal dose/endpoint was not identified since no dermal or systemic toxicity was seen at the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits. A long-term dermal endpoint was chosen from a one-year feeding study in dogs. The HIARC selected the LOAEL of 137 mg/kg/day based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle. The HIARC determined that since an oral NOAEL was selected, a dermal absorption (DA) factor of 50%, obtained by comparing the oral maternal LOAEL in the rabbit developmental study (500 mg/kg/day) to the dermal NOAEL (1,000 mg/kg/day) in the 21-day dermal toxicity study in rabbits, should be used for risk assessment purposes.

Short-, Intermediate-, and Long-Term Inhalation Endpoints: No appropriate inhalation studies

were available for endpoint selection; therefore, HIARC selected oral NOAELs for inhalation exposure risk assessment and route-to-route extrapolation. For MOE calculations, the short- and intermediate-term inhalation exposure NOAEL is 350 mg/kg/day (based on the maternal oral NOAEL of 350 mg/kg/day due to decreased body weight gain and food consumption at the LOAEL of 500 mg/kg/day in the developmental toxicity study in rabbits) and use of 100% inhalation absorption. A long-term inhalation endpoint was chosen from a one-year feeding study in dogs. The HIARC selected the LOAEL of 137 mg/kg/day based on the increased incidence of minimal degeneration and/or necrosis of skeletal muscle.

Dermal exposure can not be combined with inhalation, since a dose/endpoint (hazard) was not identified for short- and intermediate-term dermal exposure risk assessment. For long-term inhalation exposure risk assessments, the dermal and inhalation exposures can be combined (using 100% absorption for inhalation and 50% absorption for dermal) since the same study was used for both endpoints and the doses selected are oral equivalent doses and the same toxic effect was observed (minimal degeneration and/or necrosis of skeletal muscle).

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, imazapic may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

The petitioner provided specimen labels for two imazapic end-use products: the 2 lb ae/gal ammonium salt soluble concentrate (SC) formulation (EPA Reg. No. 241-365; Product Name = Plateau™ Herbicide), and the 0.0625 lb ai/packet imazapic acid water dispersible granule (WDG) formulation in water soluble packets (EPA Reg. No. 241-393; Product Name = Plateau™ DG Herbicide). For both formulations, the petitioner is proposing to amend the previously registered uses for weed control in noncrop areas to include use on pasture and rangeland grasses.

The 2 lb ae/gal ammonium salt SC formulation is proposed for one or more pre-emergence or postemergence spot or broadcast applications to pasture and rangeland grasses at 2-12 oz. product (0.03125-0.1875 lb ae/A/application) with a maximum seasonal rate of 0.1875 lb ae/A. The 0.0625 lb ai/packet acid WDG formulation is proposed for one or more pre-emergence or postemergence spot or broadcast applications to pasture and rangeland grasses at 0.0625-0.1875 lb ai/A/application with a maximum seasonal rate of 0.1875 lb ai/A. Both labels state that the treated area may not be cut for hay within 7 days after treatment.

Applications may be made using ground equipment (minimum of 2 gal of water/A (GPA)) or aerial equipment (minimum of 5 GPA). Postemergence applications are to be made using a spray adjuvant (methylated seed oils, vegetable oil concentrates, nonionic surfactants, silicone-based surfactants, or fertilizer/surfactant blends). In addition, the labels allow tank mixes with dicamba, diuron, glufosinate-ammonium, glyphosate, imazapyr, N-methyl pyrrolidone, metsulfuron-methyl, MSMA, pendimethalin, sulfometuron-methyl, and triclopyr. Tank mixing with organophosphate insecticides or use of organophosphate insecticides during the same year as imazapic applications is prohibited.

The following minimum plant back intervals (PBIs) for rotational crops are proposed for both products: 4 months following application for Bahiagrass, rye, and wheat; 9 months following application for field corn, snap beans, southern peas, soybeans, and tobacco; 18 months following application for barley, cotton, sorghum grain, oats, and sweet corn; and 40 months following application for canola, potatoes, red table beets, and sugar beets. All other crops for which a minimum PBI is not specified may be planted 26 months following application.

HED Conclusions: **The proposed Section B is not adequate.** No field trial data have been submitted reflecting application of the 0.0625 lb ai/packet acid WDG formulation which was previously registered for noncrop uses only. The petitioner should provide grass field trial data using the WDG formulation or remove the proposed use from the Plateau™ DG Herbicide label.

Both Plateau™ labels allow imazapic to be used with other pesticides in tank mixes. RD should ensure that all tank mix active ingredients have established tolerances or tolerance exemptions

for use on grass commodities.

With respect to the proposed PBIs, the 4-month PBI for rye and wheat and the 9-month PBI for legume vegetables are not supported by rotational crop data reflecting the current maximum application rate for grasses. PBIs of 6 months for small grains, 11 months for root and tuber crops, and 12 months for leafy vegetables are supported by the available data. **The petitioner should submit additional rotational crop data (confined or field) reflecting the proposed grass use rate *and* desired PBI or a revised Section B with updated rotational crop intervals for rye and wheat (6 months), and legume vegetables (12 months).**

4.2 DIETARY EXPOSURE/RISK PATHWAY

4.2.1 RESIDUE PROFILE

Background: Permanent tolerances have been established for residues of imazapic in/on peanuts; time-limited tolerances for residues of imazapic have been established for residues of imazapic in/on grass commodities and livestock commodities. Grass residue data were reviewed in a HED memo dated 6/12/01 (D269038, W. Donovan).

American Cyanamid Company submitted a registration application for use of imazapic on pasture and rangeland grasses, along with a petition to establish permanent tolerances for residues in/on grass forage and hay and livestock commodities as a result of the proposed uses. Section F of the current petition proposes to establish permanent tolerances for residues of imazapic applied either as the free acid or its ammonium salt and its metabolites CL 263284 and CL 189215 in/on:

Grass, forage	35 ppm
Grass, hay	15 ppm

Tolerances are also being proposed for residues of imazapic and its metabolite CL 263284 in the following livestock commodities:

Milk	0.1 ppm
Meat of cattle, goats, horses, and sheep	0.1 ppm
Fat of cattle, goats, horses, and sheep	0.1 ppm
Meat byproducts (except kidney) of cattle, sheep, goats, and horses	0.1 ppm
Kidney of cattle, sheep, goats, and horses	2.0 ppm

Nature of the Residue

Plants: The petitioner submitted a grass metabolism study adequately depicting the nature of the residue in grass. The HED Metabolism Assessment Review Committee (MARC) determined

that for grass, the residues of concern for the tolerance expression and risk assessment are parent imazapic, CL 263284, and CL 189215 (D275136, W. Donovan and W. Dykstra, 07-JUN-2001). This decision was based on the structural similarity of these three compounds and the significant levels of each found in the grass metabolism and field trial studies.

Livestock: The petitioner submitted goat metabolism and bovine feeding studies where only parent imazapic was fed and identified. Because compounds CL 263284 and CL 189215 are grass metabolites, these compounds may also be consumed by ruminants. Thus, a more realistic feeding study would involve feeding CL 263284. However, as imazapic displays little propensity to accumulate in livestock tissues and the greater polarity of CL 263284 and CL 189215 make them even less likely to accumulate, no new metabolism or feeding studies are needed at this time. This decision should be carefully considered in any future petitions involving livestock feed items. In a meeting held 22-MAY-2001, the HED MARC determined that the residues of concern in/on livestock commodities include imazapic and CL 263284 (D275136, W. Donovan and W. Dykstra, 07-JUN-2001). The decision to regulate metabolite CL 263284 was based on its prevalence in the livestock feed items of grass forage and hay.

Residue Analytical Methods

The petitioner has proposed CE method M 3114 for the enforcement of tolerances for grass forage and hay. This method was used for the determination of residues of imazapic and its metabolites CL 263284 and CL 189215 in/on grass forage and hay samples collected from the grass field trials and is similar to the peanut enforcement method CE M 2379. Concurrent method recoveries submitted in conjunction with the grass field trials indicate that this method adequately recovers residues of imazapic and its metabolites CL 263284 and CL189215 from grass forage and hay. Adequate independent method validation and radiovalidation data have been submitted for this method. This method was forwarded to the Analytical Chemistry Branch of the Biological and Economics Analysis Division (ACB/BEAD) for petition method validation (D271474, W. Donovan, 17-JAN-2001).

The petitioner has proposed CE methods M 3188 and M 3222 for the enforcement of tolerances of imazapic and CL 263284 in milk (M 3188) and livestock tissues (M 3222), and HPLC/MS method M 3233 for the enforcement of tolerances in fat. Concurrent method recoveries submitted in conjunction with a ruminant feeding study indicate that these methods adequately recover residues of imazapic and CL 263284 from ruminant tissues and milk.

Adequate independent method validation studies have been submitted in support of all methods. Adequate radiovalidation data have been submitted for the CE enforcement methods. Although no radiovalidation data were submitted in support of HPLC/MS method M 3233 for determination of residues of imazapic in fat, in consideration of the concurrent validation data, and the fact that TRR in goat fat from the metabolism study (0.003 ppm) were below the method LOQ for fat of 0.050 ppm, no radiovalidation data are required for this method. The methods were forwarded to ACB/BEAD for petition method validation (D271474, W. Donovan, 17-JAN-2001). **Until successful method validation of an enforcement method is reported by EPA's**

ACB, the data requirement for analytical methods have not been satisfied.

Multiresidue Method (MRM)

The petitioner previously submitted data pertaining to the multiresidue methods testing of imazapic and its metabolites CL 263284 and CL 189215 in conjunction with PP#4F4390 (DP Barcode D211846, 2/9/95, F. Griffith). Methods testing indicated that residues of imazapic and its metabolites CL 263284 and CL 189215 do not fluoresce; therefore, no additional work was done for Protocol A. Because all three compounds are nicotinic acid derivatives, they were methylated by Protocol B and analyzed by GC as described by Protocol C; however, no response was observed using GC/ECD analysis, and multiple peaks were observed only at the 1-μg level, indicating thermal decomposition. Methylated imazapic was detected by nitrogen-phosphorus detection; however, no response was observed with a Florisil column, thus no further work was done with Protocols D and E. The results of the multiresidue testing for imazapic and its metabolites CL 263284 and CL 189215 were forwarded for inclusion in PAM Volume I (DP Barcode D211846, 2/9/95, F. Griffith).

Crop Field Trials

The submitted grass field trial data are inadequate to support the proposed uses of imazapic on pastures and rangeland. The petitioner has not provided adequate residue data reflecting the maximum proposed use pattern of imazapic on grasses (a single postemergence application at 0.1875 lb ae/A with a 0-day PHI for forage and a 7-day PHI for hay). Only eight grass field trials were conducted according to the maximum proposed use pattern; yet Table 5 of OPPTS 860.1500 recommends a total of 12 trials (geographic distribution unspecified) for the establishment of tolerances for residues in/on grass commodities, with four trials each to be conducted on the representative cultivars of Bermuda grass, bluegrass, and bromegrass or fescue. Also, no field trial data were submitted in support of the 0.0625 lb ai/packet WDG acid formulation, which represents a different formulation class as well as a different chemical form of imazapic. HED requests the results of trials reflecting a representative of each formulation type and/or major form of an active ingredient (e.g., the acid vs. salt) to determine if there is an effect of formulation type/chemical form on the relationship between application rate and residue level.

In support of postemergence use of imazapic on grasses, the petitioner should conduct four additional field trials reflecting a single postemergence application of the 2 lb ae/gal ammonium salt SC formulation at 0.1875 lb ae/A. Because it appears that residues may be higher in trials conducted in late summer or fall, the petitioner is advised to conduct the required trials during these seasons, preferably in Regions 7 and 8.

In support of the 0.0625 lb ai/packet WDG acid formulation, field trials reflecting a 25% reduction in the number of trials (i.e., 9 instead of 12) would be appropriate to support registration of the WDG acid formulation for use on grasses. **Should the petitioner choose to conduct these trials side-by-side with the maximum rate ammonium salt SC formulation trials, then only 4 side-by-side trials are necessary.**

The maximum combined residue levels of imazapic, CL 26284, and CL 189215 in grass forage and hay (7-day PHI) were <25.1 and 9.9 ppm, respectively. Thus, the available field trial data support tolerance levels for residues of imazapic and its metabolites CL 263284 and CL 189215 in/on grass forage at 30 ppm and grass hay at 15 ppm. However, these levels may be adjusted as necessary when the requested additional data have been submitted and evaluated. In the tolerance expression, HED recommends that the petitioner remove references to the form of imazapic applied. **A revised Section F should be submitted.**

Meat, Milk, Poultry, Eggs

The submitted dairy cattle feeding study is tentatively determined to be acceptable; however, the recommended tolerance levels in livestock commodities are subject to revision upon assessment of additional crop field trial data required under OPPTS 860.1500. When the field trial data have been submitted and evaluated, HED will reevaluate the feeding study and update recommended tolerances for livestock commodities as necessary based on any changes to the MTDB for beef and dairy cattle.

In the submitted study, Holstein dairy cows were dosed orally once daily for 28 consecutive days with imazapic at dose levels equivalent to 67 ppm, 223 ppm, and 676 ppm. Detectable residues of imazapic were observed in samples of milk, milk fat, and kidney at all doses; residues of imazapic were less than the LOQ (<0.05 ppm) in samples of fat, liver, and muscle at 67-ppm. Residues of the metabolite CL 263284 were less than the respective LOQs in all samples of milk and milk fat (<0.01 ppm), and tissues (<0.05 ppm).

Overall, residues of imazapic increased in milk and tissues with increasing dose level. Residues in whole milk appear to plateau at Day 1 and did not significantly increase with subsequent doses. Residues in milk fat were lower than those in whole milk, confirming that residues do not tend to partition into fats. In tissues, residues were lowest in fat and highest in kidney.

Based on the information presently available, the appropriate tolerance level for meat, fat, milk and meat byproducts (except kidney) is 0.10 ppm. For kidney, the appropriate tolerance level is 1.0 ppm. However, these levels may be adjusted as necessary when the requested additional grass field trial data have been submitted and evaluated. **A revised Section F should be submitted.**

There are no poultry feed items associated with the proposed uses of imazapic on pasture and rangeland grasses; therefore, a poultry feeding study is not required, and tolerances on eggs and poultry tissues need not be proposed in conjunction with this petition request.

Confined Accumulation in Rotational Crops

The petitioner submitted a new confined rotational crop study in support of the grass petition. The TRRs, expressed as [^{14}C]imazapic equivalents, did not accumulate at levels ≥0.01 ppm in/on the RACs of winter wheat (181 days after treatment (DAT)), spring wheat (318 DAT), carrots

(318 DAT), and lettuce (363 DAT) planted in sandy loam soil treated with [^{14}C]imazapic at 0.195 lb ae/A (~1x the maximum proposed seasonal rate for grasses).

Currently, the label for the 2 lb ae/gal ammonium salt SC formulation specifies the following minimum PBIs for rotational crops: 4 months following application for Bahiagrass, rye, and wheat; 9 months following application for field corn, snap beans, southern peas, soybeans, and tobacco; 18 months following application for barley, cotton, sorghum grain, oats, and sweet corn; and 40 months following application for canola, potatoes, red table beets, and sugar beets. All other crops for which a minimum PBI is not specified may be planted 26 months following application.

HED notes that the 4-month PBI for bahiagrass, rye, and wheat was based on confined rotational crop data submitted in support of the peanut petition (use rate = 0.0625 lb ae/A). As the present petition for pasture and rangeland use involves an application rate three times higher than the peanut use rate, the confined rotational crop data at 0.0625 lb ae/A can not be translated to the Plateau™ labels for grass use.

The submitted rotational crop data reflecting the grass use rate support establishment of a 6-month PBI for small grains, an 11-month PBI for root and tuber crops, and a 12-month PBI for leafy vegetables. The proposed 4-month PBI for rye and wheat and 9-month PBI for legume vegetables are not currently supported by rotational crop data. If the petitioner wishes to establish PBIs less than those reflected in the current confined rotational crop study, limited field rotational crop studies or additional confined rotational crop studies making use of the grass application rate *and* desired PBI are recommended. Alternatively, the petitioner may increase the rye and wheat PBIs from 4 to 6 months, and increase the PBI for legume vegetables to 12 months. **The petitioner should submit additional rotational crop data or a revised Section B with updated rotational crop intervals for rye, wheat, and legume vegetables.**

International Harmonization of Tolerances

There are no CODEX, Canadian, or Mexican maximum residue limits (MRLs) for imazapic residues. Thus, harmonization is not an issue at this time.

4.2.3 CHRONIC DIETARY EXPOSURE ANALYSIS

Permanent and temporary tolerances have been established for imazapic, as listed in 40 CFR 180.490. Tolerances are currently established under §180.490(a) for residues of imazapic and its metabolites CL 263284 and CL 189215 in/on peanut, nutmeat at 0.1 ppm. Time-limited tolerances set to expire 12/31/01 are established under §180.490(b) in connection with Section 18 emergency exemptions (99NE0009) for residues of imazapic and its metabolites CL 263284 and CL 189215 for grass forage at 30 ppm, grass hay at 15 ppm, milk at 0.10 ppm, fat, meat, and meat byproducts (except kidney) of cattle, goats, hogs, horses, and sheep at 0.10 ppm, and kidney of cattle, goats, hogs, horses, and sheep at 1.0 ppm. The present analyses included the published peanut values together with re-evaluated tolerance levels for livestock-derived commodities,

based on the new grass use proposed in the present Section 3 request.

Dietary Exposure Evaluation Model (DEEM™) analysis indicates that the estimated dietary exposure and risk associated with the existing and proposed new uses of the herbicide imazapic are below the HED's level of concern for chronic exposure scenarios. The chronic analysis presented here is highly conservative, making use of tolerance level residues, 100% crop treated assumptions, and default concentration factors (Tier 1 analysis).

Chronic Analysis
DEEM™ analysis (version 7.73) evaluated the individual food consumption as reported by respondents in the USDA 1989-92 nationwide Continuing Surveys of Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. HED's level of concern is for exposures >100% cPAD. The chronic DEEM™ analysis used mean consumption (3 day average) data and gave the results listed in Table 4:

Table 4. Summary of Results from Chronic Dietary Exposure Analysis for Imazapic.

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.000269	0.1
All infants (< 1 year)	0.000505	0.1
Children 1-6 years old	0.000684	0.1
Children 7-12 years old	0.000425	0.1
Females 13-50 years old	0.000189	<0.1
Males 13-19 years old	0.000297	0.1
Males 20+ years old	0.000208	<0.1
Seniors 55+ years old	0.000165	<0.1

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years). Thus, the population subgroups listed in Table 4 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey to be considered statistically reliable.

4.3 WATER EXPOSURE/RISK PATHWAY

The following information concerning the environmental fate and drinking water assessment of imazapic was provided by EFED (D267228 and D267288A (Addendum), J. K. Wolf, 10-MAY-2001 and 23-MAY-01 (Addendum). At the present time, surface and ground water monitoring

data are not available.

Environmental Fate Assessment: Except for rapid aqueous photolysis, imazapic appears to be extremely persistent, mobile and highly soluble. The major route of dissipation of imazapic appears to be transport with water (D256432). Therefore, contamination of ground water and surface water by imazapic appears possible. Once in ground water or surface water where light can not penetrate imazapic will be very persistent. This assessment is consistent with other imidazolinone chemicals.

In laboratory studies, except for rapid aqueous photolysis (T½ =< 8 hours), imazapic is stable (≥94.3% parent remained after 30 days) to hydrolysis at pH 5, 7, and 9, soil photolysis (T½ = 106 days), aerobic soil metabolism (T½ = 2010 days), and anaerobic aquatic metabolism (T½ = 2400 days). Based on batch equilibrium data conducted on six soils, imazapic appears to be very mobile to mobile in soil (K_d = 0.17 - 2.99). The K_{oc} model does not appear to be valid for imazapic. Volatility does not appear to be a major route of dissipation since very little (≤1%) volatile compounds were isolated in the laboratory studies and the vapor pressure of < 10^{-7} mm Hg indicates that the compound would not be volatile. Imazapic has a very low bioconcentration factor of 0.11 demonstrating a lack of accumulation in fish; further the compound was rapidly excreted within three days of exposure to less than the detection limits. The low Kow value of < 1 supports the conclusion of low bioaccumulation of imazapic. The 2010 day half-life for imazapic is beyond the 1500 day upper bound used in the development of SCI-GROW.

Ground and Surface Water EECs: The HED MARC determined that the residue of concern in water is imazapic *per se* (D275136, W. Donovan and W. Dykstra, 07-JUN-2001).
Any photolysis products are expected to be no more toxic than the parent compound and are expected to occur in low levels; thus, inclusion of parent only in the drinking water assessment should adequately account for risks posed by this chemical. Since there is no monitoring data available, EFED screening models are used to make estimates concerning possible contamination of surface water and ground water from the use of imazapic for both drinking water and ecological exposure assessments.

The FIRST and GENEEC2 models were used for Tier 1 assessments. EFED management has determined, that after May 1, 2001, the FIRST model will be used for the drinking water exposure assessments and GENEEC2 model for the ecological exposure assessments. FIRST produces both a peak value and an annual average value based on the Index Reservoir scenario. It uses a PCA (Percent Cropped Area factor) to adjust the EECs for the fraction of the watershed which is planted in the modeled crop. The model assumes that all of the area planted in the crop is treated with the pesticide. To generate EECs, the screening models assumed one application of 0.1875 lb ai/A (12 oz.) per year.

ground water estimate:	14 ppb
surface water estimate:	17 ppb; peak concentration
	1.5 ppb; annual average concentration

The estimated concentration of imazapic in ground water for drinking water using the SCI-GROW model was 13.67 µg/L when the half-life was assumed to be equal to 1500 days (upper bound used for the model's development) and the median K_{oc} of 71 was used. Using the half-life of 2010 days, the estimated concentrations is 13.73 µg/L. Because EECs are generally expressed to only 2 significant figures, the choice of 1500 or 2010 days for half-life does not affect the risk assessment.

4.4 RESIDENTIAL EXPOSURE/RISK PATHWAY

There are no residential uses (proposed or registered non-occupational uses) of imazapic. Therefore, there are no residential exposure risks from this chemical.

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 data base 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

An aggregate exposure risk assessment was performed for the following: chronic aggregate exposure (food + drinking water). An acute aggregate risk assessment was not performed because an acute dietary endpoint was not selected by the HIARC due to the absence of a toxicological hazard for a single oral dose. Short- and intermediate-term and cancer aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses and imazapic is not carcinogenic, respectively.

Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, drinking water levels of concern (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 toxic 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. HED compares DWLOC values for each relevant population subgroup to the estimated concentration of imazapic in surface water and ground water from EFED's screening models. If the DWLOC values are greater than the estimated concentration of imazapic in surface water and ground water, HED concludes with resonable certainty that exposures to imazapic in drinking water do not pose a significant human health risk.

To calculate the chronic DWLOCs, the dietary food estimates (from DEEM™) were subtracted from the appropriate 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 (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children). Because there is no residential exposure to imazapic, only chronic aggregate exposures are necessary.

5.1 Chronic Aggregate Risk (food + drinking water)

The chronic dietary exposure analysis assumed tolerance level residues and 100% crop treated for all proposed commodities (Tier 1). The EECs generated by EFED are less than HED's DWLOCs. **Thus, chronic aggregate risk estimates are below HED's level of concern.** Table 5 summarizes the chronic aggregate exposure to imazapic residues.

Table 5. Chronic Aggregate Exposures to Imazapic Residues.

Scenario/ Population Subgroup	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure[1], mg/kg/day	Ground Water EEC[2], ppb	Surface Water EEC[2], ppb	Chronic DWLOC[3], ppb
U.S. Population	0.5	0.000269	0.499731	14	1.5	17,000
All infants (< 1 year old)	0.5	0.000505	0.499495	14	1.5	5,000
Children (1-6 years old)	0.5	0.000684	0.499316	14	1.5	5,000
Children (7-12 years old)	0.5	0.000425	0.499575	14	1.5	5,000
Females (13-50 years old)	0.5	0.000189	0.499811	14	1.5	15,000
Males (13-19 years old)	0.5	0.000297	0.499703	14	1.5	17,000
Males (20+ years old)	0.5	0.000208	0.499792	14	1.5	17,000

Seniors (55+ years old)	0.5	0.000165	0.499835	14	1.5	17,000

[1] Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM (mg/kg/day).

[2] EECs resulting from the maximum proposed application rate.

[3] Because there are no residential uses, the chronic DWLOCs were calculated as follows:

$$DWLOC\ (\mu g/L) = \frac{maximum\ water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

DWLOCs were calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

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

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether imazapic shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for imazapic need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with imazapic, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf

In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

SUMMARY OF PROPOSED NEW USE PATTERN

Imazapic may be applied aerially, (fixed wing or helicopter), by ground equipment for broad area applications and by ground equipment or backpack for "spot treatments." The maximum rate of application is 0.19 lb ae/Acre. There is a 7 day PHI for areas cut for hay. The REI is 12 hours (proposed amended labels). Table 6 presents a summary of the proposed new use pattern.

Table 6. Summary of Proposed Use Pattern of Imazapic Applied to Pastureland, Rangeland and Conservation Reserve Program Land

Formulation	2.0 lb ae/gallon liquid; 70% dispersible granule in WSP
Use Site	pasture, range, conservation reserve program land
Pest	"weed" species
Application Method	aerial, ground (broadcast and spot), backpack
Frequency/Timing	One or more pre- or post-emergence applications, with a maximum seasonal rate of 0.1875 lb ae/A.
PHI	7 day for hay
REI	12 hours
Manufacturer	American Cyanamid Company

7.1 Handler Exposure Assumptions and Risk Assessments

In light of the proposed new use patterns, HED presents estimates of exposure and risk to a mixer/loader using open liquid pour and a mixer/loader/applicator as being the most conservative (i.e., worst case) handler functions involved with these proposed uses. Based on worker exposure study data in the Pesticide Handlers Exposure Database (PHED), in this case HED believes loaders supporting aerial operations receive the highest exposures due primarily to the large volumes of pesticide handled during the course of a work day and to the "method" of handling. In this assessment, liquid, open-pour loading is assessed. The DG formulation is packaged in water soluble packages which essentially eliminates loader exposure and is considered a closed loading system. In terms of applicators, HED believes that the most conservative (worst case) handler function is likely to be a handler who mixes, loads, and applies imazapic for spot treatment using high pressure "hand wand" equipment. For broadcast ground applications, ground boom application is most likely. However, it is not expected to result in as much exposure as the mixer/loader/applicator using hand wand equipment. The proposed labels also list backpack as a method of application for spot treatments. Since backpack can potentially be a "high" exposure handler situation, an assessment for mixer/loader/applicator using liquid, open pour, for backpack application, is also presented.

There are no chemical specific data available with which to estimate pesticide handler exposure in this case. Therefore, study data contained in the Pesticide Handlers' Exposure Database (PHED) Surrogate Exposure Guide, Version 1.1 (August 1998) are used to estimate exposures. It is HED's policy to present estimates of dermal exposure for individuals wearing a single layer of clothing (i.e., long pants, long sleeved shirt, shoes plus socks) and wearing or not wearing gloves. This is done to the extent there are available data with which to do so. Both registered labels direct the handler to wear long sleeved shirt, long pants, shoes plus socks and waterproof gloves.

Table 7 presents a summary of the exposure estimates.

Table 7. Estimated Exposures to Pesticide Handlers Applying Imazapic to Pasture, Range and Conservation Reserve Program Land

Unit Exposure[1] mg a.i./lb handled	**Application Rate**[2] (maximum rate) lb a.i. handled/A	**Units Treated**[3]	**Average Daily Dose**[4] mg/kg bw/day	**Margin of Exposure**[5]
Mixer/Loader - Liquid - Open Pour - Supporting Aerial Application				
Inhalat. 0.0012 HC	0.19	1200 A/day	4.56×10^{-3}	>76K
Mixer/Loader/Applicator - Liquid/Open Pour - High Pressure - HandWand				

Table 7. Estimated Exposures to Pesticide Handlers Applying Imazapic to Pasture, Range and Conservation Reserve Program Land				
Inhalat. 0.12 LC	0.19	1000 gallons spray/day[3] (20.8 lb a.i./day)[3a]	0.042	>8K
Mixer/Loader/Applicator - Liquid/Open Pour - Back Pack				
Inhalat. 0.03 LC	0.19	40 gallons spray/day[3] (0.83 lb a.i./day)[3b]	$4.15x10^{-4}$	>800K

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database
PHED Surrogate Exposure Guide version 1.1; August 1998; Inhalat. = Inhalation. HC = high confidence data; LC = low confidence data
2. Application Rate from proposed amendments Plateau® and Plateau® DG herbicide labels (Reg. No's. 241365 and 241-393)
3. units Treated from Science Advisory Council for Exposure Policy No. 9 Rev. 5 July 2000
The Plateau label (2.0 lb a.i./gallon) lists 12 oz/A *as the maximum rate of application.* Therefore 2.0 lb a.i./gal ÷ 128 fl oz/gal = 0.016 lb a.i./fl oz and at 12 oz/A = 0.19 lb a.i./A.
a. Further, for spot treatments the label directs the use of 1.3 oz/gallon of water ∴ 1.3 oz * 0.016 lb ai/fl oz = 0.021 lb ai/gal * 1000 gal/day (Sci. Expo. Council Policy) = 21.0 lb ai/day
b. 0.021 lb ai/gal * 40 gal/day (Sci. Expo. Counc) = 0.83 lb ai/day
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated (or lb a.i./day) ÷ 60 kg body weight (NOAEL from developmental study). Inhalation exposure assumes 100% inhalation absorption.
5. Margin of Exposure (MOE) For Short and Intermediate Term Inhalation = No Adverse Effect Level (350 mg a.i./kg bw/day) ÷ ADD. K = 1000

7.2 Post-Application Exposures and Assumptions

HED believes that the only likely post-application exposure that might occur to agricultural workers is scouting. The Science Advisory Council for Exposure (Policy No. 003.1 - Rev. 7 August 2000) lists irrigation, scouting, and mechanical harvesting as activities that might follow pesticide application to alfalfa. HED considers pastures that may be cut for hay to be similar to alfalfa in some respects. It is unlikely that pastures are irrigated with methods requiring hand labor. In HED's view, scouting is the most likely, if any, post-application activity that might occur following an herbicide application for grass "release" to pastures or prairie land and that could result in significant human exposure.

Hay is mechanically mowed and after drying for several days, it is mechanically raked or wind-rowed. It is mechanically baled whether the large round or "cube" bales or "small" (i.e., typical) bales. The large round or cube bales are mechanically handled for storage or shipment or movement. Many operations use a "kicker" to pick up small bales and "load" them loose into a wagon. Some small operations may use manual labor to pick up and load bales as well as stack them for storage. In this last case, workers typically wear gloves to protect their hands from abrasion from the hay bales and binder twine. These factors combined with a 7 day preharvest (mowing) interval lead HED to conclude that any dermal exposure that might occur is expected to be negligible.

Since no dermal toxicological endpoints are identified and since inhalation post-application exposures are expected to be negligible, a post-application exposure assessment is not presented here.

7.3 Restricted Entry Intervals (REIs)

The proposed new uses are amendments to currently registered products, EPA Registration Numbers 241-365 and 241-393. The label REI is 12 hours.

7.4 Incidents

According to REFs Reports (5/16/01), one incident regarding Plateau herbicide was reported. A male caller "accidentally touched his mouth with Plateau herbicide." After he rinsed his mouth, symptoms subsided.

In view of the preceding discussion and since the estimated inhalation Margins of Exposure exceed 100, the estimated exposures are not of concern to HED.

Based on the proposed use patterns, commercial handlers are expected to have short-term and intermediate-term dermal and inhalation exposures. Growers are expected to have short-term dermal and inhalation exposures. Workers entering fields following applications are anticipated to have short-term dermal exposures. The proposed label for all three herbicides specifies that handlers must wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, protective eyewear, shoes with socks, and waterproof gloves.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Agency validation of the analytical methods for grass and livestock commodities.
- Additional grass field trial data.
- Additional rotational crop data or a revised Section B with updated rotational crop intervals for rye, wheat, and legume vegetables.

8.2 Toxicology

- *28-day inhalation toxicity study.* This study was requested by HIARC for further characterization of inhalation risk assessments. Due to the potential for inhalation exposure, there is concern for toxicity by the inhalation route. The 28-day inhalation

014653

toxicity study would give a dose and endpoint examined via the route of exposure of concern (i.e., route specific study) and thus would avoid using an oral study and route-to-route extrapolation. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

8.3 Occupational Exposure

- None.

cc: W. Dykstra, W. Donovan, M. Dow
RDI: RAB1 Chemists (05-JUL-2001), Team (xx-JUL-2001), Branch (xx-JUL-2001), G. Herndon (19-JUL-2001), RARC (26-JUL-2001)
W. Dykstra:806Q:CM#2:(703)305-7432:7509C:RAB1

13544

031395

Chemical:	**3-Pyridinecarboxylic acid, 2-(4,5-dihydr; 3-Pyridinecarboxylic acid, *2-(4,5-dihydr***
PC Code:	**128943; 129041**
HED File Code	**14000 Risk Reviews**
Memo Date:	**08/01/2001**
File ID:	**TX014653**
Accession Number:	**412-02-0010**

HED Records Reference Center
01/31/2002