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February 15, 1996

MEMORANDUM

SUBJECT: **Ammonium Salt of (±) 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid - 128943 and 129041:** Health Effects Division Risk Characterization for Ammonium Salt of (±) 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridine carboxylic acid for Use as a Herbicide in/on Peanuts.

FROM: Barbara Madden, Biologist
Registration Section
Risk Characterization and Analysis Branch
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THROUGH: Michael Metzger, Acting Chief
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and

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TO: Karen Hicks/Robert Taylor PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

I. EXECUTIVE SUMMARY

CL 263,222 or CADRE® are trade names for the new chemical, ammonium salt of (±) 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid. The pending common (ANSI) name for this chemical is imazameth. American Cyanamid Company is pursuing registration of ammonium salt of (±) 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid. Data have been submitted to support the application for registration of CADRE® technical, 96.4 percent active ingredient (a.i.), EPA File Symbol 241-GAG and

a formulated end use product, CADRE® Herbicide, 23.6 percent a.i., EPA File Symbol 241-GAU.

A summary of the findings and an assessment of human risk resulting from the proposed use of CL 263,222 are provided in this document. The Hazard Assessment was provided by Edwin R. Budd, of Toxicology Branch I, the Product and Residue Chemistry review by Joel Garbus, PhD. of Chemistry Branch 1 - Tolerance Support, the Occupational Exposure Assessments by Tina Manville of the Occupational and Residential Exposure Branch.

The toxicology data base has been reviewed and is complete. There are still data deficiencies in the residue chemistry data base but it is sufficient to support a conditional registration allowing time for the deficiencies to be satisfied. Both dietary and occupational/residential risk for use of CL 263,222 on peanuts are minimal.

II. USE PATTERN

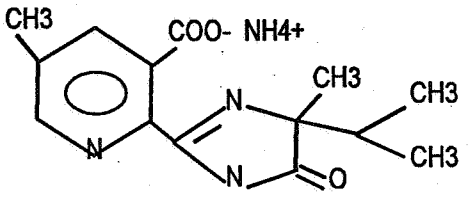
The proposed use is for registration of CL 263,222 in the form of CADRE® Herbicide, 23.6 percent a.i., as a herbicide to control certain broadleaf weeds and grass weeds in/on peanuts.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

SYNONYMS: Cadre; 2-(4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-imidazol-2-yl)-5-methyl-3-pyridinecarboxylic acid.

STRUCTURE:



With the submission of analytical standards all Product Chemistry requirements for CL 263,222 have been met.

B. Human Risk Assessment

1. HAZARD ASSESSMENT

Toxicology Data Requirements (40 CFR §158.340) for a Food Use

Test		Technical CL 263,222		
		Required	Satisfied	MRID
81-1	Acute Oral Toxicity (Rat)	Y	Y	427114-07
81-2	Acute Dermal Toxicity (Rabbit)	Y	Y	427114-08
81-3	Acute Inhalation Toxicity (Rat)	Y	Y[1]	427114-09
81-4	Primary Eye Irritation (Rabbit)	Y	Y	427114-10
81-5	Primary Dermal Irritation (Rabbit)	Y	Y	427114-11
81-6	Dermal Sensitization (Guinea Pig)	Y	Y	427114-12
81-7	Acute Delayed Neurotox. (Hen)	N	-	-
81-8-ss	Acute Neurotox. Screening Battery (Rat)	Reserved[2]	-	-
82-1(a)	Oral Subchronic, Rodent (Rat)	Y	Y	427114-19
82-1(b)	Oral Subchronic, Non-Rodent (Dog)	Y	Y[3]	-
82-2	21-Day Dermal	Y	Y	427114-20
82-3	90-Day Dermal	N	-	-
82-4	90-Day Inhalation	N	-	-
82-6	28-Day Delayed Neurotoxicity (Hen)	N	-	-
82-7	90 Day Neurotoxicity Screening Battery (Rat)	Reserved[2]	-	-
83-1(b)	Chronic Toxicity, Non-rodent (Dog)	Y	Y	427114-21
83-3(a)	Developmental Toxicity, Rodent (Rat)	Y	Y	427114-22
83-3(b)	Developmental Toxicity, Non-rodent (Rabbit)	Y	Y	427114-23
83-4	2-Generation Reproduction (Rat)	Y	Y	433203-05
83-5	Chronic/Oncogenicity (Rat)	Y	Y	433203-07
83-5	Chronic/Oncogenicity (Mouse)	Y	Y	433203-06
83-6	Postnatal Developmental Toxicity	N	-	-
84-2(a)	Mutagenicity—Gene Mutation	Y	Y	427114-24
84-2(b)	Mutagenicity—Structural Chromosomal Aberrations	Y	Y	427114-26 & -27
84-4	Other	Y	Y	427114-25
85-1	General Metabolism	Y	Y	427114-29
85-2	Dermal Penetration	N	-	-
85-4	Visual System Studies	N	-	-
85-7	Immunotoxicity	Reserved[2]	-	-
86-1	Domestic Animal Safety	N	-	-

Y yes
N no

[1] The submitted study was originally classified as unacceptable due to large particle size. The applicant was required to provide an explanation for the large particle size or repeat the study. An explanation has been provided in this submission and when evaluated together with other information on the toxicity of this chemical, the study has been reclassified as acceptable. The requirement for an acute inhalation toxicity study on the technical grade product is now considered to be satisfied.

[2] This study requirement is reserved at this time. A study may be required to be submitted at some time in the future.

[3] This requirement is satisfied by the 1-year chronic feeding study on dogs (MRID No. 427114-21).

a. Acute Toxicity

The table below is a summary of the acute toxicity of the Technical Grade Active Ingredient (TGAI) for CL 263,222.

TEST	RESULTS	CATEGORY
Oral LD50 - rat	> 5000 mg/kg for males & females	IV
Dermal LD50 - rabbit	> 2000 mg/kg for males & females	III
Inhalation LC50 - rat	> 5.52 mg/L	IV
Eye irritation - rabbit	Minimally irritating	III
Dermal irritation - rabbit	Non-irritating	IV
Dermal sensitization- guinea pig	Nonsensitizer	

b. Subchronic Toxicity

i. Subchronic Oral Toxicity in Rats

A subchronic oral toxicity study in rats (MRID 427114-19) was conducted with CL 263,222 technical for thirteen weeks. CL 263,222 was administered orally to rats at dose levels of 0, 5000, 10,000 or 20,000 ppm (0, 386, 760, or 1522 mg/kg/day in males and 0, 429, 848, or 1728 mg/kg/day in females). No overt signs of toxicity were observed at dietary levels of 5000, 10,000, or 20,000 ppm CL 263,222. Although a Lowest Observed Effect Level (LOEL) was not established, the highest dose tested exceeded 1000 mg/kg body weight/day, the limit dose. A statistically significant ($p<0.05$) reduction in mean body weight gain was observed in mid-dose females and high-dose males and females at week 11 only. Body weight gains were also reduced in low-dose animals (66-67% of controls) and mid-dose males (86% of controls) at week 11 only; and in low-dose females (33% of controls) at week 13 only. However, total body weight gains for weeks 1-13 were comparable to or in excess of controls for both sexes. No trends or statistically significant changes in mean body weights were observed. No treatment-related effects were observed for any of the following parameters: mortality, clinical observations, food consumption, hematology, clinical chemistries, urinalysis, gross necropsy, absolute or relative organ weiths, or histopathology. No Lowest Observed Effect Level (LOEL) was established. The No Observed Effect Level (NOEL) is 1522 mg/kg/day in males and 1728 mg/kg/day in females.

ii. Twenty-one Day Dermal Toxicity Study in Rabbits

In a 21 day repeated dose dermal toxicity test (MRID 427114-

20), rabbits were exposed to CL 263,222 technical as a repeated dermal dose to clipped backs (6 hours/day, 5 days/week, for 3 weeks) at doses of 0, 250, 500, or 1000 mg/kg/day. The highest dose tested is the limit dose (1,000 mg/kg). No significant effects were attributed to treatment with CL 263,222. No LOEL was established. The NOEL is $\geq$1000 mg/kg/day for dermal irritation and systemic toxicity.

c. Chronic Toxicity and Carcinogenicity

i. Chronic Oral Toxicity in Dogs

In a chronic oral toxicity study (MRID 427114-21) Beagle dogs received CL 263,222 technical in the diet for 1 year at doses of 0, 5000, 20,000 or 40,000 ppm (0, 137, 501 or 1,141 mg/kg/day in males and 0, 180, 534, or 1,092 mg/kg/day in females). At 5000 ppm, the following treatment-related effects were observed: minimal degeneration and/or necrosis with minimal lymphocyte and macrophage infiltration in the skeletal muscle of the thigh and/or abdomen of males and females [first observed at 1 year]; minimal infiltration in the diaphragm of 1 male and 1 female dog [first observed at 1 year]; and decreased serum creatinine in females [first observed at 6 months]. At 20,000 ppm dose level and above, both males and females showed increased salivation and effects on muscle, blood, and liver. Decreased serum creatinine was also observed in males. Effects on the liver included increases in serum cholesterol, the liver-to-brain weight ratio in both males and females, and the absolute liver weight in males. Effects on the blood included anisocytosis and decreases in hematocrit and hemoglobin in both males and females; increases in reticulocyte count and hyperchromatic red cells and decreases in mean corpuscular volume and mean corpuscular hemoglobin in males; and decreases in red blood cell count in females. Females also showed decreases in food consumption, and males showed increases in serum phosphate. At the highest dose tested, 40,000 ppm, both males and females showed vomiting and decreased body weight gain, as well as effects on muscle, liver, and the hematopoietic system. Additional effects on the muscle observed only at 40,000 ppm included serum creatine kinase and potassium in both males and females, decreased serum creatinine in males, and degeneration/necrosis of the muscle of the esophagus in females. Effects on the blood in both males and females included decreases in mean corpuscular hemoglobin concentration; increases in the normoblast and platelet content of the blood; increased incidence of macrocytes, poikilocytes, polychromatic cells, and target cells in the blood; and increased incidence of congestion of the bone marrow. In addition, male dogs showed decreased red cell count; female dogs showed decreased mean corpuscular hemoglobin, decreased mean corpuscular volume, increased reticulocyte count, increased hypochromatic red cells, and increased erythropoiesis in the spleen. Effects on the liver

in both males and females included increased liver-to-body weight ratio, and aminotransferase, and decreased serum albumin. Male dogs also showed increased serum lactate dehydrogenase, increased aspartate and alanine aminotransferase, and decreased serum albumin:globulin ratio; females showed increased absolute liver weight and serum phosphate. In addition, males had decreased food consumption. The LOEL for systemic toxicity is 137 mg/kg/day in males and 180 mg/kg/day in females based on minimal degeneration and/or necrosis of the abdomen of males and females and decreased serum creatinine in females. No NOEL was established.

ii. Chronic Toxicity/Carcinogenicity Study in Rats

In a 24-month combined chronic toxicity/carcinogenicity study (MRID 433203-07), technical grade CL 263,222 (96.9% purity) was administered in the diet to rats at dose levels of 0 (control), 5000, 10000, or 20000 ppm (equivalent to 0, 253, 505, or 1029 mg/kg/day in males and to 0, 308, 609, or 1237 mg/kg/day in females). At the highest dose level tested (20000 ppm, limit dose), no treatment-related effects were observed. Also, no treatment-related increase in tumors of any kind was observed at any dose level. Increased incidences of C-cell adenomas and carcinomas in the thyroid gland of the high-dose male rats were determined to not be of concern because the increases were not statistically significant by pair-wise comparison to the control group and the incidences did not exceed the maximum percent incidences in the historical control data. Further, an increased incidence of thyroid neoplasms was not observed in the female rats. Similarly, an increased incidence of endometrial stromal polyps in the uterus of the high-dose female rats was not considered to be treatment-related because the increase was not statistically significant by pair-wise comparison to the control group and the incidence did not exceed the maximum percent incidence in the historical control data. One stromal sarcoma was also observed in the uterine body/cervix of the high-dose female rats, but was not considered to be related to treatment with the test material. A LOEL was not established. The NOEL in this study is 1029 mg/kg/day for males and 1237 mg/kg/day for females.

iii. Chronic Toxicity/Carcinogenicity Study in Mice

In a 18-month combined chronic toxicity/carcinogenicity study (MRID 433203-06), technical grade CL 263,222 (96.9% purity) was administered in the diet to mice at dose levels of 0, 1750, 3500, or 7000 ppm (equivalent to 0, 271, 551, or 1134 mg/kg/day in males and to 0, 369, 733, or 1442 mg/kg/day in females). At the highest dose level tested (7000 ppm, limit dose), no treatment-related effects were observed in either male or female mice. Statistically significant decreases in high- and mid-dose male body weights during the first 26 weeks of the study were not convincing

indicators of toxicity because the decreases were small, were noted even before initiation of treatment and were not dose-related. No treatment-related increase in tumors of any kind was observed in either male or female mice at any dose level. No LOEL was established. The NOEL in this study is 1134 mg/kg/day for males and 1442 mg/kg/day for females.

This study is classified as Core-Guideline as a carcinogenicity study. As a chronic feeding study, this study is classified as Core-Supplementary because no ophthalmological, clinical chemistry or urinalysis examinations were conducted.

d. Developmental Toxicity

i. Developmental Toxicity in Rats

In a developmental toxicity study in rats (MRID 427114-22), CL 263,222 was administered via oral gavage at daily doses of 0, 250, 500, or 1000 mg/kg/day on gestational days 6-15, inclusively. No maternal toxicity was observed at any dose level. No compound-related effects were observed at any dose level for developmental toxicity. No Maternal LOEL was established. The Maternal NOEL is $\geq$1000 mg/kg/day (limit dose). No Developmental LOEL was established. The Developmental NOEL is $\geq$1000 mg/kg/day (limit dose).

ii. Developmental Toxicity in Rabbits

In a developmental toxicity study (MRID 427114-23), rabbits were administered CL 263,222 via oral gavage at daily doses of 0, 175, 350, 500 or 700 mg/kg/day on gestation days 7-19, inclusively. High mortality among animals at 700 mg/kg/day precluded results from this dose level to be included in the determination of the LOELs and NOELs for maternal and developmental toxicity. Compound-related maternal toxicity was observed in all treatment groups. It was manifested as decreased survival at all dose levels (80%, 80%, 85% and 45% at 175, 350, 500 and 700 mg/kg/day, respectively) and decreased body weight gain and food consumption mainly during the dosing period at 500 mg/kg/day. The Maternal LOEL is 500 mg/kg/day, based on decreased body weight gain and decreased food consumption in does. The mortalities observed in the control group and at dose levels $\leq$ 500 mg/kg/day were considered most likely to be due to errors during the gavage dosing procedure and to not be treatment-related. The Maternal NOEL is 350 mg/kg/day.

Since the results from the 700 mg/kg/day group have been excluded because of high mortality among doses and too few litters remaining to conduct a meaningful evaluation, no compound-related developmental toxicity was observed in this study. Fetal incidences of rudimentary ribs at 350 and 500 mg/kg/day increased

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significantly above control. However, in the absence of a dose-related effect on the corresponding litters or other developmental effects at these dose levels, this was not considered to be toxicologically relevant. No Developmental LOEL was established. The Developmental NOEL is 500 mg/kg/day.

e. Reproductive Toxicity

i. Reproductive Toxicity Study in Rats

In a reproductive toxicity study (MRID 433203-05), CL 263,222 technical] was administered in the diet to rats at 0, 5000, 10000 or 20000 ppm (male premating dose levels 0, 301, 605 or 1205 mg/kg/day; female premating dose levels 0, 378, 737 or 1484 mg/kg/day) (test material consumption was calculated by the report author) for 14 weeks premating, through mating, gestation and lactation (for F1 offspring) for P1 parents and F1 parents and through 21 days of lactation for the F2 offspring. No dose related effects were demonstrated for any parameter studied in parents or offspring. Parameters studied were observational data, body weight, body weight gain, food consumption, mating, fertility, pregnancy, gestation length in P1 and F1 adults and necropsy data on organs of reproduction in P1 and F1 adults. In offspring, the following data were recorded, observational data, live births and pup weight, number live and pup weights at day 4 pre-reduction and post-reduction, day 7, day 14 and 21 for the F1 and F2 pups. The NOEL/LOEL are $\geq$1484/>1484 mg/kg/day in parental females and offspring based on no effects at the HDT ($\geq$1g/kg/day = limit dose) in either the P1 or F1 or F1 or F2 offspring.

f. Mutagenicity

Study Type	Reported Results
Microbial/Mammalian Microsome Mutagenicity Assay (MRID 427114-24)	Negative in independently performed bacterial mammalian microsome reverse mutation assays with Salmonella typhimurium strains TA 1535, TA1537, TA1538, TA98, or TA100 and Escherichia coli strain WP2 uvrA at doses up to 5000 µg/plate CL 263,222 in the presence or absence of s9-metabolic activation.
In Vivo Cytogenetic Assay with Rats (MRID 427114-26)	Negative in the rat bone marrow in vivo cytogenetic assay in male and female rats orally administered 5000 mg/kg using 6-, 18-, and 30-hour harvest. Male and female rats were also treated with 500 and with 1667 mg/kg, but cells from these animals were not analyzed.
In Vitro Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells (MRID 427114-27)	Negative in the Chinese hamster ovary in vitro cytogenetics assay conducted with nonactivated and S9-activated concentrations of 250, 1000, and 3000 µg/mL and cell harvests at 10 and 20 hours. No cytotoxicity was seen under any condition; however, the high dose (actual concentration by analytical analysis = 2430 µg/mL) was based on the maximum solubility of the test material in the selected solvent (dimethyl sulfoxide).

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Study Type	Reported Results
Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT) (MRID 427114-25)	Negative for the induction of forward mutations at the HGPRT locus in Chinese hamster ovary (CHO) cells in either the presence or absence of S9 activation in two independent assays. The highest soluble concentration (5 mg/mL -S9 or 4.9 mg/mL +S9) was not cytotoxic.

g. Metabolism

i. Metabolism in Rats

In a metabolism study in rats (MRID 427114-29) the absorption, distribution, metabolism, and excretion of ^{14}C-CL 263,222 were studied. Male and female rats were administered orally via gavage a single dose of 10 or 1000 mg/kg ^{14}C-CL 263,222, 10 mg/kg/day of nonlabeled CL 263,222 for 14 days followed by a single oral dose of radiolabeled CL 263,222 (10 mg/kg), or a single intravenous dose of 10 mg/kg ^{14}C-CL 263,222. CL 263,222 was rapidly absorbed and excreted in rats at all dosing levels. Total recovery of administered dose was 98%-106% at 7 days postexposure. The urine was the major route of excretion (94%-102% of the administered dose); the feces were only a minor route of excretion (0.6%-3.5% of the administered dose). For all dose groups, the majority of radioactivity was rapidly absorbed and excreted as the unchanged parent compound within the first 6 hours postdosing. Intravenous dosing indicated >95% absorption from the gastrointestinal tract. There was no evidence of bioaccumulation of CL 263,222 or its metabolites in the tissues. CL 263,222 and its metabolites are excreted in expired air. There were no sex- or dose-related differences is the absorption, distribution, metabolism, or excretion of CL 263,222 in rats following oral or intravenous administration.

2. DOSE RESPONSE ASSESSMENT

a. Reference Dose

The Health Effects Division-RfD/Peer Review Committee met for the first time on April 21, 1994 to discuss and evaluate the toxicology data submitted in support of CL 263,222 (CADRE) registration for an experimental use permit and associated temporary tolerances and to assess a Reference Dose (RfD) for this chemical. Material available for review at that time consisted of data evaluation records (DERs) for a chronic (one-year) toxicity study in dogs (MRID 427114-21), developmental toxicity studies in rats and rabbits (427114-22 and -23), a subchronic oral toxicity study (3-month) in rats (427114-19) and a repeated-dose (21-day) dermal toxicity study in rabbits (427114-21).

The Committee was asked at that time to specifically address

two issues: 1) whether a new chronic toxicity study in dogs would be required since the existing study (MRID 427114-21) failed to demonstrate a "no-observable effect level", and 2) whether maternal toxicity effects observed at the lowest dose level in the developmental toxicity study in rabbits (MRID 427114-23) and thought to be treatment-related were biologically significant and whether a new study would be required.

With respect to the first issue, the Committee determined that the overall "no-observable effect level" most likely would not be much lower than the "lowest-observable effect level" and, therefore, that a new study would not be required. With respect to the second issue, the Committee discounted the biological significance of what appeared to be maternal toxicity at the lowest dose level and recommended raising the "lowest-observable effect level". The study was considered to be acceptable.

The Health Effects Division-RfD/Peer Review Committee met once again on August 24, 1995 to discuss and evaluate the toxicology data submitted in support of CL 263,222 (CADRE) registration and associated permanent tolerances and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats (MRID 433203-07), a carcinogenicity study in mice (MRID 433203-06), a multi-generation reproductive toxicity study in rats (MRID 427114-22), and a battery of mutagenicity studies (MRID 427114-24, -25, -26, -27).

The Committee recommended that an RfD for this chemical be established based upon the 1-year chronic toxicity study in dogs (MRID 427114-21) with a LOEL 137 mg/kg/day for males, and 180 mg/kg/day for females. At this dose level, the lowest dose level tested, slight degeneration/necrosis and lymphocyte/macrophage infiltration in single skeletal muscle fibers were observed in both males and females and a slight decrease in creatinine levels was observed in females.

An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability and an additional UF of 3 was applied to account for the lack of an overall NOEL for the study. On this basis, the RfD was estimated to be 0.5 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and therefore an acceptable daily intake (ADI) has not been established by that Committee.

b. <u>Carcinogenicity Classification</u>

The RfD Committee considered the carcinogenicity phases of the combined chronic toxicity/carcinogenicity studies in rats (MRID 433203-07) and mice (MRID 433203-06) to be acceptable. The highest dose levels tested in both the rat (20,000 ppm) and mouse (7,000 ppm) studies were considered to be a limit dose.

In rats, there were no treatment-related effects observed up to the highest dose level tested (20,000 ppm). Also, no treatment-related increase in tumors of any kind was observed at any dose level. Increased incidences of thyroid gland C-cell adenomas in males (15% in the high-dose males compared to 10% in controls), carcinomas (5% in the high-dose males compared to 0% in controls), and adenomas/carcinomas combined (20% in the high-dose males compared to 10% in controls) were observed. However, none of the increases were statistically significant ($p < 0.05$) by pair-wise comparison to the concurrent control group. Each of the increases also were within the historical control range for these types of tumors.

Historical control incidences for thyroid gland C-cell tumors in males submitted for three laboratories were: 1) Charles River 1984-1988; 0.0-17.4% (mean 6.4%) for C-cell adenomas and 0.0-6.7% (mean 2.3%) for C-cell carcinomas, 2) Pharmaco LSR; 1.3-18.8% (mean 8.9%) for C-cell adenomas and 0.0-5.7% (mean 1.1) for C-cell carcinomas, and 3) Hazleton Laboratories 1988-1992; 2.1-16.9% (mean 8.5%) for C-cell adenomas and 0.0-9.4% (mean 5.2%) for C-cell carcinomas.

Because the C-cell neoplasms observed in male rats were often microscopic, additional step-sectioning (4-sections/animal) of the thyroid glands of all male rats in the study was performed in order to identify additional neoplasms, if any. This technique resulted in revised incidences of adenomas of 17% in the high-dose males compared to 13% in controls, of carcinomas of 5% in the high-dose males compared to 0% in controls, and of adenomas/carcinomas combined of 22% in the high dose males compared to 13% in the controls. Statistical analysis of the step-sectioned data indicated no statistically significant ($p < 0.05$) positive trend or pair-wise differences between any treatment group and the control group.

In females, no increase in the incidences of C-cell adenomas and/or carcinomas of the thyroid gland was observed. In females, uterine stromal polyps and stromal polyps/stromal sarcoma combined appeared to be increased at the middle and high dose levels. The incidences of uterine stromal polyps were 1.6, 4.8, 7.7 and 7.7 % respectively, for the 0, 5000, 10000, and 20000 ppm groups. In the high dose group, one stromal sarcoma also was observed. The incidences of the stromal polyps/stromal sarcoma combined were 1.6, 4.8, 7.7 and 9.2%, respectively, for the 0, 5000, 10000, and 20000 ppm groups. The increases in the stromal polyps/stromal sarcoma combined attained a statistically significant level for dose-

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response trend (P = 0.0383), but no statistically significant pair-wise difference (p = 0.0599) between the high dose group and the control groups was observed. The incidences were also within the historical control range for these types of tumors. Historical control incidences submitted for three laboratories were: 1) Charles River 1984-1988; endometrial stromal polyp 0.0-10.0% (mean 4.1%), endometrial stromal sarcoma 0.0-1.6% (mean 0.2%), 2) Pharmaco LSR; endometrial stromal polyp 0.0-8.8% (mean 3.4%), and 3) Hazleton Laboratories 1988-1992; endometrial stromal polyp 1.7-13.3% (mean 5.0%).

In mice, no treatment-related increase in tumors of any kind was observed at any dose level. The Committee, therefore, concluded that the treatment did not alter the spontaneous tumor profile in this strain of mouse.

On this basis, the Committee concluded that the chemical should be classified as **"Group E"**, evidence of non- carcinogenicity for humans; i.e. the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposure. This weight of the evidence judgment is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that the designating of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

c. Other Toxicological Endpoints

Based upon review of the toxicology database for CL 263,222 by the Less Than Lifetime (LTL) Committee, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. For more information on studies discussed in this section refer to the Hazard Assessment section of this document.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data used to clarify the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

i. Dermal Absorption Data

A dermal absorption study on CL 263,222 is not available. Oral and dermal NOELs from short-term studies in rabbits, however, are available.

Studies Selected - Guideline Nos.: 83-3(b), developmental toxicity study in rabbits (gavage study) (MRID 427114-23) and

82-2, 21-day dermal toxicity study in rabbits (MRID 427114-20).

In the developmental toxicity study in rabbits (MRID 427114-23) CL 263,222 was administered via gavage at daily doses of 0, 175, 350, 500 or 700 mg/kg/day on gestation days (GDs) 7-19, inclusive. High mortality among does at 700 mg/kg/day precluded results from this dose level being considered in the determination of the NOELs and LOELs for maternal and developmental toxicity. [The time of death for the first treatment-related mortality at 700 mg/kg/day in this study was not reported in the DER.] The maternal LOEL is 500 mg/kg/day, based on decreased body weight gain and decreased food consumption both beginning within 7 days after initiation of dosing. At 700 mg/kg/day, increased mortality was also observed in the treated does. The maternal NOEL is 350 mg/kg/day. The developmental LOEL was not determined (> 500 mg/kg/day). The developmental NOEL is 500 mg/kg/day.

In the 21-day dermal toxicity study in rabbits (MRID 427114-20) doses of 0, 250, 500 or 1000 mg/kg/day of CL 263,222 were applied to the clipped backs of rabbits for 6 hours/day, 5 days/week, for 3 weeks. The highest dose tested was the limit dose (1000 mg/kg/day) specified in the guideline. A LOEL was not established. The NOEL $\geq$ 1000 mg/kg/day for dermal irritation and systemic toxicity.

Generally HED would use the NOEL from a dermal toxicity study as a toxicological endpoint for dermal routes of exposure. However, in the case of CL 263,222 the dermal toxicity study did not exhibit any effects at the limit dose (1000 mg/kg/day). Therefore a percent dermal absorption was estimated using a route to route extrapolation by taking the NOEL from the developmental toxicity study in rabbits (MRID 427114-23) and dividing it by the NOEL from the 21-day dermal toxicity study in rabbits (MRID 427114-20).

$$\text{Estimated Percent Dermal Absorption} = \frac{\text{oral NOEL}}{\text{dermal NOEL}} = \frac{350 \text{ mg/kg/day}}{\geq 1000 \text{ mg/kg/day}} = \leq 35\%$$

ii. Acute Dietary Endpoint (One Day)

Study evaluated for potential endpoint for an acute dietary endpoint - Guideline No.: 84-2, In Vivo Chromosome Aberration in Rat Bone Marrow Cells (MRID 427114-26).

Negative in the rat bone marrow in vivo cytogenetic assay in fasted male and female rats administered 5000 mg/kg of technical grade CL 263,222 by gavage using 6-, 18-, and 30-hour harvests. Male and female rats were also treated with 500 and with 1667 mg/kg, but cells from these animals were not analyzed. The diarrhea reported by the study author in "several" animals (group and sex not specified) was attributed to the corn oil solvent. No other signs of toxicity were reported. No treatment-related

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effects were observed at a dose level of 5000 mg/kg.

An acute dietary risk assessment is not required since there were no treatment-related effects observed at the dose level of 5000 mg/kg in either male or female rats.

iii. Short Term Occupational or Residential Exposure (1 to 7 Days)

Study evaluated for potential endpoint for short term occupational or residential exposure - Guideline No.: 83-3(b), developmental toxicity study in rabbits (gavage study) (MRID 427114-23).

In the developmental toxicity study in rabbits (MRID 427114-23) CL 263,222 was administered via gavage at daily doses of 0, 175, 350, 500 or 700 mg/kg/day on gestation days (GDs) 7-19, inclusive. High mortality among does at 700 mg/kg/day precluded results from this dose level being considered in the determination of the NOELs and LOELs for maternal and developmental toxicity. [The time of death for the first treatment-related mortality at 700 mg/kg/day in this study was not reported in the DER.] The maternal LOEL is 500 mg/kg/day, based on decreased body weight gain and decreased food consumption both beginning within 7 days after initiation of dosing. At 700 mg/kg/day, increased mortality was also observed in the treated does. The maternal NOEL is 350 mg/kg/day. The developmental LOEL was not determined (> 500 mg/kg/day). The developmental NOEL is 500 mg/kg/day.

The toxicological effects of concern are decreased body weight gain and decreased food consumption in does beginning within 7 days after initiation of dosing at the LOEL of 500 mg/kg/day. Dose to be used for risk assessment is the NOEL of 350 mg/kg/day.

Although maternal effects in developmental toxicity studies are ordinarily used as endpoints for intermediate term exposures (7 days to several months), rather than for short term exposures (1 to 7 days), in this particular study the effects were observed to begin to occur within 7 days after initiation of dosing (actually during GDs 7-14). These same effects continued through the remainder of the dosing period (GDs 14-19), but were observed to diminish thereafter in the post-dosing period. Treatment-related mortality for does was not observed at the dosage level of 500 mg/kg/day.

When adjusted for percent dermal absorption ($\leq$ 35%), the maternal NOEL in this study is > 1000 mg/kg/day therefore this risk assessment is not required.

iv. Intermediate Term Occupational or Residential Exposure (1 Week to Several Months)

Study evaluated for potential endpoint for intermediate term occupational or residential exposure - Guideline No.: 83-1(b), 1-year chronic feeding study in dogs (dietary study) (MRID 427114-21).

In the 1-year chronic feeding study in dogs (MRID 427114-21) Cl 263,222 was administered to beagle dogs via the diet for 1 year at dietary levels of 0, 5000, 20000 or 40000 ppm (0, 137, 501 and 1141 mg/kg/day in males and 0, 180, 534 and 1092 mg/kg/day in females). The LOEL is 137 mg/kg/day in males and 180 mg/kg/day in females, based on minimal effects on the skeletal muscle. The NOEL was not established.

The toxicological effects of concern are changes in hematological parameters indicative of anemia and compensatory erythropoiesis first observed at 35 days and changes in clinical chemistry enzymes indicative of liver damage also first observed at 35 days. The effects were observed at the dose levels of 20000 ppm and above. No NOEL was established for the 1-year chronic feeding study in dogs. For the purposes of the intermediate term risk assessment the NOEL to be used is 137 mg/kg/day since that value represents the NOEL for effects of concern (< 1-year). A MOE of 100 or greater would not exceed the level of concern for the intermediate term risk assessment.

The most sensitive endpoint in this 1-year chronic feeding study was degeneration/necrosis in the skeletal muscle (with infiltration of lymphocytes/macrophages) accompanied by decreases in serum creatinine in females. These effects, however, were not observed until after 6 months. The changes in hematological parameters and changes in clinical chemistry enzymes, although observed at higher dose levels, were considered to be the appropriate endpoints for the intermediate term risk assessment (1 week to several months) because these effects were first observed at 35 days.

This risk assessment is required.

v. Chronic Occupational Exposure (Longer than Several Months)

Study evaluated for potential endpoint for chronic occupational or residential exposure - Guideline No.: 83-1(b), 1-year chronic feeding study in dogs (dietary study) (MRID 427114-21).

The toxicological effects of concern are minimal degeneration/necrosis of skeletal muscle fibers (with minimal infiltration by lymphocytes/ macrophages) in males and females (first observed at 1 year) and decreased serum creatinine in females (first observed at 6 months). The LOEL is 137 mg/kg/day in males. No NOEL was established. Dose to be used for risk assessment is the LOEL 137 mg/kg/day in males.

The most sensitive endpoint in this 1-year chronic feeding study was minimal degeneration/necrosis in the skeletal muscle (with minimal infiltration of lymphocytes/ macrophages) accompanied by decreases in serum creatinine in females. These effects were observed at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females), the lowest dose level tested in both males and females. Since minimal treatment-related effects were observed at the lowest dose level tested, the LTL Peer Review Committee concluded that for the purposes of chronic risk assessment the level of concern for this MOE would be < 300.

This risk assessment is required.

3. OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

a. Occupational and Residential Exposure

The table below describes the Cadre label.

CADRE® Herbicide 23.6 % a.i. (EPA File Symbol 241-GAU) LABEL	
Crop	peanuts
Pest	broadleaf & grass weeds
Application method	ground boom (open cab)
Maximum application rate	0.0625 lb ai/acre
Minimum final spray volume	10 gal/acre
No. of applications	does not specify
Manufacturer	American Cyanamid Company
Use period	early peanut postemergence

The average size of a peanut farm in Georgia, the largest peanut producing state, is 103 acres (1992 Census of Agriculture, Vol. 1, part 51, Ch. 2, Table 27).

HED exposure assessment is based on the following assumptions:

ASSUMPTIONS	
Applicator weight	70 kg
Mixer/loader weight	70 kg
Acres treated/day	103 acres

ASSUMPTIONS	
Mixer/loader unit of exposure PHED, open pour, (OPN.LIQ.MLOD)[1].	0.044 mg/lb ai
Applicator unit of exposure PHED, ground boom open cab, (BRUCE.APPL)[1].	0.015 mg/lb ai
Adjustment for dermal absorption	None

1. PHED run with normal work clothing of long pants, long sleeved shirt, and gloves.

CALCULATIONS

Total A.I. handled per day:
0.0625 lb ai/acre x 103 acres/day = 6.4 lb ai/day

Mixer/Loader Daily Exposure (DE):
0.044 mg/lb ai x 6.4 lb ai/day ÷ 70 kg = 4.0×10^{-3} mg/kg/day

Mixer/Loader Annual Average Daily Exposure (AADE):
0.044 mg/kg/day x 1 Day ÷ 365 days = 1.1×10^{-5} mg/kg/day

Applicator DE:
0.15 mg/lb ai x 6.4 lb ai/day ÷ 70 kg = 1.4×10^{-3} mg/kg/day

Applicator AADE:
0.0014 mg/kg/day x 1 Day ÷ 365 days = 3.8×10^{-6} mg/kg/day

Mixer/loader and applicator exposures are based on an open pour and open cab scenario with the worker wearing long-sleeved shirt, long pants, shoes and socks, and gloves.

The CADRE® Herbicide, 23.6 percent a.i., (EPA File Symbol 241-GAU) label states that the following personal protective equipment (PPE) are required: long-sleeved shirt and long pants, waterproof gloves, and shoes plus socks. This is in accordance with the Worker Protection Standard (WPS).

The REI for CADRE® listed on the label is 12 hours, which is in agreement with WPS since the technical product is in toxicology category III compound for acute dermal toxicity.

b. Occupational and Residential Risk Characterization

The Margin of Exposure (MOE) is a measure of how closely the

exposure comes to the NOEL. The MOE is calculated as the ratio of the NOEL to the exposure which in this case was adjusted to account for the percent dermal absorption (NOEL/exposure x % dermal absorption = MOE). For the purposes of the intermediate term risk assessment the NOEL used was 137 mg/kg/day from the chronic feeding study in dogs (MRID 427114-21) since that value represents the NOEL for effects of concern for the timeframe for intermediate term exposure (< 1-year). The chronic exposure MOEs are calculated for systemic toxicity based on a LOEL of 137 mg/kg/day from a 1-year chronic feeding study in dogs (MRID 427114-21), no NOEL was established. For purposes of this risk assessment 35 percent was the value used for dermal absorption.

The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. Since minimal treatment-related effects were observed at the lowest dose level tested in the 1 year chronic dog study, the LTL Peer Review Committee concluded that for the purposes of chronic risk assessment the level of concern for a chronic MOE, based on this data would be < 300.

Using the toxicology endpoints (refer to Other Toxicological Endpoints section) and the occupational exposure estimates (refer to Occupational and Residential Exposure section) the following MOEs were calculated for occupational risk for the proposed seed treatment and greenhouse uses.

CADRE® Herbicide (23.6 % a.i.) For Use On Peanuts			
Job Function	**Endpoint mg/kg/day**	**Daily Exposure (DE) mg/kg/day**	**Intermediate MOE**
Mixer/Loader	137	4.0×10^{-3}	9.8×10^{4}
Applicator	137	1.4×10^{-3}	2.8×10^{5}
Job Function	**Endpoint mg/kg/day**	**Average Annual Daily Exposure (AADE) mg/kg/day**	**Chronic MOE**
Mixer/Loader	137	1.1×10^{-5}	3.5×10^{7}
Applicator	137	3.8×10^{-6}	1.0×10^{8}

Based on the estimated MOEs the Agency has no concern for mixers, loaders and applicators when CADRE® Herbicide (23.6 % a.i.) used on peanuts when applied according to label directions.

4. DIETARY EXPOSURE AND RISK CHARACTERIZATION

a. Dietary Exposure

i. Plant Metabolism

The petitioner submitted the results of ^{14}C-Cl 263,222 metabolism study in peanuts (MRID # 427114-39). The petitioner prepared ^{14}C-CL 263,222 labeled in the 6 position of the pyridine ring. The specific activity was 23.3 uCi/mg with a radiochemical and chemical purity being greater 98.6%. This material was diluted with ^{13}C-CL 263,222 to give a final specific activity of 11.76 uCi/gram. This specific activity is designed to give a minimum detection level in peanut nutmeats and peanut hulls at 0.01 ppm. The ^{13}C-CL 263,222 served as a mass marker for the isolated unknown metabolites. The ^{13}C- and ^{14}C-Cl 263,222 were formulated as the ammonium salts in an aqueous soluble formulation (2ASU), then just prior to application this formulation is diluted with water for a spray solution.

To obtain fractions for characterization and identification of the radioresidues, samples of the green peanut plants, peanut hay, hulls, and the nutmeat were all extracted by the same procedure. The solvent used in the initial extraction of 50 grams of green plant material, or 200 grams of peanut hay was methanol:water:acetone (1:1:1, v/v/v). This extraction recovered 81-96% of the TRR in the green plants, 79% from peanut hay, 82% from peanut hulls, and 76% from nutmeats. To complete the extractions from green plants, hulls, and hay the solids were extracted with methanol:water (4:1) containing 2% HCl. This recovered an additional 3-8% of the TRR. The green plants solids were extracted next with methanol:water (4:1) containing 0.5N NaOH, which recovered an additional 1% of the TRR. The peanut hay was incubated after the acid methanol:water extraction with cellulase at 37°C for 72 hours, which recovered an additional 4% of the TRR. The various extractions recovered a total of 82-94% of the TRR in the green plants, 80% from peanut hay, and 82% from hulls.

At 4 hours after application the parent compound was 3.62 ppm (76%) out of 4.76 ppm with the hydroxymethyl metabolite (CL 263,284) at 0.05 ppm and the glucoside conjugate (CL 189,215) at 0.1 ppm. At 31 days after application the residues of the parent CL 263,222 had declined to 0.001 ppm out of 0.071 ppm. The free hydroxymethyl metabolite was 0.009 ppm (12%) with the major residue being the glucoside conjugate at 0.023 ppm (32% of the TRR). The same basic residue profile also occurred at 61 days after treatment with the parent being 0.003 ppm out of 0.085 ppm. The hydroxymethyl was 0.01 ppm (12%) and the bound glucoside metabolite was 0.04 ppm (46% of the TRR).

In mature peanut hay residues of the parent CL 263,222

declined further to 0.006 ppm out of 0.20 ppm. The hydroxymethyl metabolite was 0.06 ppm (28% of the TRR) while the bound glucoside was 0.03 ppm (16% of the TRR). In peanut hulls the parent CL 263,222 was 0.002 ppm out of 0.089 ppm. The free hydroxymethyl was 0.025 ppm (28% of the TRR) and the bound glucoside metabolite was 0.032 ppm (36% of the TRR). Essentially no parent residues of CL 263,222 (<0.001 ppm) were detected in the nutmeats. Little free Hydroxymethyl metabolite was detected at 0.001 ppm with major metabolite in peanut nutmeat being the bound glucoside at 0.006 ppm (35% of the TRR).

The HED Metabolism Committee at its meeting of 9/18/95 concluded that the residue of concern should be the parent and its hydroxymethyl metabolite, both free and conjugated.

ii. Animal Metabolism

The petitioner submitted the results of a CL 263,222 metabolism study in lactating goats (MRID 427114-40 & 433203-17). The test substance was pyridine-^{14}C-labeled in the 6 position CL 263,222 with a specific activity of 22.2 uCi/mg and a radio and chemical purity > 95%. The material fed at a low dose of 4 mg (3.76 mg actual dose) which was 2 ppm based on feed consumption and a high dose of 20 mg (15.1 mg actual dose) which was 11.8 ppm based on actual feed consumption. The control goat received a placebo lactose filled gel cap daily.

Samples of control goat tissues and milk were fortified with 0.01 ppm of ^{14}C-CL 263,222 to validate the limit of quantitation (LOQ). Recovery from milk and tissues was essentially 100%.

Total radioactive residues in milk from all 7 days, leg and loin muscles, and liver from both doses were < 0.01 ppm. No CL 263,222 equivalents from either dose were detected in omental fat to 0.04 ppm. Results of the ^{14}C-CL 263,222 equivalents in caprine kidney from the low dose were < 0.01 ppm and from the high dose were 0.05 ppm.

From the high dose of 11.8 ppm, CL 263,222 was 0.016 ppm (32%) of the 0.05 ppm residue in kidney. The hydroxymethyl metabolite was 0.005 ppm (9%) of the residue. Two unidentified metabolites were detected on the HPLC chromatograms, one at 0.004 ppm (7%) and the other being a possible mixture at 0.017 ppm (33%). The remaining radioactivity at 0.017 ppm (34%) contained no discrete peaks.

In an additional metabolism study in lactating goats (MRID 433203-19) the metabolic fate of radiolabeled CL 263,284, the hydroxymethyl metabolite of CL 263,222, was determined in lactating goats. The material was fed at rates of 39X and 242X the level expected at the proposed tolerance level of 0.1 ppm.

After 7 days, radioactivity in blood, milk, liver, muscle, and fat was less than 0.01 ppm at all feeding rates. In kidney, 0.03 ppm was found at the 242X exaggerated rate; less than 0.01 ppm at the 39X rate. The kidney material was tentatively identified as predominantly a labile salt of the parent plus small amounts of the parent. The labile salt readily reverted to parent in aqueous media.

In summary, HED concludes that the ruminant metabolism studies show that the residue of concern in ruminants consisted of CL 263,222 and its hydroxymethyl metabolite. However, if future uses were to result in higher residues on feed items, additional ruminant metabolism studies would be required. HED suggests studies at 50 ppm.

The petitioner also presented the results of a CL 263,222 metabolism study in poultry (MRID # 427114-41). The petitioner conducted a CL 263,222 poultry metabolism study using laying hens. ^{14}C-CL 263,222 was administered in 0, 2, or 10 ppm doses.

The petitioner used ^{14}C-CL 263,222 to validate the limit of quantitation (LOQ) for the radioactivity measurements. Control samples of eggs, muscle, liver, kidney, skin with fat, and excreta were spiked with ^{14}C-CL 263,222 at the 0.01 ppm LOQ. Recoveries ranged from 0.008 ppm in kidney and skin with fat to 0.10 ppm in blood and excreta. The petitioner has adequately validated the 0.01 ppm LOQ for the radioactivity measurements.

Total radioactivity in eggs from all 3 test groups dosed for 7 consecutive days were less then 0.01 ppm. In the eggs from the 10 ppm dose we note the counts were well above background, but less then 0.01 ppm. HED would estimate the level is in the 0.004-0.007 ppm range. Results for the ^{14}C-CL 263,222 equivalents in poultry kidney, liver, muscle, skin with fat were all less then 0.01 ppm. The counts for these tissues could no be distinguished from the counts in the corresponding control tissues. Since radioactive residues from the 11.4 ppm dose of ^{14}C-CL 263,222 were all less then 0.01 ppm characterization and identification of residues is not feasible, nor is it required for the trace amount in detected in eggs.

HED concludes the nature of the CL 263,222 residue in poultry has not been defined. However, in this poultry metabolism study where laying hens were fed at an exaggerated level greater then 100X the proposed tolerance in peanuts, no residues were detected in poultry tissues and eggs; thus there is no evidence of bioconcentration. It is our conclusion that there is no reasonable expectation of finite CL 263,222 residues occurring in poultry, thus there is no need for secondary tolerances in poultry and eggs from feeding CL 263,222 treated peanuts poultry feed items.

iii. Residue Analytical Method

The petitioner has submitted a residue analytical method for CL 263,222 and its hydroxymethyl metabolite, CL 263,284 in peanut hulls and peanut nutmeats (MRID # 427114-42). Additional chromatographic data were submitted 7/19/95 (MRID 433203-21).

CL 263,222 has been satisfactorily subjected to the Food and Drug Administration"s Multi Residue Method protocol.

The Agency"s Analytical Chemistry Laboratory has successfully validated the capillary electrophoretic method with suggested minor revisions. The petitioner has submitted a description of the revised method. It is known as M-2379.02.

HED concludes the petitioner has presented an adequately validated HPLC residue analytical method to gather the magnitude of the residue data for CL 263,222 and its metabolite CL 263,284 ranging from 0.1 ppm to 5 pm in peanut hulls and nutmeats. This method, M-2253.02, is suitable to enforce the proposed permanent tolerances of 0.1 ppm.

iv. Storage Stability

The petitioner submitted storage stability intermin report with commodities treated with CL 263,222 (MRID 432203-23). The petitioner has begun a study to determine the stability of residues of CL 263,222, CL 263,284, and CL 189,215 in peanut rac"s fortified with materials and kept in frozen storage over a 2 year interval. This interim report dated 4/18/94 gives the results after 1 month of storage. The author concluded that there was no evidence of storage instability over this interval.

The petitioner has submitted storage stability studies (MRID 438650-04 & 438650-02) that demonstrate that the components of the toxic residue of concern are stable over a one year period. This interval encompasses the maximum 6 month interval samples were stored in the field trial studies.

v. Magnitude of the Residue - Crop Field Trials/Processed

The petitioner submitted magnitude of the residue data (MRID# 427114-43) from 3 crop field trials for the temporary tolerances proposed in the EUP petition. For permanent tolerances the petitioner conducted 9 additional trials (MRID 433203-24).

In the 9 additional trials CL 263,222 was applied at rates of 0.063 (1X) or 0.189 (3X) lbs ai/A to peanuts as a post emergent application. Samples of vines were collected 32-35 days after treatment (DAT), hay at about 60-90 DAT, peanut straw at about 100 DAT, and nutmeats and hulls at about 100 DAT. Samples were kept frozen 3 to 5 months prior to analysis for CL 263,222, CL 263,284 (the hydroxymethyl metabolite of CL 263,222), and CL 189,215 (the glucose conjugate of the hydroxy-methyl metabolite).

In all, 14 samples of peanut meats and hulls were examined. In all instances, residues of parent and of the two metabolites were less than the LOQ of 0.1 ppm.

Based upon a LOQ of 0.1 ppm for the analytical method all of the residue data support the proposed tolerances of 0.1 ppm for peanut nutmeat and hulls.

HED concludes that the residue data of the field trials support the proposed tolerances of 0.1 ppm for peanut nutmeats and hull.

As long as a restriction is placed on the label against feeding treated hay, data and tolerances are not needed for this commodity.

The tolerance expression should be for the free acid of CL 263,222 applied as the ammonium salt and the hydroxymethyl metabolite (free and/or conjugated).

The absence of quantifiable residues in nutmeats even at a 3X application rate obviates the need for the determination of residues in processed peanut commodities.

vii. Magnitude of the Residue - Meat/Milk/Poultry/Eggs

The absence of quantifiable residues in the peanut rac"s nutmeats and hulls even at a 3X application rate renders it unlikely that secondary residues would accrue in the meat, milk, poultry, and eggs from the feeding of these rac"s. For a permanent tolerance of CL 263,222 on peanuts a conventional ruminant feeding study and secondary tolerances in meat and milk is not required.

The petitioner may need to conduct a conventional bovine feeding study if tolerances higher then 0.1-0.2 ppm are proposed on other livestock feed items. If a bovine feeding study is necessary, then the petitioner will need to develop and validate a residue analytical for CL 263,222 and any other residue(s) of toxicological concern in meat and milk that is adequate to gather the residue data. If tolerances in animal commodities are needed, the ILV data will also be necessary for the method(s) used to enforce the proposed tolerances in meat and milk. HED also suggests the petitioner complete the plant and ruminant metabolism studies to fully identify the nature of the residue that can be in the bovine feed items and in the animals themselves, then conduct the additional crop field trials to determine the residue levels in the feed items; ie, determine the appropriate range of doses to be used before starting any bovine feeding study.

Based on the results of the CL 263,222 poultry metabolism study where hens were fed at greater then 100X and no residue were

identified, HED concludes that the petitioner does not need to conduct a conventional CL 263,222 poultry feeding study to support a 0.1 ppm tolerance on peanuts. However, HED reminds the petitioner that if (and when) additional petitions are submitted proposing use and tolerances for CL 263,222 on poultry feed items that have higher tolerance levels, then the conventional Cl 263,222 poultry feeding study may be required after the nature of the residue in poultry is adequately understood; ie, additional poultry metabolism study may be necessary.

viii. Nature of the Residue - Confined Rotational Crops

The petitioner presented the results of a ^{14}C-CL 263,222 confined accumulation study (MRID# 427114-47) in rotational crops. The petitioner determined the total ^{14}C-CL 263,222 in rotational crops following a single spray application at a 0.064 lb a.i./acre rate to sandy loam soil in the three test plots. The ^{14}C-CL 263,222 had a specific activity of 23.3 uCi/mg and a chemical purity of 98.6%. This was diluted with ^{13}C-CL 263,222, which served as a mass marker, to a specific activity of 10.87 uCi/mg. The application rate is the proposed use or 1X application rate.

The leafy vegetable used in this study was lettuce, the root crop was carrots, and the small grain was barley. The petitioner also provided additional confined rotational crop data for cotton and field corn. Plant parts collected as samples for analysis from lettuce were foliage at mid maturity and at harvest, and from carrots were roots at both mid-maturity and maturity. From corn the whole plant was harvested at mid maturity and at maturity corn ears, dried stalks, leaves, and husks were collected as samples. From barley the whole plant as forage was harvested at mid maturity while at maturity barley straw and the head containing the grain were collected. At mid-maturity the whole cotton plant was harvested as forage and at maturity the bolls were harvested.

The residue analytical method used to determine the ^{14}C-CL 263,222 and its hydroxymethyl metabolites in the rotational crops is essentially the same method as used in the ^{14}C-CL 263,222 plant metabolism study. The method has been reviewed above.

The TRR in mature lettuce from the 300 days after treatment (DAT) planting was 0.006 ppm and for mature carrots was <0.004 ppm. Characterization and identification of residues at this low level are neither feasible nor required. For a permanent tolerance HED can accept a 10 month plantback restriction for root crops based on residues found in carrots and a 10 month plantback restriction for leafy vegetables based on the result presented from lettuce.

In cottonseed and linters from the 300 DAT plantings the TRR was 0.009 ppm. The TRR from the 270 DAT cotton plantings was 0.017

ppm in cottonseed and 0.015 ppm in linters. 74% of the radioresidue was extractable from the 270 DAT cottonseed; however no characterization/ identification of the residue was reported. HED does not consider 0.009 ppm to be analytically significantly different from 0.01 ppm. Thus, for a permanent tolerance HED declines to accept a 9 or 10 month plantback restriction for cotton without additional data. Several options are 1) to repeat the extraction on reserve cottonseed sample and characterize those residues, 2) repeat the confined rotational crop study and characterize/ identify the residues, or 3) complete field rotational crop studies for cotton. HED would consider a 12 month/1 year plant back restriction for cotton if the petitioner does not wish to generate additional data to support a shorter cottonseed plantback interval.

Corn planted at 270 DAT had the TRR of 0.01 ppm for forage harvested at mid-maturity, 0.007 ppm in the mature grain, and 0.019 ppm in the fodder. The TRR in corn planted at 300 DAT was slightly higher with residues at 0.016 ppm in forage harvested at mid-maturity, 0.028 ppm in the fodder, and 0.008 ppm in the grain. Using the HPLC profiles with authentic standards the petitioner identified the residues from the 270 DAT corn fodder at < 0.001 ppm (2.5%) for the parent CL 263,222, 0.006 ppm (31%) for the free and conjugate hydroxymethyl metabolites, and at 0.002 ppm (8%) for a polar unknown compound(s). From the 300 DAT corn forage the petitioner identified the parent CL 263,222 at 0.001 ppm (7.3%), the free and conjugated hydroxymethyl metabolite at 0.005 ppm (28%), and the polar unknown(s) at 0.007 ppm (41%). The residues identified in corn fodder from the 300 DAT corn planting were nearly identical to those identified in the 270 DAT corn fodder. They were < 0.001 ppm (3.5%) for the parent CL 263,222, 0.008 ppm for the combined free and conjugated hydroxymethyl metabolite, and < 0.001 ppm (5.7%) for the polar unknown(s).

For a full section 3 registration HED will not accept a 9 month plantback interval for corn. The petitioner needs to provide CL 263,222 residue data on corn from field rotational crop studies to support a shorter plantback interval. A rotational tolerance for CL 263,222 on corn may be necessary. If the petitioner does not wish to generate additional rotational crop residue data, then the residue data generated from the barley field rotational crop study will be translated to corn to support our decision.

In barley forage harvested at mid-maturity from the 90 DAT planting the TRR was < 0.004 ppm, from the 120 DAT planting the TRR was 0.009 ppm, and from the 270 DAT barley planting the TRR was 0.023 ppm. The TRR in barley grain was 0.014 ppm from the 90 DAT planting, 0.03 ppm from the 120 DAT planting, and was 0.045 ppm from the 270 DAT planting. The TRR was highest in the barley straw with residues at 0.013 ppm, 0.056 ppm, and 0.070 ppm respectively. Using HPLC profiles with authentic standards the petitioner identified residues from the 120 DAT barley straw at 0.003 ppm

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(5.5%) parent CL 263,222, 0.021 ppm (37%) combined free and conjugate hydroxymethyl metabolite, and 0.002 ppm (2.7%) polar unknown(s); and from the 270 DAT planting residues in barley straw were identified at 0.004 ppm (5.4%) as the parent CL 263,222, 0.031 ppm (44%) as the combined free and glucose conjugate hydroxymethyl metabolite, and 0.002 ppm (4.2%) as the polar unknown(s). The barley grain from the 120 DAT planting residues were identified at 0.007 ppm (23%) parent CL 263,222, 0.006 ppm (18%) free plus conjugate hydroxymethyl metabolite, and < 0.001 ppm (1.5%) as polar unknown(s); and in barley grain from the 270 DAT planting residues were identified at 0.004 ppm (9.6%) parent CL 263,222, 0.015 ppm (33%) as the combined free and conjugated hydroxymethyl metabolite, and 0.002 ppm (4.2%) as the polar unknown(s).

For a full section 3 registration the petitioner will need to conduct field rotational crop studies for CL 263,222 on barley as residues in the proposed tolerance expression exceed 0.01 ppm. HED will not accept a 4 month plantback restriction for barley or other small cereal grains without additional data. A rotational crop tolerance may be necessary for CL 263,222 on barley. The 4 month plantback for other cereal grains; eg wheat, rye, and oats needs to be removed from the permanent tolerance label, or be supported with confined or field rotational crop studies. If the petitioner does not wish to generate additional rotational crop data for other small cereal grains, then our decision on barley will be translated to other small cereal grains. HED points out that the petitioner is always free to conduct additional confined or field rotational crop studies to support short plantback intervals.

For a full section 3 registration the petitioner will need to provide additional confined rotational crop residue data as is described in the Subdivision N Guidelines, § 165-1(c)(2). Although carrots (root crop) and lettuce (leafy vegetable) can have a 9 month plantback as residues are <0.01 ppm, the petitioner may also wish to include them in a 30 day plot. Confined rotational crop studies for other crops with other proposed specific plantback restrictions such as Bahiagrass and legume vegetables (snap beans and soybeans) should be supported with specific residue data, or the petitioner could use the longest accepted interval for other crops which in this petition is 12 months. The petitioner is encouraged to include grain sorghum in additional rotational crop studies as an 18 month plantback restriction is normally not practical. HED policy considers 12 months to be the longest practical plantback interval and those plantbacks proposed for longer than 12 months need to be removed from the permanent label. If the petitioner insists that 18 months or longer are essential, then a detailed explanation with supporting data need to be presented for our consideration.

If the petitioner wishes to propose specific plantback restriction to assess the effects of crop failure, then a plot treated with ^{14}C-CL 263,222 should have a 30 day aging interval

before planting with the three required crops and any other crops for which such a plantback interval is desired. The petitioner is encouraged to have this plot divided into appropriate shares and planted with each of the crops, harvest the crops at maturity and have them analyzed.

The extractability of radioactive CL 263,222 residues from rotational crops ranged from 71% in cotton linters to 91% in corn forage. For TRR residues greater then 0.01 ppm the petitioner identified 31.3% to 35.5% of the residue in corn fodder and forage. The petitioner identified 41% to 49.5% of the radioactive residues in barley straw and grain.

The nature of the CL 263,222 residue in rotational crops appears to be the same as that identified in the plant metabolism study. The parent herbicide is taken up from the soil with oxidation of the methyl group on the pyridine ring followed by rapid conjugation with glucose. The residues of concern in rotational crops are the parent CL 263,222 and its combined free and glucose conjugate metabolites. For a time-limited tolerance the nature of the CL 263,222 residue in rotational crops is adequately understood.

Based on the confined rotational crop study, the petitioner"s proposed rotational crop restrictions are acceptable for the purposes of time-limited tolerance only.

The petitioner is reminded that the criteria is for residues of concern in confined rotational crops to be less then 0.01 ppm for the minimum plantback interval (which can normally be no longer than 12 months) to avoid having to present limited field rotational crop studies.

b. Dietary Risk Characterization

A Dietary Exposure Analysis for use of CL 263,222 in/on peanuts was conducted using the proposed tolerance of 0.1 ppm. The proposed permanent tolerance petition, 4F4390, represents the first food use.

An acute dietary toxicological endpoint was not identified by the Less-Than-Lifetime Committee. An acute dietary risk assessment is not required for CL 263,222 (refer to Other Toxicological Endpoints section).

The HED chronic dietary risk assessment used a RfD of 0.5 mg/kg body weight/day, based upon a 1-year chronic toxicity study in dogs (MRID 427114-21) with a lowest effect dose level (LOEL) of 5000 ppm (137 mg/kg/day for males, and 180 mg/kg/day for females). The 1-year dog study failed to demonstrate a no-observable effect

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level (NOEL). The RfD committee determined that the overall NOEL most likely would not be much lower than the LOEL and therefore, that a new study would not be required. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability and an additional UF of 3 was applied to account for the lack of an overall NOEL for the 1-year dog study.

No anticipated residue data or percent crop treated information was included in this analysis. The chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups.

For chronic dietary exposure from the use of CL 263,222 on peanuts the TMRC for the general U.S. population and the most highly exposed subgroups are as follows (as percent of the Reference Dose):

U.S. population	0.0015%
Children (1-6 Years Old)	0.0047%
Children (6-12 Years Old)	0.0034%

The analysis for CL 263,222 has been a worst case estimate of dietary risk and exposure, using tolerance level residues and 100% crop treated assumptions. Even considering this overestimation, the dietary risk from exposure to CL 263,222 appears to be minimal for peanuts.

IV. DATA REQUIREMENTS - WHICH MUST BE SATISFIED PRIOR TO FULL SECTION 3 REGISTRATION

A. Residue Chemistry

HED will not accept a 9 month plantback interval for corn. The petitioner needs to provide CL 263,222 residue data on corn from field rotational crop studies to support a shorter plantback interval. A rotational tolerance for CL 263,222 on corn may be necessary. If the petitioner does not wish to generate additional rotational crop residue data, then the residue data generated from the barley field rotational crop study will be translated to corn to support our decision.

The petitioner will need to conduct field rotational crop studies for CL 263,222 on barley as residues in the proposed tolerance expression exceed 0.01 ppm. HED will not accept a 4 month plantback restriction for barley or other small cereal grains

without additional data. A rotational crop tolerance may be necessary for CL 263,222 on barley. The 4 month plantback for other cereal grains; eg wheat, rye, and oats needs to be removed from the permanent tolerance label, or be supported with confined or field rotational crop studies. If the petitioner does not wish to generate additional rotational crop data for other small cereal grains, then our decision on barley will be translated to other small cereal grains. HED points out that the petitioner is always free to conduct additional confined or field rotational crop studies to support short plantback intervals.

The petitioner must provide additional confined rotational crop residue data as is described in the Subdivision N Guidelines, § 165-1(c)(2). Although carrots (root crop) and lettuce (leafy vegetable) can have a 9 month plantback as residues are <0.01 ppm, the petitioner may also wish to include them in a 30 day plot. Confined rotational crop studies for other crops with other proposed specific plantback restrictions such as Bahiagrass and legume vegetables (snap beans and soybeans) should be supported with specific residue data, or the petitioner could use the longest accepted interval for other crops which in this petition is 12 months. The petitioner is encouraged to include grain sorghum in additional rotational crop studies as an 18 month plantback restriction is normally not practical. HED policy considers 12 months to be the longest practical plantback interval and those plantbacks proposed for longer than 12 months need to be removed from the permanent label. If the petitioner insists that 18 months or longer are essential, then a detailed explanation with supporting data need to be presented for our consideration.

If the petitioner wishes to propose specific plantback restriction to assess the effects of crop failure, then a plot treated with ^{14}C-CL 263,222 should have a 30 day aging interval before planting with the three required crops and any other crops for which such a plantback interval is desired. The petitioner is encouraged to have this plot divided into appropriate shares and planted with each of the crops, harvest the crops at maturity and have them analyzed.

V. LABELING REQUIREMENTS

A restriction must be on the label that allows for only one application per peanut crop.

As long as a restriction is placed on the label against feeding treated hay, data and tolerances are not needed for this commodity.

The CADRE® Herbicide, 23.6 percent a.i., (EPA File Symbol 241-GAU) label states that the following personal protective equipment (PPE) are required: long-sleeved shirt and long pants, waterproof

gloves, and shoes plus socks. This is in accordance with the Worker Protection Standard (WPS).

The REI for CADRE® listed on the label is 12 hours, which is in agreement with WPS since the technical product is a toxicity category III compound for acute dermal toxicity.

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