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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: July 8, 1999

SUBJECT: ID# 99NE0009. SECTION 18 EXEMPTION FOR THE USE OF **IMAZAPIC-AMMONIUM** ON **PASTURE/RANGELAND** IN **NEBRASKA.**

DP Barcode: D256433
Submission #: S562739
Chemical#: 128943
Trade Name: Plateau
EPA Reg#: 241-365

PRAT Case#: 292007
Caswell#: NONE
Class: Herbicide
40 CFR: 180.490

TO: Libby Pemberton/Robert Forrest, PM Team 5
MUIERB/RD (7505C)

William Dykstra William H. Donovan Myrta R. Christian

FROM: William Dykstra, William Donovan, and Myrta Christian
RAB1/HED (7509C)

THRU: Melba Morrow, Branch Senior Scientist
RAB1/HED (7509C)

INTRODUCTION

The **Nebraska Department of Agriculture** is proposing a **Section 18 emergency exemption** for the use of **imazapic** on **pasture/rangeland** for control of **leafy spurge.** This is **the first** §18 request for this use. The proposed program will entail application of **15,141** gallons of **Plateau [30,281 lbs ai]** on **50% of 323,000** acres during the period **August 1, 1999 to July 1, 2000.**

SUMMARY

Occupational exposure and aggregate risk estimates **do not** exceed HED's level of concern. This Section 18 exemption should not pose an unacceptable aggregate risk to infants, children, or adults. Therefore, HED **has no objection** to the issuance of this Section 18 exemption for the use of **imazapic** on **pasture/rangeland** in the State of **Nebraska.** The following time-limited tolerances for residues of **imazapic and its hydroxymethyl metabolite** should be established to support this Section 18 exemption:

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grass forage	30 ppm
grass hay	15 ppm
milk	0.10 ppm
fat*	0.10 ppm
meat*	0.10 ppm
meat byproducts (except kidney)*	0.10 ppm
kidney*	1.0 ppm

* Cattle, goats, hogs, horses, and sheep

Note to RD: The 40 CFR 180.490 citation title should be changed from the name Cadre to imazapic-ammonium.

TOXICOLOGICAL ENDPOINTS

1) *Acute Toxicity.* **Acute RfD = 1.75 mg/kg/day; Acute PAD = 0.175 mg/kg/day.** For acute dietary risk assessment, the HIARC recommended **(6/15/99)** use of the NOAEL of **175** mg/kg/day, based on **developmental effects [increased incidence of fetuses with rudimentary ribs]** at the LOAEL of **350** mg/kg/day, from the **developmental** study in **rabbits (MRID# 42711423).** This risk assessment will evaluate acute dietary risk to pregnant females 13+, the population subgroup of concern. The acute dietary PAD is defined as the RfD/10x FQPA safety factor. The acute RfD is 1.75 mg/kg day is based on the developmental NOAEL of 175 mg/kg/day and the usual 100x uncertainty factor for intra- and inter-species differences and variations. The acute dietary aPAD is 0.175 mg/kg/day, based on the RfD of 1.75 mg/kg/day, and an additional uncertainty factor of 10x for FQPA. The 10x FQPA factor is being retained for this Section 18 only and is based on the HIARC determination of developmental effects below the level of maternal toxicity in the rabbit developmental study. There is no acute dietary aPAD for other population subgroups, including infants and children. **The acute dietary aPAD applies to this Section 18 only.**

2) *Chronic Toxicity.* **RfD = 0.5 mg/kg/day; cPAD = 0.05** mg/kg/day. The Reference Dose (RfD) was established based on a **one year feeding study** in **dogs (MRID# 42711421)** with a LOAEL of **137** mg/kg/day [lowest dose tested] based on **skeletal muscle degeneration. A NOAEL was not established in the study** (HIARC, **6/15/99**). An uncertainty factor of 3000x was recommended and was based on 10x for interspecies differences, 10x for intraspecies variations, 10x for FQPA, and 3x for absence of a NOAEL. **This cPAD only applies to this Section 18.**

NON-DIETARY

1) *Short-Term Toxicity.* For short-term Margin of Exposure (MOE) calculations, the HIARC **[6/15/99]** recommended use of the **developmental** NOAEL of **175** mg/kg/day from the **developmental** study in **rabbits (MRID# 42711423).** At the LOAEL of **350** mg/kg/day, there were **increased rudimentary ribs below a level of maternal toxicity.** The short term NOAEL can be used for both dermal and inhalation. An MOE of 100 is required for both dermal and inhalation exposure.

2) *Intermediate-Term Toxicity.* For intermediate-term dermal exposures, the HIARC recommended **[6/15/99]** use of the LOAEL of **137** mg/kg/day [lowest dose tested] from the **one year feeding study** in **dogs (MRID# 42711421).** At the LOAEL of **137** mg/kg/day, there was **skeletal muscle degeneration in both sexes.** The intermediate term LOAEL can be used for both dermal and inhalation exposures. An MOE of 300 is required for both dermal and inhalation exposure and is based on the usual 100x safety factor for intra- and inter-species differences and an addtional 3x safety factor for the absence of a NOAEL in the critical study.

3) *Chronic Toxicity.* The HIARC determined **[6/15/99]** that a chronic toxicity endpoint and risk assessment for **imazapic** is not required for workers for this Section 18.

4) *Dermal Penetration.* For short and intermediate-term exposure, a dermal penetration of **35%** has been determined by extrapolation methods by the HIARC. The dermal penetration value of 35% was based on the comparison of the maternal toxicity NOAEL of 350 mg/kg/day in the rabbit developmental study and the systemic NOAEL of 1000 mg/kg/day in the 21 day dermal toxicity study in rabbits. The NOAEL of 350 mg/kg/day divided by the NOAEL of 1,000 mg/kg/day yeilded 35% dermal penetration.

CANCER

Imazapic has been classified as a Group **"E" (evidence of non-carcinogenicity for humans)** chemical by the **RfD Committee [8/24/95].**

EXPOSURES AND RISKS

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor and/or outdoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

1. From Food and Feed Uses:

A permanent tolerance has been established (40 CFR 180.490) for residues of **imazapic and its hydroxymethyl metabolite** both free and conjugated, in or on peanut nutmeat at 0.1 ppm. *Note to RD:* 40 CFR 180.490 lists imazapic according to one of its trade names (Cadre). The ISO provisional name for this compound is imazapic; no ANSI name has been assigned yet. The CFR citation title should be changed from Cadre to imazapic-ammonium.

Acute Risk. The acute dietary (food only) risk assessment used the **TMRC (theoretical maximum residue contribution).** At the 95th percentile of exposure for user-days and per-capita days, the Tier 1 acute DEEM™ analysis predicts an exposure level of 0.000494 mg/kg/day for the females (13+, pregnant, not nursing) population subgroup, which is equivalent to 0.3% of the aPAD. This should be viewed as a **conservative** risk estimate; refinement using anticipated residue values and percent crop-treated data in conjunction with Monte Carlo analysis would result in a lower acute dietary exposure estimate.

Chronic Risk. In conducting this chronic dietary risk assessment, HED has made very conservative assumptions -- 100% of **grass hay and forage** and all other commodities having **imazapic** tolerances will contain **imazapic** residues and those residues would be at the level of

the tolerance -- which result in an overestimation of human dietary exposure. Thus, in making a safety determination for this tolerance, HED is taking into account this conservative exposure assessment.

The existing **imazapic** tolerances (published and including the necessary Section 18 tolerance(s)) result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

U.S. Population (48 States)	0.5 %
Nursing Infants (<1 year old)	**0.3 %**
Non-Nursing Infants (<1 year old)	**1.3 %**
Children (1-6 years old)	**1.4 %**
Children (7-12 years old)	**0.9 %**
Hispanics	0.6 %
Males 13-19 yrs	0.6 %

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; and, (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

2. *From Drinking Water:*

A Drinking Water Level of Comparison (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, with drinking water consumption, and body weights. Different populations will have different DWLOCs.

In a June 2, 1999 memo from J. Lin of EFED to W. Cutchin of RAB2, the following Tier I Drinking Water Modeling assessment was presented for imazapic for the pasture/rangeland Section 18.

GENeric Expected Environmental Concentration (GENEEC)

Acute and chronic (56-day) DWECs [drinking water estimated concentration] for surface water were calculated by GENEEC (GENeric Expected Environmental Concentration) screening model to be 7.57 and 4.16 ppb, respectively. According to HED drinking water guidance (HED SOP 98.4) the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the Tier 1 chronic surface water value is 1.39 ppb.

Surface Water Estimated Concentrations from GENEEC

Application Rate (lb. ai/A/yr)	Maximum Concentration (ppb)	56-Day Average Concentration (ppb)	56-Day Average Concentration (ppb) ÷ 3
0.1875	7.57	4.16	1.39

The modeling results indicate that imazapic herbicide does have the potential to move into surface waters under a conservative scenario, i.e., a soil with high runoff potential and a heavy rainfall event. The estimated maximum concentration of imazapic in surface water is 7.57 ppb and the 56-day average concentration divided by three is 1.39 ppb. These estimates are based on a maximum application rate of 0.1875 lbs ai/A/year, an aerobic soil half-life of 2010 days, a mean soil organic carbon partition coefficient (K_{oc}) of 112 L/kg, and a spray drift estimate of 5%. GENEEC estimates represent an upper bound on the maximum and average concentrations of imazapic in surface waters as a result of this use.

Screening Concentration In GROund Water (SCI-GROW)

A ground water estimate was made using the SCI-GROW (Screening Concentration In GROund Water) screening model based on actual ground water monitoring data collected from small-scale prospective ground water monitoring studies for the registration of a number of pesticides that serve as benchmarks for the model. EFED calculated the following DWEC for imazapic in ground water: 5.95 ppb. This concentration may be used for both the acute and chronic scenarios.

Ground Water Estimated Concentrations from SCI-GROW *

Application Rate	Concentration in Ground Water (ppb)
0.1875 lb a.i./A/yr	5.95

* Value used for comparison against the $DWLOC_{acute}$ and the $DWLOC_{chronic(cancer\ and\ non\text{-}cancer)}$.

Imazapic herbicide has the use patterns and environmental fate characteristics associated with a compound that could leach to ground water. The concentration estimated in ground water is 5.95 ppb. This estimate is based on a maximum application rate of 0.1875 lbs ai/A/year, an aerobic soil half-life of 2010 days, and a soil organic carbon partition coefficient (K_{oc}) of 112 l/kg. The estimate from SCI-GROW represents an upper bound on the concentration of imazapic in ground waters as a result of agricultural use.

HED followed OPP's Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments issued on 15-OCT-1998 (SOP 98.4). Thus, acute and chronic DWLOC values can be calculated from the acute and chronic food exposure values as follows:

$$DWLOC\ (\mu g/L) = \frac{water\ exposure\ (mg/kg/day)\ x\ (body\ weight)\ (kg)}{consumption\ (L)\ x\ 10^{-3}\ mg/\mu g}$$

where water exposure (mg/kg/day) = [(aPAD or PAD) - ((acute or chronic food) + residential exposure*) (mg/kg/day)]

* Residential exposure is only included when calculating chronic water exposure.

The DWLOC is the concentration in drinking water as a part of the aggregate exposure that occupies no more than 100% of the aPAD or cPAD. The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (child).

Table 1. Summary of DWLOC Calculations - Acute Scenario.

Population Subgroup[1]	Acute Scenario					
	aPAD mg/kg/day	Food Exposure mg/kg/day	%aPAD	SCI-GROW (ppb)[2]	Geneec (ppb)[2]	DWLOC (ppb)
Pregnant females, 13+ years	0.175	0.000494	0.3	6.0	7.6	5,200

[1] Population subgroup chosen was pregnant females, 13+ (60 kg body weight assumed), since this was the only population subgroup for which an acute dietary endpoint was selected.

Table 2. Summary of DWLOC Calculations - Chronic (Non-Cancer) Scenario.

Population Subgroup[1]	Chronic (Non-Cancer) Scenario					
	cPAD mg/kg/day	Food Exposure mg/kg/day	%cPAD	SCI-GROW (ppb)[2]	GENEEC (ppb)[2]	DWLOC (ppb)
U.S. Population (48 states)	0.05	0.000269	0.5	6.0	1.4	1,700
Non-nursing infants	0.05	0.000655	1.3	6.0	1.4	500
Pregnant Females, 13+	0.05	0.000218	0.4	6.0	1.4	1,500
Children, 1-6 years	0.05	0.000684	1.4	6.0	1.4	500

[1] Population subgroups chosen were U.S. population (70 kg body weight assumed), the infant/child subgroup with the highest food exposure (10 kg body weight assumed), the female subgroup with the highest food exposure (60 kg body weight assumed), and the other general population subgroup with the highest food exposure (70 kg body weight assumed).
[2] Based on the imazapic use rate on pasture grass/rangeland.

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For acute exposure to imazapic in surface and ground water, the DWLOC is 5,200 ppb for pregnant females, 13+, which is the population subgroup at risk. The acute DWEC values for imazapic in surface and ground water are 7.57 ppb and 5.95 ppb, respectively. The estimated peak concentrations of imazapic in surface and ground water are less than OPP's level of comparison for imazapic in drinking water as a contribution to acute aggregate exposure. Therefore, taking into account the Section 3 peanut use and the use proposed in this action, OPP concludes with reasonable certainty that residues of imazapic in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

For chronic (non-cancer) exposure to imazapic in surface and ground water, the DWLOCs are 1,700 ppb for the U.S. Population, 1,500 ppb for pregnant females, 500 ppb for children 1-6 years, and 500 ppb for non-nursing infants (< 1 year). The chronic DWEC values for imazapic in surface and ground water are 1.39 ppb and 5.95 ppb, respectively. The estimated average concentrations of imazapic in surface and ground water are less than OPP's level of comparison for imazapic in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of imazapic in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

3. *From Non-Dietary Uses:*

Imazapic is currently **not** registered for use on residential non-food sites. Therefore, exposures from non-dietary sources are not expected.

4. *From Cumulative Exposure To Substances with a Common Mechanism of Toxicity:*

Imazapic is a member of the **imidazolinone** class of pesticides. Other members of this class include imazapyr, imazethapyr, imazaquin, and imazamethabenz-methyl.

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

pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific data, much of which may not be presently available.

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

HED does not have, at this time, available data to determine whether **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, HED has not assumed that **imazapic** has a common mechanism of toxicity with other substances.

DETERMINATION OF SAFETY FOR U.S. POPULATION

1. Acute Aggregate Risk. For the population subgroup of concern, pregnant females 13+ years, the acute aggregate exposure only includes food and water. For pregnant females, 13+, 0.3% of the aPAD is occupied by dietary (food) exposure. The estimated maximum concentrations of imazapic in surface and ground water are less than HED's DWLOC for imazapic in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that the acute aggregate risks resulting from residues of imazapic in food and drinking water are below OPP's level of concern.

2. Chronic Aggregate Risk. For the U.S. population, 0.5% of the cPAD is occupied by dietary (food) exposure. Other highly exposed population subgroups include children 1-6 years [1.4% cPAD], hispanics [0.6% cPAD], pregnant females 13+ [0.4% cPAD] and males 13-19 years [0.6% cPAD]. HED generally has no concern for exposures below 100 percent of the cPAD, because the cPAD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. The estimated average concentrations of imazapic in surface and ground water are less than HED's DWLOC for imazapic in drinking water as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty that the chronic aggregate risks resulting from residues of imazapic in food and drinking water are below HED's level of concern.

3. Short- and Intermediate-Term Aggregate Risk. Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water (considered to be a background

exposure level) plus indoor and outdoor residential uses. Since there are no residential uses for imazapic, both short- and intermediate term aggregate risk assessments are not required.

DETERMINATION OF CANCER RISK

A cancer risk assessment is not required, since imazapic has been classified as a Group "E" [non-carcinogenicity for humans based on a negative tumorigenic potential in two acceptable animal studies].

ENDOCRINE DISRUPTER EFFECTS

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

DETERMINATION OF SAFETY FOR INFANTS AND CHILDREN

In assessing the potential for additional sensitivity of infants and children to residues of **imazapic**, HED considered data from developmental toxicity studies in the rat and rabbit and a 2-generation reproductive toxicity study in the rat. Developmental toxicity studies are designed to evaluate adverse effects on the developing fetus resulting from maternal pesticide exposure during gestation. Reproductive toxicity studies provide information relating to pre- and post-natal effects from exposure to the pesticide; information on the reproductive capability of mating animals, and data on systemic toxicity.

FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans. In either case, EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the no observed effect level in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. HED believes that reliable data support using the 100-fold margin/factor, rather than the 1000-fold margin/factor, when EPA has a complete data base under existing guidelines, and when the severity of the effect in infants or children, the potency or unusual toxic properties of a compound, or the quality of the exposure data do not raise concerns regarding the adequacy of the standard margin/factor.

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1. Developmental Toxicity Studies.

a. Rats.. In the developmental study **(MRID# 42711422)** in rats, the maternal (systemic) NOAEL was **1,000** mg/kg/day [HDT]. The developmental (fetal) NOAEL was **1,000** mg/kg/day [HDT].

b. Rabbits. In the developmental toxicity study **(MRID# 42711423)** in rabbits, the maternal (systemic) NOAEL was **350** mg/kg/day, based on **decreased body weight and food consumption** at the LOAEL of **500** mg/kg/day. The developmental (fetal) NOAEL was **175** mg/kg/day, based on **increased incidence of rudimentary ribs** at the LOAEL of **350** mg/kg/day.

2. Reproductive Toxicity Studies.

Rats. In the 2-generation reproductive toxicity study **(MRID# 43320305)** in rats, the maternal (systemic) NOAEL was **1,484** mg/kg/day [HDT]. The developmental (pup) NOAEL was **1,484** mg/kg/day [HDT]. The reproductive NOAEL was **1,484** mg/kg/day [HDT].

3. Pre- and Post-Natal Sensitivity.

The toxicological data base for evaluating pre- and post-natal toxicity for **imazapic** is complete with respect to current data requirements. **There appears to be extra-sensitivity based on the pre-natal results in the rabbit developmental study. The developmental NOAEL was 175 mg/kg/day based on the increased incidence of rudimentary ribs at the LOAEL of 350 mg/kg/day. In contrast, the maternal NOAEL was 350 mg/kg/day based on decreased body weight and food consumption at the LOAEL of 500 mg/kg/day. Therefore, pre-natal developmental toxicity occurred at a dose level [350 mg/kg/day], which did not demonstrate any maternal toxicity.** Based on the above, HED concludes that reliable data support use of a 1000-fold margin of exposure/uncertainty factor to protect infants and children. Based on the conclusions of the rabbit developmental study, RAB1 used the FQPA Tier I approach which retains the **10X** safety factor for purposes of this Section 18 only.

4. Acute Aggregate Risk.

The aPAD only applies to pregnant females, 13+ and is not required for infants (<1 year), non-nursing infants, and children (1-6 years). For pregnant females, 13+, dietary exposure utilized 0.4% of the aPAD. The estimated average concentrations of imazapic in surface and ground water are less than OPP's level of concern for imazapic in drinking water as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that the acute aggregate risks resulting residues of imazapic in food and drinking water are below OPP's level of concern.

5. Chronic Aggregate Risk.

The %cPAD utilized for chronic dietary exposure were 1.3% for non-nursing infants, 1.4% for children 1-6 years, and 1.0% for all infants (<1 year). The estimated average concentrations of imazapic in surface and ground water are less than OPP's level of concern for imazapic in drinking water as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that the chronic aggregate risks resulting residues of imazapic in food and drinking water are below OPP's level of concern.

Taking into account the completeness and reliability of the toxicity data and this conservative exposure assessment, HED concludes that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to **imazapic** residues.

6. Short- and Intermediate-Term Aggregate Risk.

Since there are no residential uses for imazapic, contributions to the aggregate risk from both short- and intermediate non-dietary exposures are not expected.

DETERMINATION OF SAFETY TO OCCUPATIONALLY EXPOSED WORKERS

1. This risk assessment was based on the Pesticide Handler Exposure Database (PHED) unit exposure estimates for workers wearing long pants, long sleeves, gloves (no gloves for aerial applicators), open cab ground equipment, and close cab aerial equipment. Work clothing assumptions are based on the Section 3 label for use of Cadre® herbicide on peanuts. The PM is advised that the label submitted for this Section 18 use does not include work clothing or PPE statements. Therefore, the above mentioned clothing requirements should be included with the label.

   Exposure risk estimates are provided for commercial aerial applications (mixer/loader and applicators) and for farmers treating their own fields.

2. The risk estimates indicate that the potential risks for occupational workers from short and intermediate-term exposures from the proposed Section 18 uses of imazapic on grass forage and hay do not exceed the Agency's level of concern. The MOEs for short- and intermediate-term dermal and inhalation exposures ranged from 8,750 to 31,800 and 52,692 to 833,300, respectively. MOEs ≥100 and ≥300 are considered acceptable for short- and intermediate-term exposure, respectively.

3. Chronic exposures are not expected from the proposed section 18 use of imazapic on grass forage and hay, therefore a risk assessment was not conducted.

4. The restricted entry interval (REI) does not appear on the label. Based on imazapic acute toxicity classification, an interim REI of 12 hours is appropriate for this Section 18.

5. There are no chemical-specific data available to determine the potential risks from post application activities associated with this proposed section 18 use of imazapic on grass forage and hay. However, potential postapplication exposures are not of concern, based on the use pattern, methods, and number of applications.

6. Occupational exposure assumptions and estimates of exposure are summarized in Tables 3 and 4, respectively.

7. Imazapic is not currently registered for any residential uses.

Table 3. Worker Exposures and Assumptions

Exposure Scenario	Assumptions					
	Dermal Unit Exposure (ug/lb ai)	Inhalation Unit Exposure (ug/lb ai)	Application rate (lb ai/A)	Acres/ Day[1]	Clothing/ PPE	Data sourc
Mixer/ Loader (aerial)	23	1.2	0.187	1000	Long-sleeved shirt, long pants, and gloves	Unit exposures: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure guide, August 1998; estimates for all liquid, open mixing/loading Data quality: high confidence for dermal and inhalation
Applicator Aerial - enclosed cockpits	5.0	0.068	0.187	1000	Long-sleeved shirt and long pants	Unit exposures: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure guide, August 1998; estimates for aerial/fixed-wing/enclosed cab/liquid. Data quality: medium confidence for dermal and inhalation
Mixer/loader + applicator (farmer)	37	1.94	0.187	500	Long-sleeved shirt, long pants, and gloves	Unit exposures were estimated by adding the M/L and applicator(groundboom) unit exposures

[1] Number of acres treated based on Census of Agriculture, part 27: 7.

Table 4. Worker Exposure and Risk Assessment

Exposure Scenario[1]	Exposure (mg/kg/day)[2]				MOE[5]			
	Dermal		Inhalation		Dermal		Inhalation	
	Short-term[3]	Inter mediate-term[4]	Short-term[3]	Inter mediate-term[4]	Short-term	Inter mediate-term	Short-term	Inter-mediate-term
Mixer/Loader (aerial)	0.025	0.022	0.0037	0.0032	7,000	6,400	47,300	42,800
Applicator Aerial - enclosed cockpits	0.0055	0.0044	0.00021	0.00018	31,800	31,100	833,300	72,100
Mixer/Loader + applicator (farmer)	0.020	0.017	0.0030	0.0026	8,750	8,060	58,300	52,700

[1] Unit exposures for M/L/A were calculated by adding the M/L and Applicator (groundboom) unit exposures

[2] Exposure = unit exposure × application rate × acres/day × 1/bw (60 kg and 70 kg for short- and intermediate-term inhalation and dermal exposure, respectively) Dermal absorption factor of 35 % for short- and intermediate- term dermal risk assessment

[3] Short-term dermal and inhalation NOAEL= 175 mg/kg/day; MOE= 100

[4] Intermediate-term dermal and inhalation NOAEL= 137 mg/kg/day; MOE = 300

[5] MOE = NOAEL ÷ Exposure

OTHER CONSIDERATIONS

Metabolism in Plants and Livestock

The nature of the residue in plants and livestock has been adequately defined for this Section 18. The residues of concern in peanuts are imazapic (CL263222) and its hydroxymethyl metabolite (CL263284), both free and conjugated, as determined at a 18-SEP-1995 meeting of the HED Metabolism Assessment Review Committee (MARC). For the purposes of this Section 18 only, the residues of concern in grass are imazapic and its hydroxymethyl metabolite, both free and conjugated. Based on the results of a goat metabolism study (MRID 43320319), the residues of concern in ruminants were identified as imazapic (CL263222) and its hydroxymethyl metabolite (CL263284) (memo, B. Madden, 15-FEB-1996). Thus, for the purposes of this Section 18 only, the residues of concern in animals are imazapic and its hydroxymethyl metabolite.

Analytical Enforcement Methodology

An adequate analytical enforcement method is available to enforce the grass forage and hay tolerances for imazapic and its hydroxymethyl metabolite. American Cyanamide Company

submitted an Independent Laboratory Validation (ILV) of a Capillary Electrophoresis (CE) determinative method (Method M3114) for determination of imazapic, CL 263284, and CL 189215 residues in grass (MRID 448177-09). Satisfactory recovery values were reported for all three compounds over a range of 0.5 to 50 ppm. A similar CE method (Method M2253.02) for peanut commodities was successfully validated by the EPA Analytical Chemistry Laboratory and found suitable for enforcement of the 0.1 ppm peanut tolerance (B. Madden, 15-FEB-1996).

Adequate analytical enforcement methods are available to enforce the animal commodity tolerances for imazapic and its hydroxymethyl metabolite. American Cyanamide Company submitted Independent Laboratory Validations (ILVs) of Capillary Electrophoresis (CE) determinative and LC/MS confirmatory methods (Methods M3118; M3222; and M3233) for determination of imazapic and CL 263284 residues in milk; cattle muscle, kidney, and liver tissue; and bovine milk fat and tissue fat, respectively (MRID 448177-10). Satisfactory recovery values were reported for both compounds over a range of 0.010 to 1.0 ppm in milk and milk fat, and from 0.050 to 1.0 ppm in the other animal commodities.

Multiresidue Method

The petitioner submitted data on the recovery of imazapic using FDA multiresidue protocols (MRID 433203-22). The results were sent to FDA in a memo from Francis D. Griffith, Jr. (09-FEB-1995). Methylated parent imazapic was the only compound detected by the nitrogen-phosphorus detector (NPD) at reasonable levels using OV-101 and OV-17 columns.

Storage Stability Data

A study is reported in MRID #448177-12 describing the stability of imazapic and its hydroxymethyl metabolite CL263284 in animal commodities. This study demonstrated the stability of both compounds for at least 5 months in cattle kidney, liver, and meat tissues. Stability in milk was demonstrated for at least 6 months.

In addition, MRID #448177-11 reports a study demonstrating the stability of wheat green forage, wheat hay, wheat straw, and wheat grain in frozen storage. In all wheat RACs, both imazapic and CL263284 were shown to be stable for at least 24 months. HED is willing to translate the wheat results to grass for the purposes of this Section 18 action and thus finds that the registrant has adequately demonstrated the stability of imazapic and CL263284 in grass and animal commodities.

Meat, Milk, Poultry, and Eggs

Grass forage and hay constitute ruminant feed items (but are not fed to poultry or swine). Calculation of the maximum theoretical dietary burden (MTDB) based on the appropriate grass tolerance levels is given in Table 5.

Table 5. Calculation of Maximum Theoretical Dietary Burdens (MTDBs) for Beef and Dairy Cattle.				
Feed Item	Tolerance[1]	%DM[2]	% in Diet[2]	MTDB[3] (ppm)
			Beef and Dairy Cattle	Beef and Dairy Cattle
Grass Forage	30	25	60	72
Grass Hay	15	88	40	6.8
TOTAL				79

1 Tolerance level residue in ppm.

2 The % dry matter (%DM) and % in diet values for each feed item were based on information contained in Table 1 of OPPTS Test Guidelines Series 860.1000.

3 The maximum theoretical dietary burden for each feed item is calculated by multiplying (Tolerance/%DM) by the % of the feed item in the diet. The total MTDB is the sum of the individual feed item dietary burdens.

Comparison of the MTDB to the results of a 28-day bovine feeding study (MRID # 448177-14) shows that animal commodity tolerances are needed since measured residues extrapolated to a 10x MTDB feeding rate exceed 0.010 ppm (Table 6). When normalizing the data in Table 6 to a 1x rate, the appropriate tolerance level for meat, fat, milk and meat byproducts is 0.10 ppm. For kidney, the expected residue at the 1x dose rate can be calculated using data from all three experimental dose rates: [(0.43 ppm/0.848) + (1.62 ppm/2.83) + (2.76 ppm/8.58)] ÷ 3 = 0.47 ppm. Thus, a tolerance level of 1.0 ppm should be adequate to cover the expected residue level in kidney based on the MTDB of 79 ppm.

Table 6. Results of 28-day Bovine Feeding Study Using the Indicated Imazapic Doses.

Matrix	66.8 ppm (0.848x)[1]			223 ppm (2.83x)[1]			676 ppm (8.58x)[1]		
	CL263222	CL263284	Total[2]	CL263222	CL263284	Total[2]	CL263222	CL263284	Total[2]
Muscle	<0.05	<0.05	<0.10	<0.05	<0.05	<0.10	0.079	<0.05	<0.129
Liver	<0.05	<0.05	<0.10	0.082	<0.05	<0.132	0.19	<0.05	<0.24
Kidney	0.38	<0.05	<0.43	1.57	<0.05	<1.62	2.71	<0.05	<2.76
Fat	<0.05	<0.05	<0.10	<0.05	<0.05	<0.10	<0.05	<0.05	<0.10
Milk	0.025	<0.01	<0.035	0.077	<0.01	<0.087	0.27	<0.01	<0.28

1 Average dosing level of three dairy cows; exaggeration rate calculated by dividing dose level by the MTDB.

2 Sum of CL263222 and CL263284 residues.

Crop Field Trials

In accord with OPPTS 860.1500 guidelines, the registrant provided the results of crop field trial studies of bermudagrass, brome grass, and big bluestem. A total of 13 residue trials were conducted in 1996 and 1997. Residues of imazapic and its hydroxymethyl metabolite, free and glucose-conjugated, are not expected to exceed 30 and 15 ppm in/on grass forage and hay, respectively, as a result of this Section 18 use. The hay tolerance applies when the seven day

haying restriction listed on the Section 18 label is observed. Time-limited tolerances should be established at these levels.

Secondary residues in animal commodities are not expected to exceed 0.10 ppm in milk, meat, fat, or meat byproducts (except kidney); or 1.0 ppm in kidney as a result of this Section 18 use. Time-limited tolerances should be established at these levels.

Processed Food/Feed

There are no processed food/feed items resulting from this Section 18 proposed use.

Rotational Crop Restrictions

The petitioner has submitted the results of a ^{14}C-imazapic confined accumulation in rotational crops study (MRID 42711447); this study was reviewed by HED (memo, B. Madden, 15-FEB-1996). To summarize, HED considers 12 months to be the longest practical plantback interval and those plantbacks proposed for longer than 12 months should be removed from the label. The petitioner has presented data indicating that crops planted 270 days after treatment show signs of phytotoxicity (memo, J. Garbus, 06-FEB-1996). If the petitioner insists that 18 months or longer are essential due to concerns about phytotoxicity, then a detailed explanation with supporting data should be submitted for our consideration.

SUPPLEMENTAL INFORMATION

DIETARY EXPOSURE

Table 7. Residue Consideration Summary Table

PARAMETER	PROPOSED USE	RESIDUE DATA
CHEMICAL	Imazapic	Imazapic
FORMULATION	Plateau	Plateau
CROP	Grass	Grass
TYPE APPLICATION	Ground or aerial	Ground
# APPLICATIONS	1 or 2	1 or 2
TIMING	For 1 application: fall or spring For 2 applications: fall and spring	For 1 application: spring For 2 applications: fall and spring
RATE/APPLICATION	0.1875 lbs ai/A for 1 application 0.125 lbs ai/A in the fall followed by 0.0625 lbs ai/A in the spring for 2 applications.	0.20 lbs ai/A for 1 application: 9 field trials 0.14 lbs ai/A in the fall followed by 0.07 lbs ai/A in the spring for 2 applications: 4 field trials.
RATE/YEAR or SEASON	0.1875 lbs ai/A	0.20 - 0.21 lbs ai/A

Table 7. Residue Consideration Summary Table		
PARAMETER	**PROPOSED USE**	**RESIDUE DATA**
MAXIMUM RESIDUE	N/A	Grass forage 25 ppm Grass hay 10 ppm (7 days after treatment)
RESTRICTIONS	Do not harvest hay for 7 days after treatment with Plateau	
RESIDUE DATA SOURCE	N/A	American Cyanamid Co.
PERFORMING LAB	N/A	American Cyanamid Co.

ADDITIONAL INFORMATION

Progress Toward Registration. The registrant submitted a Section 3 request for registration of Plateau for use on pastures/rangeland and Conservation Reserve Program (CRP) land to EPA in April of 1999.

Reregistration Status. Imazapic is not a reregistration list chemical.

International Residue Limits. There are no CODEX, Canadian, or Mexican maximum residue limits for imazapic on pastures/rangeland (see Attachment 1).

Attachments:
1) International residue limit status sheet
2) DEEM Analyses: Acute and Chronic: D256953, W. Donovan, 24-JUN-1999

cc with Attachments: W. Dykstra
cc without Attachments: W. Donovan, M. Christian, O. Odiott, Section 18 File
RDI: M. Morrow (30-JUN-1999), RAB1 Branch Reviewers (30-JUN-1999)
W. Dykstra:CM#2:806R:(703)305-7432

Attachment 1

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	X□ Proposed tolerance □ Reevaluated tolerance □ Other	Date: 6/21/99
(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid	Imazapic (ISO 1750 (provisional))		

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: 99NE0009 DP Barcode: D256433 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: W. Donovan/RAB1
	Residue definition: Imazapic and its hydroxymethyl metabolite CL263284

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		grass forage	30
		grass hay	15
		meat, fat, meat byproducts (except kidney), and milk	0.10
		kidney	1.0
		peanuts	0.1

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	X No Limits □ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions:

Rev. 1998