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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS

MEMORANDUM

DATE: 24-JUN-1999

SUBJECT: ID# 99NE0009. Section 18 Exemption for the Use of Imazapic on Rangeland/Pastureland to Control Leafy Spurge in Nebraska: **Acute and Chronic Dietary Exposure Analysis**. Chemical#: 128943. DP Barcode: D256953.

FROM: William H. Donovan, Ph.D., Chemist
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THROUGH: William Cutchin, Chemist
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TO: William Dykstra, Ph.D., Toxicologist
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Action Requested

Provide an estimate of the acute and chronic dietary exposure and associated risk for imazapic and its hydroxymethyl metabolite resulting from published tolerances and the appropriate Section 18 tolerance levels from the proposed use on grass forage at 30 ppm and on grass hay at 15 ppm (99NE0009). Because grass forage and hay are ruminant feed items, tolerances of 0.10 ppm are needed for milk, meat, meat byproducts (except kidney), and fat; for kidney, a tolerance of 1.0 ppm is appropriate. A previous chronic dietary exposure analysis incorporating peanut tolerances (0.1 ppm) using the Dietary Risk Evaluation System (DRES) was completed on 01-DEC-1995 (B. Madden) and utilized in a risk assessment document supporting the imazapic registration on peanuts (15-FEB-1996, B. Madden).

Executive Summary

Tier 1 Dietary Exposure Evaluation Model (DEEM™) analysis indicates that dietary (food only) risk associated with the proposed use of imazapic on rangeland/pastureland is below the Agency's levels of concern for acute and chronic exposure scenarios. The acute and chronic analyses are highly conservative, representing likely overestimations of the actual exposure resulting from the registered and proposed uses.

Toxicological Endpoints

Acute

Acute Reference Dose (aRfD) = 1.75 mg/kg/day. For acute dietary risk assessment, the Hazard Identification Assessment Review Committee (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). The population subgroup of concern for acute dietary exposure is pregnant females 13+. The aRfD is 1.75 mg/kg/day, based on the developmental NOAEL and an uncertainty factor of 100x [10x for interspecies differences and 10x for intraspecies variations]. There is no aRfD for other population subgroups, including infants and children.

Chronic

Chronic Reference Dose (cRfD) = 0.5 mg/kg/day. The cPAD was established based on a one year feeding study in dogs (MRID# 42711421) with a LOAEL of 137 mg/kg/day [lowest dose tested] and an uncertainty factor of 300 based on skeletal muscle degeneration. A NOAEL was not established in the study (HIARC, 6/15/99). The 300x uncertainty factor was based on 10x for interspecies differences, 10x for intraspecies variations, and 3x for absence of a NOAEL. This cRfD applies only to this Section 18.

Cancer

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

FQPA Safety Factor

Because imazapic has not been evaluated by the FQPA Safety Factor Committee, a value of 10x was assumed for both the acute and chronic analyses. 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. A reference dose (RfD) which includes the FQPA safety factor (10x, 3x, or 1x) is defined as the Population Adjusted Dose (PAD). In the case of imazapic, *for this Section 18 only*, the acute PAD (aPAD) is 0.175 mg/kg/day, and the chronic PAD (cPAD) is 0.05 mg/kg/day. These values are appropriate for use in the acute and chronic dietary analyses, respectively.

Residue Information

The only permanent tolerance for imazapic (also known as Cadre or CL263222) and its hydroxymethyl metabolite (CL263284) in/on peanut nutmeat at 0.1 ppm has been published under 40 CFR §180.490. Derivation of the appropriate animal commodity tolerances is given in Tables 1 and 2; the feeding study data were taken from MRID 448177-14. Complete listings of the DEEM™ input values are given in Attachments 1 and 3 for the acute and chronic scenarios, respectively.

Table 1. 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.

Table 2. 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.

When normalizing the data in Table 2 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.

Results and Discussion

The present Tier 1 DEEM™ analysis employed the following assumptions for both the acute and chronic analyses: tolerance-level residues, default processing factors, and 100% percent crop treated.

Acute Analysis
The DEEM™ analysis 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. The acute endpoint applies to two population subgroups in the DEEM™ program: females (13+, pregnant, not nursing) and females (13-50 years). At the 95th percentile of exposure, the Tier 1 acute DEEM™ analysis gave the results shown in Table 3. Identical results were obtained when expressing exposure in terms of user-days or per-capita days.

Table 3. Summary of Results from Acute DEEM™ Analysis of Imazapic.

Subgroup	Exposure (mg/kg/day)	% aPAD
Females (13+, pregnant, not nursing)	0.000494	0.3
Females (13-50 years)	0.000475	0.3

The results of this analysis indicate that the acute dietary risk associated with the existing use and the proposed use of imazapic is below HED's level of concern.

Chronic Analysis
The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 nationwide CSFII and accumulated exposure to the chemical for each commodity. 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 DEEM™ Analysis of Imazapic.

Subgroup	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.000269	0.5
Hispanics	0.000288	0.6
Children (1-6 years old)	0.000684	1.4
Males (13-19 years)	0.000297	0.6

The population subgroups listed in Table 4 include 1) the U.S. Population (48 states), 2) the most highly exposed subgroup from the infants and children subgroups, and 3) other subgroups with exposures higher than that of the U.S. Population (48 states). The results of this analysis indicate that the chronic dietary risk associated with the existing use and the proposed use of imazapic is below HED's level of concern.

Attachment 1: Imazapic residue file for acute and chronic analyses.
Attachment 2: Imazapic acute DEEM™ analysis.
Attachment 3: Imazapic chronic DEEM™ analysis.

cc with Attachments: W. Donovan (RAB1); M. Sahafeyen (CEB1)
RDI: W. Cutchin (23-JUN-1999), S. Piper (22-JUN-1999)
W. Donovan:CM#2: 806-T:(703)305-7330:24-JUN-1999

Attachment 1: Imazapic residue file for acute and chronic analyses.

Filename: C:\deemepa\128943.R96Chemical name: Imazapic
RfD(Chronic): .05 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): .175 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 06-21-1999/12:49:37/8 Program ver. 6.77
Comment: aPAD & cPAD include a 10x safety factor

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
323	M	Beef-dried	0.100000	0	1.920	1.000	99NE0009
324	M	Beef-fat w/o bones	0.100000	0	1.000	1.000	99NE0009
325	M	Beef-kidney	1.000000	0	1.000	1.000	99NE0009
327	M	Beef-lean (fat/free) w/o bones	0.100000	0	1.000	1.000	99NE0009
326	M	Beef-liver	0.100000	0	1.000	1.000	99NE0009
321	M	Beef-meat byproducts	0.100000	0	1.000	1.000	99NE0009
322	M	Beef-other organ meats	0.100000	0	1.000	1.000	99NE0009
330	M	Goat-fat w/o bone	0.100000	0	1.000	1.000	99NE0009
331	M	Goat-kidney	1.000000	0	1.000	1.000	99NE0009
333	M	Goat-lean (fat/free) w/o bone	0.100000	0	1.000	1.000	99NE0009
332	M	Goat-liver	0.100000	0	1.000	1.000	99NE0009
328	M	Goat-meat byproducts	0.100000	0	1.000	1.000	99NE0009
329	M	Goat-other organ meats	0.100000	0	1.000	1.000	99NE0009
334	M	Horsemeat	0.100000	0	1.000	1.000	99NE0009
319	D	Milk-fat solids	0.100000	0	1.000	1.000	99NE0009
318	D	Milk-nonfat solids	0.100000	0	1.000	1.000	99NE0009
320	D	Milk sugar (lactose)	0.100000	0	1.000	1.000	99NE0009
403	O	Peanuts-butter	0.100000	0	1.890	1.000	4F4390
940	O	Peanuts-hulled	0.100000	0	1.000	1.000	4F4390
293	O	Peanuts-oil	0.100000	0	1.000	1.000	4F4390
344	M	Pork-fat w/o bone	0.100000	0	1.000	1.000	99NE0009
345	M	Pork-kidney	1.000000	0	1.000	1.000	99NE0009
347	M	Pork-lean (fat free) w/o bone	0.100000	0	1.000	1.000	99NE0009
346	M	Pork-liver	0.100000	0	1.000	1.000	99NE0009
342	M	Pork-meat byproducts	0.100000	0	1.000	1.000	99NE0009
343	M	Pork-other organ meats	0.100000	0	1.000	1.000	99NE0009
338	M	Sheep-fat w/o bone	0.100000	0	1.000	1.000	99NE0009
339	M	Sheep-kidney	1.000000	0	1.000	1.000	99NE0009
341	M	Sheep-lean (fat free) w/o bone	0.100000	0	1.000	1.000	99NE0009
340	M	Sheep-liver	0.100000	0	1.000	1.000	99NE0009
336	M	Sheep-meat byproducts	0.100000	0	1.000	1.000	99NE0009
337	M	Sheep-other organ meats	0.100000	0	1.000	1.000	99NE0009
429	M	Veal-dried	0.100000	0	1.920	1.000	99NE0009
424	M	Veal-fat w/o bones	0.100000	0	1.000	1.000	99NE0009
426	M	Veal-kidney	1.000000	0	1.000	1.000	99NE0009
425	M	Veal-lean (fat free) w/o bones	0.100000	0	1.000	1.000	99NE0009
427	M	Veal-liver	0.100000	0	1.000	1.000	99NE0009
430	M	Veal-meat byproducts	0.100000	0	1.000	1.000	99NE0009
428	M	Veal-other organ meats	0.100000	0	1.000	1.000	99NE0009

Attachment 2: Imazapic acute DEEM™ analysis.

U.S. Environmental Protection Agency Ver. 6.78
DEEM ACUTE analysis for IMAZAPIC (1989-92 data)
Residue file: 128943.r96 Adjustment factor #2 NOT used.
Analysis Date: 06-22-1999/11:41:14 Residue file dated: 06-21-1999/12:49:37/8
Acute Reference Dose (aRfD) = 0.175000 mg/kg body-wt/day
Run Comment: aPAD & cPAD include a 10x safety factor

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
Females (13+/preg/not nsg):	0.000494	0.28	0.000633	0.36	0.000758	0.43
Females (13-50 years):	0.000475	0.27	0.000704	0.40	0.001108	0.63

Attachment 3: Imazapic chronic DEEM™ analysis.

U.S. Environmental Protection Agency Ver. 6.76
DEEM Chronic analysis for IMAZAPIC (1989-92 data)
Residue file name: C:\deemepa\128943.r96 Adjustment factor #2 NOT used.
Analysis Date 06-21-1999/12:51:12 Residue file dated: 06-21-1999/12:49:37/8
Reference dose (RfD, CHRONIC) = .05 mg/kg bw/day
COMMENT 1: aPAD & cPAD include a 10x safety factor

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000269	0.5%
U.S. Population (spring season)	0.000268	0.5%
U.S. Population (summer season)	0.000269	0.5%
U.S. Population (autumn season)	0.000274	0.5%
U.S. Population (winter season)	0.000266	0.5%
Northeast region	0.000263	0.5%
Midwest region	0.000297	0.6%
Southern region	0.000266	0.5%
Western region	0.000249	0.5%
Hispanics	0.000288	0.6%
Non-hispanic whites	0.000267	0.5%
Non-hispanic blacks	0.000269	0.5%
Non-hisp/non-white/non-black)	0.000269	0.5%
All infants (< 1 year)	0.000505	1.0%
Nursing infants	0.000147	0.3%
Non-nursing infants	0.000655	1.3%
Children 1-6 yrs	0.000684	1.4%
Children 7-12 yrs	0.000425	0.9%
Females 13-19(not preg or nursing)	0.000237	0.5%
Females 20+ (not preg or nursing)	0.000168	0.3%
Females 13-50 yrs	0.000189	0.4%
Females 13+ (preg/not nursing)	0.000218	0.4%
Females 13+ (nursing)	0.000223	0.4%
Males 13-19 yrs	0.000297	0.6%
Males 20+ yrs	0.000208	0.4%
Seniors 55+	0.000165	0.3%
Pacific Region	0.000245	0.5%