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PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: May 3, 2001

MEMORANDUM

SUBJECT: *IMAZAPIC* - Report of the Hazard Identification Assessment Review Committee.

FROM: William Dykstra, Toxicologist. *William Dykstra*
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair *E.A. Doyle for 5/7/01*
and
Elizabeth Doyle, Co-Chair *E.A. Doyle 5/7/01*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: William Donovan, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 129041

On April 17, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for *IMAZAPIC* with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. *IMAZAPIC* has been previously examined by the HED RfD/Peer Review Committee for a registration on peanuts and the HIARC for a Section 18 in/on pasture grass and rangeland. The potential for increased susceptibility of infants and children from exposure to *IMAZAPIC* was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.



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Committee Members in Attendance

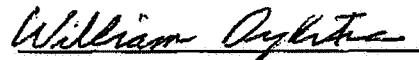
Members present were: Jess Rowland, Elizabeth Doyle, Pamela Hurley, Yung Yang, David Nixon, William Burnam, Elizabeth Mendez, Jonathan Chen, Brenda Tarplee (Executive Secretary)

Member(s) in absentia: Ayaad Assaad

Data evaluation prepared by: William Dykstra, RAB1, Marion Copley, SIMB

Also in attendance were: Paula Deschamp (RARC Chair), William Hazel, Chief (RAB1), Mark Dow (RAB1), William Donovan (RAB1)

Data Evaluation / Report Presentation


William Dykstra, Ph.D.
Toxicologist

1. INTRODUCTION

On April, 19, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for IMAZAPIC with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. IMAZAPIC was previously evaluated by the HED RfD/Peer Review Committee for a Section 3 registration on peanuts and by the HIARC for a Section 18 in/on pasture grass and rangeland. The potential for increased susceptibility of infants and children from exposure to IMAZAPIC was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. Imazapic (Cadre) is a member of the imidazolinone class of herbicides that selectively inhibit acetohydroxyacid synthetase, an enzyme in the target organism's biosynthetic pathway of three amino acids - valine, leucine, and isoleucine. In contrast to the target plant species, mammals do not possess the pathway to synthesize these three amino acids and, therefore, they are essential amino acids consumed in dietary protein. Other members of this group are Arsenal, Assert, Scepter, and Pursuit.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

An acute RfD was not established, since an appropriate endpoint attributable to a single dose was not available. No developmental toxicity was seen in rats or rabbits and maternal toxicity in rabbits occurred on days 7-19 of gestation.

2.2 Chronic Reference Dose (RfD)

Study Selected: One Year Dog Feeding Study §870.4100

MRID No.: 42711421

Executive Summary: In a one-year dietary toxicity study in dogs (MRID 42711421), AC 263, 222 technical, free acid (96.9% purity, Lot No. CL 7591-51A) was administered via the diet to groups of 6/sex/dose beagle dogs at nominal concentrations of 0, 5,000, 20,000 or 40,000 ppm (equivalent to mean achieved dosages of 137, 501, and 1,141 mg/kg/day in males and 180, 534, and 1,092 mg/kg/day in females). Parameters measured included mortality, clinical signs, body weight, food consumption, water consumption, clinical pathology, organ weights, gross necropsy, and histopathology.

At 5,000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females), treatment-related effects consisted of minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both male and, to a lesser extent, female dogs. This histological finding was

associated with minimal lymphocyte and macrophage infiltration. Minimal infiltration was also observed in the diaphragm of one dog of each sex. Decreased serum creatinine was also present in females.

At 20,000 ppm (501 mg/kg/day in males and 534 mg/kg/day in females), both sexes had increased salivation and effects on muscle, blood, and liver. Additional effects on muscle included increased incidence of lymphocyte and macrophage infiltrates in the muscle fibers of the esophagus of both males and females and degeneration/necrosis of the muscle of the esophagus of one male. 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 sexes, and the absolute liver weight in males. Effects on the blood included anisocytosis and decreases in hematocrit and hemoglobin in both sexes. Also present were increases in reticulocytes and hyperchromatic red cells and decreases in mean corpuscular volume and mean corpuscular hemoglobin in males and decreases in red blood cells in females. In addition, slightly increased hematopoiesis was observed in the bone marrow of one dog of each sex and in the spleen of one male. Food consumption was decreased in females, whereas, males showed increased serum phosphate.

At 40,000 ppm (1,141 mg/kg/day in males and 1,092 mg/kg/day in females), both sexes exhibited vomiting and decreased 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 increased serum creatine kinase and potassium in both sexes, decreased serum creatinine in males, and degeneration/necrosis of the muscle of the esophagus in females. Effects on the blood in both sexes included decreases in mean corpuscular hemoglobin concentration and increases in normoblasts, macrocytes, poikilocytes, polychromatic cells, target cells, and platelets. In addition, in males, there was decreased red cell count, and, in females, there was decreased mean corpuscular hemoglobin, decreased mean corpuscular volume, increased reticulocytes, increased hypochromatic red cells, and increased erythropoiesis of the spleen. Effects in the liver in both sexes included increased liver-to-body weight ratio, increased lactate dehydrogenase, aspartate and alanine aminotransferase, and decreased serum albumin. Males dogs also showed increased serum globulins and decreased albumin: globulin ratio, whereas females showed increased absolute liver weight and serum phosphate. Males also had decreased food consumption.

The LOAEL is 137 mg/kg/day in males and 180 mg/kg/day in females based minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen in both male and, to a lesser extent, female dogs. This histological finding was associated with minimal lymphocyte and macrophage infiltration. Minimal infiltration was also observed in the diaphragm of one dog of each sex. Decreased serum creatinine was also present in females.

A NOAEL was not established in this study.

Dose and Endpoint for Establishing RfD: The LOAEL of 137 mg/kg/day for males based on an increased incidence of minimal degeneration and/or necrosis of the skeletal muscle of the thigh

and/or abdomen. This histological finding was associated with minimal lymphocyte and macrophage infiltration. Minimal infiltration was also observed in the diaphragm of one dog of each sex.

Uncertainty Factor(s): An uncertainty factor of 300 was selected for the chronic RfD, with 10x for interspecies differences, 10x for intra species variations, and 3x due to the use of a LOAEL rather than a NOAEL for this critical study/endpoint.

Comments about Study/Endpoint/Uncertainty Factor: This effect occurred in dogs only (1 species), and may, in part, be due to the enterohepatic recycling of organic acids, such as imazapic, in this species. The use of a 3x uncertainty factor, rather than a 10x, was, in part, due to the minimal (grade of 1) severity of the skeletal muscle degeneration and/or necrosis and the fact that the severity/incidence was relatively flat across doses and increased in incidence/severity only at the highest dose (>1,000 mg/kg/day).

$\text{Chronic RfD} = \frac{137 \text{ mg/kg/day (LOAEL)}}{300 \text{ (UF)}} = 0.5 \text{ mg/kg/day}$

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Rabbit Developmental Toxicity Study §870.3700

MRID No.: 42711423

Executive Summary: In a developmental toxicity study (MRID 42711423), groups of 20 impregnated New Zealand White rabbits were administered AC 263, 222 technical, free acid (93.7% purity, Lot No. AC 5270-111) dissolved in 0.4% carboxymethyl cellulose, via gavage during gestation days 7 through 19, inclusive, at daily doses of 0, 175, 350, 500, or 700 mg/kg/day. All surviving rabbits were sacrificed on gestation day 29.

High mortality (11/20) at 700 mg/kg/day occurred during the study. Although there were a few deaths in the other treated groups of rabbits, these findings were considered to be due to gavage errors and not related to the test material. There were no compound-related abortions at any dose prior to gestation day 29. Clinical signs of few or no feces and languid behavior occurred in the 700 mg/kg/day group. At 700 and 500 mg/kg/day, body weight gain and food consumption was decreased in a dose related manner during the dosing period.

The LOAEL for maternal toxicity is 500 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. The NOAEL for maternal toxicity is 350 mg/kg/day.

Fetal (but not litter) incidences of rudimentary ribs were increased significantly ($p < 0.05$) at 350 (32%), 500 (31%), and 700 mg/kg/day (38%) in comparison to controls (17%) and historical controls (22%). At 175 mg/kg/day, the fetal incidence of rudimentary ribs was 21%. The litter incidence of rudimentary ribs was 70%, 78%, 86%, 85%, and 100% in the 0, 175, 350, 500, and 700 mg/kg/day groups, respectively. The historical control litter incidence of fetuses with rudimentary ribs from 22 studies conducted between 1981-1993 from Hazleton Laboratories provided by the Registrant ranged from 43.5% (10 of 23 litters) - 100% (15 of 15 litters). This range of historical control data encompasses the litter incidence of fetuses with rudimentary ribs in the present study at all treated dose levels. These historical control data support the conclusion that the increased occurrence of fetuses with rudimentary ribs was not related to treatment. The occurrence of only 7 litters at 700 mg/kg/day precluded a meaningful evaluation of developmental findings at this dose.

The LOAEL for developmental toxicity is greater than 500 mg/kg/day. The NOAEL for developmental toxicity is 500 mg/kg/day.

Dose and Endpoint for Risk Assessment: The maternal NOAEL of 350 mg/kg/day based on decreased body weight gain and food consumption at the LOAEL of 500 mg/kg/day.

Comments about Study/Endpoint: The decreased body weight gain and food consumption occurred during the dosing period between gestation days 7-19 and is appropriate for the population (infants and children) of concern.

2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: Rabbit Developmental Toxicity Study §870.3700

MRID No.: 42711423

Executive Summary: see short-term.

Dose and Endpoint for Risk Assessment: The maternal NOAEL of 350 mg/kg/day based on decreased body weight gain and food consumption at the LOAEL of 500 mg/kg/day.

Comments about Study/Endpoint: The HIARC noted that alterations in hematological and clinical chemistry parameters were seen at 501 mg/kg/day in the one-year dog study; however, these changes were not considered to be toxicologically significant, thus making

this dose a NOAEL for these effects (LOAEL = 1141 mg/kg/day). The Committee also determined that the use of the NOAEL of 350 mg/kg/day would be protective of the hematological effects seen at higher doses.

2.3.3 Dermal Absorption

Dermal Absorption Factor: 50%. Since a dermal absorption study is unavailable, a comparison of an oral LOAEL and a dermal NOAEL from short-term studies in rabbits was made. The oral maternal LOAEL of 500 mg/kg/day (rabbit developmental study; MRID 42711423) was divided by the dermal NOAEL of 1,000 mg/kg/day in the 21-day dermal toxicity study in rabbits (MRID 42711420). The upper bound estimated percent dermal absorption was 50%.

2.3.4 Short- and Intermediate-Term Dermal (1-7 Days and 7 Days to Several Months) Exposure

Study Selected: 21-Day Dermal Toxicity Study in Rabbits §870.3200

MRID No. 42711420

Executive Summary: In a repeat dose dermal toxicity study (MRID 42711420), AC 263, 222 technical, free acid (93.7% purity, Lot No. AC 5270-111) was applied to the clipped backs of New Zealand albino rabbits at targeted doses of 0, 250, 500, or 1,000 mg/kg/day for 6 hours per day, 5 days per week, for 3 weeks. Parameters measured included clinical signs, dermal irritation, mortality, body weight, food consumption, hematology, clinical chemistry, organ weight, necropsy findings and histopathology.

The LOAEL for both dermal irritation and systemic toxicity is greater than 1067.2 mg/kg/day. The NOAEL for both dermal irritation and systemic toxicity is 1067.2 mg/kg/day.

Proposed Dose and Endpoint: No hazard has been identified to quantitate risk, since the systemic LOAEL has not been established in this study.

Comments about Study/Endpoint: A study/endpoint was not selected for the short and intermediate-term dermal exposure scenarios, since there were no systemic effects up to the limit dose of 1,000 mg/kg/day in the 21-day dermal toxicity study in rabbits and no developmental effects were observed up to the limit dose (1,000 mg/kg/day) or at a maternally toxic dose in developmental studies in rats and rabbits. Additionally, the use of the rabbit developmental maternal NOAEL of 350 mg/kg/day with a dermal penetration of

50% results in a dermal equivalent dose of 700 mg/kg/day. This equivalent dose is comparable to the systemic NOAEL of 1,000 mg/kg/day in the 21 day dermal toxicity study in rabbits, which was a dose without effects.

2.3.5 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: One Year Dog Feeding Study §870.4100

MRID No.: 42711421

Executive Summary: see chronic RfD

Dose and Endpoint for Risk Assessment: The LOAEL of 137 mg/kg/day for males based on an increased incidence of minimal degeneration and/or necrosis of the skeletal muscle of the thigh and/or abdomen. This histological finding was associated with minimal lymphocyte and macrophage infiltration. Minimal infiltration was also observed in the diaphragm of one dog of each sex.

Comments about Study/Endpoint: Since a NOAEL was not established in the one year dog feeding study, the LOAEL of 137 mg/kg/day was selected for the study/endpoint for the long-term dermal exposure scenario. The duration of the study (chronic) is appropriate to the duration of the long term scenario (several months to lifetime). Since an oral study was selected, a dermal penetration of 50% should be used. Additionally, an MOE of 300 is required for this scenario due to the use of a LOAEL.

2.3.6 Inhalation Exposure (All Durations)

The acute inhalation LC₅₀ for imazapic is greater than 5.52 mg/l for both sexes and places imazapic in Toxicity Category IV. There are no subchronic inhalation studies for use in determining inhalation risks. Inhalation exposure is anticipated based on current use patterns. A 28 day inhalation toxicity study in rats is required by the HIARC. Therefore, the selected oral NOAELs for inhalation exposure risk assessments should be combined with route-to-route extrapolation as indicated below:

Convert the inhalation exposure component (i.e., $\mu\text{g}/\text{kg}/\text{day}$) using 100% absorption and the application rate to an oral equivalent dose.

Compare the oral equivalent dose to the oral NOAELs indicated below to calculate the Margins of Exposure.

Short-term: maternal systemic toxicity NOAEL = 350 mg/kg/day - Developmental Toxicity Study - Rabbits (MOE of 100 required)

Intermediate-term: maternal systemic toxicity NOAEL = 350 mg/kg/day - Developmental Toxicity Study - Rabbits (MOE of 100 required)

Long-term: systemic oral toxicity LOAEL = 137 mg/kg/day - One Year Oral Toxicity Study - Dogs (MOE of 300 required)

2.3.7 Margins of Exposure for Occupational/Residential Risk Assessments

An MOE of 100 is required for short- and intermediate-term inhalation occupational exposure. An MOE of 300 is required for both long-term dermal and long-term inhalation occupational exposures.

The acceptable MOEs for residential exposure will be determined by the FQPA SF Committee.

2.4 Recommendation for Aggregate Exposure Risk Assessments

There are no residential uses for imazapic. For short and intermediate-term aggregate risk assessments, oral and inhalation exposures can be combined. For long-term aggregate risk assessments, oral, dermal and inhalation exposures can be combined.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 43320307

Executive Summary: In a 24-month combined chronic feeding/carcinogenicity study (MRID 43320307), AC 263,222 technical, free acid (96.9% purity, Lot No. AC7591-51A) was administered in the diet to groups of 65 male and 65 female Sprague-Dawley strain rats at dose levels of 0 (control), 5,000 ppm, 10,000 ppm, or 20,000 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). Ten rats/sex/group were sacrificed at 12 months and the remaining survivors were sacrificed at 24 months. Mortality, clinical signs of toxicity, body weights and food consumption were monitored at appropriate times during the study. Ophthalmological examinations were conducted. Standard hematology, clinical chemistry and urinalysis examinations were performed on 10 rats/sex/group at 6, 12, 18 and 24 months. Necropsies were performed on all animals and organ weight determinations were made on 10 rats/sex/group at the 12-month interim and 24-month terminal sacrifices.

Histopathological examinations were made on a complete set of organs/tissues from all animals that died or were sacrificed in extremis during the study and on all control and 20000 ppm animals at the 12 month and 24 month scheduled sacrifices. Histopathological examinations were also

performed on the kidney, liver and lung and any gross lesions from the other dose level groups at the scheduled sacrifices.

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. **The NOAEL in this study for both male and female rats is 20,000 ppm (1029 mg/kg/day for males and 1237 mg/kg/day for females). A LOAEL was not determined. No increase in treatment-related neoplasms was observed in this study for either male or female rats.**

Discussion of Tumor Data: 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.

Adequacy of the Dose Levels Tested: Dosing was adequate for evaluation of carcinogenic potential, since the highest dose tested of 20,000 ppm is the limit dose for carcinogenicity studies.

3.2 Carcinogenicity Study in Mice

MRID No.: 43320306

Executive Summary: In an 18-month chronic feeding/carcinogenicity study (MRID 43320306), technical grade, free acid AC 263,222 (96.9% purity, Lot No. AC 7591-51 A) was administered in the diet to groups of 65 male and 65 female CD-1 strain mice at dose levels of 0 (control), 1750 ppm, 3500 ppm, 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). Ten mice/sex/dose level were sacrificed at 12

months and the remaining survivors were sacrificed at 18 months. Mortality, clinical signs of toxicity, body weights and food consumption were monitored at appropriate times during the study. Standard hematology parameters were determined on 10 mice/sex/dose level at 12 and 18 months. Necropsies were performed on all animals and organ weight determinations were made on 10 mice/sex/dose level at the 12-month interim and 18-month terminal sacrifices. Histopathological examinations were made on a complete set of organs/tissues from all animals that died or were sacrificed in extremis during the study and on all control and 7000 ppm animals at the 12 month and 18 month scheduled sacrifices. Histopathological examinations were also conducted on the kidney, liver, lung and gross lesions from the other dose level groups at the scheduled sacrifices.

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. **The NOAEL in this study for both male and female mice is 7000 ppm (1134 mg/kg/day for males and 1442 mg/kg/day for females). A LOAEL was not determined.**

Discussion of Tumor Data: There were no treatment related increases of tumors of any type in exposed male and female albino mice up to and including the limit dose of 7,000 ppm.

Adequacy of the Dose Levels Tested: The highest dose tested in the study was the limit dose of 7,000 ppm for both sexes, which did not produce any significant systemic toxicity.

Classification of Carcinogenic Potential: In accordance with the 1986 Carcinogen Risk Assessment, Imazapic was classified as a "Group E" chemical (no evidence of carcinogenicity) based on lack of evidence for carcinogenicity in two acceptable rodent (mice and rats) carcinogenicity studies (memo of the second RfD/Peer Review Report dated 9/25/95)

4 MUTAGENICITY

In a reverse gene mutation assay (MRID 42711424), imazapic was negative in *S. typhimurium* TA strains and *E.coli* WP2 uvrA strain at doses up to 5000 $\mu\text{g}/\text{plate}$ (limit dose) both in the presence and absence of S-9 metabolic activation.

In an in vitro chromosomal aberration assay (MRID 42711427), imazapic was negative for chromosome aberrations in Chinese hamster Ovary cells (CHO) exposed up to 3000 $\mu\text{g}/\text{ml}$ both with and without metabolic activation.

In an Chinese hamster Ovary cells/HGPRT forward mutation assay (MRID 42711425), imazapic was negative for forward mutation up to soluble levels (5000 $\mu\text{g}/\text{ml}$ without S-9 and 4000 $\mu\text{g}/\text{ml}$ with S-9).

In an in vivo rat bone marrow/chromosomal aberration assay (MRID 42711426), imazapic was negative for aberrations in bone marrow cells of rats treated orally up to 5000 mg/kg.

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The toxicology database is adequate for an FQPA assessment, since there are rat and rabbit developmental toxicity studies and a 2-generation rat reproduction toxicity study with imazapic.

5.2 Neurotoxicity

There are no neurotoxicity studies in rats or hens and there were no neurotoxic clinical signs or histopathology observed in any of the other toxicity studies with imazapic.

5.3 Developmental Toxicity

Executive Summary: In a developmental toxicity study (MRID 42711422), groups of 25 impregnated Sprague-Dawley rats were administered AC 263, 222 technical, free acid (93.7% purity, Lot No. AC 5270-111), dissolved in corn oil, via gavage at daily doses of 0, 250, 500, or 1,000 mg/kg/day on gestational days 6 through 15, inclusively. All surviving animals were sacrificed on gestation day 20.

There were no treatment-related effects in mortality, abortions, clinical signs, body weight, body weight gain, food consumption, or Caesarean section parameters up to and including 1,000 mg/kg/day.

The maternal LOAEL is greater than 1,000 mg/kg/day. The maternal NOAEL is 1,000 mg/kg/day.

There were no treatment-related effects in resorptions, pre- and post-implantation losses, fetal body weight and sex ratio, or external, visceral, and skeletal malformations and anomalies.

The developmental LOAEL is greater than 1,000 mg/kg/day. The developmental NOAEL is 1,000 mg/kg/day.

Executive Summary: In a developmental toxicity study (MRID 42711423), groups of 20 impregnated New Zealand White rabbits were administered AC 263, 222 technical, free acid (93.7% purity, Lot No. AC 5270-111) dissolved in 0.4% carboxymethyl cellulose, via gavage during gestation days 7 through 19, inclusive, at daily doses of 0, 175, 350, 500, or 700 mg/kg/day. All surviving rabbits were sacrificed on gestation day 29.

High mortality (11/20) at 700 mg/kg/day occurred during the study. Although there were a few deaths in the other treated groups of rabbits, these findings were considered to be due to gavage errors and not related to the test material. There were no compound-related abortions at any dose prior to gestation day 29. Clinical signs of few or no feces and languid behavior occurred in the 700 mg/kg/day group. At 700 and 500 mg/kg/day, body weight gain and food consumption was decreased in a dose related manner during the dosing period.

The LOAEL for maternal toxicity is 500 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. The NOAEL for maternal toxicity is 350 mg/kg/day.

Fetal (but not litter) incidences of rudimentary ribs were increased significantly ($p < 0.05$) at 350 (32%), 500 (31%), and 700 mg/kg/day (38%) in comparison to controls (17%) and historical controls (22%). At 175 mg/kg/day, the fetal incidence of rudimentary ribs was 21%. The litter incidence of rudimentary ribs was 70%, 78%, 86%, 85%, and 100% in the 0, 175, 350, 500, and 700 mg/kg/day groups, respectively. The historical control litter incidence of fetuses with rudimentary ribs from 22 studies conducted between 1981-1993 from Hazleton Laboratories provided by the Registrant ranged from 43.5% (10 of 23 litters) - 100% (15 of 15 litters). This range of historical control data encompasses the litter incidence of fetuses with rudimentary ribs in the present study at all treated dose levels. These historical control data support the conclusion that the increased occurrence of fetuses with rudimentary ribs was not related to treatment. The occurrence of only 7 litters at 700 mg/kg/day precluded a meaningful evaluation of developmental findings at this dose.

The LOAEL for developmental toxicity is greater than 500 mg/kg/day. The NOAEL for developmental toxicity is 500 mg/kg/day.

5.4 Reproductive Toxicity

Executive Summary: In a 2-generation rat reproduction study (MRID 43320305), AC 263, 222 technical, free acid (96.9% purity, Lot No. AC 7591-5 IA) was administered by diet to groups of 30 per sex Sprague-Dawley rats (Cr):CDBR at levels of 0, 5,000, 10,000, or 20,000 ppm (301/378, 605/737, and 1205/1484 mg/kg/day for 5,000, 10,000 and 20,000 ppm groups, respectively, for P1 animals [M/F] and 365/425, 737/884, and 1447/1703 mg/kg/day for 5,000, 10,000, and 20,000 ppm groups, respectively, for F1 animals [M/F]) for 14 weeks pre-mating through mating, gestation, and lactation (for F1 offspring) for P1 parents and F1 parents and through 21 days of lactation for the F2 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 on day 4, pre-reduction and post-reduction, day 7, 14, and 21 for F1 and F2 pups.

There were no compound-related effects in any parameter evaluated in either male or female parental animals or offspring of the first or second generation.

The parental LOAEL is greater than 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]). The parental NOAEL is 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]).

The reproductive LOAEL is greater than 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]). The reproductive NOAEL is 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]).

The offspring LOAEL is greater than 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]). The offspring NOAEL is 20,000 ppm (1205/1484 mg/kg/day for the P1 animals [M/F] and 1447/1703 mg/kg/day for F1 animals [M/F]).

5.5 Additional Information from Literature Sources (if available)

There were no additional data in the open literature (Internet) which related to the FQPA evaluation.

5.6 Determination of Susceptibility

There is **no evidence** of quantitative/qualitative increased susceptibility of rats or rabbit fetuses to in utero exposure in developmental studies.

There is **no evidence** of quantitative/qualitative increased susceptibility in multi-generation reproduction study in rats.

5.7 Recommendation for a Developmental Neurotoxicity Study

The HIARC recommended that a DNT is not required.

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

There is no evidence which supports the requirement for a developmental neurotoxicity study.

5.7.2 Evidence that do not support a need for a Developmental Neurotoxicity study:

There is no evidence of increased susceptibility in rat and rabbit developmental studies and a 2-generation reproduction study in rats.

There is no SAR for the imidazolinone class of herbicides which supports the requirement for a DNT.

There is no relevant data available in the open literature which supports the requirement for a DNT.

There is no evidence of neurotoxicity in any of the studies submitted.

6 HAZARD CHARACTERIZATION

Imazapic is of low acute toxicity by oral, dermal, and inhalation routes of exposure, as well as eye and skin irritation, since all studies are in Toxicity Category III or IV. Additionally, imazapic is not a dermal sensitizer. There were no toxic effects up to the limit dose in the subchronic oral toxicity study in rats, the subchronic dermal toxicity study in rabbits, the developmental toxicity study in rats, the chronic toxicity/carcinogenicity feeding study in rats, the carcinogenicity feeding study in mice, and the 2-generation reproduction toxicity study in rats. The mutagenic potential was negative in a full battery of studies.

Dermal penetration was estimated to be 50%, based on a comparison of the maternal LOAEL in the rabbit developmental study and the systemic NOAEL in the subchronic dermal toxicity study in rabbits. In the developmental toxicity study in rabbits, there was decreased weight gain and food consumption in the does at the LOAEL of 500 mg/kg/day, with the NOAEL being 350 mg/kg/day. There were no developmental effects in rabbit fetuses in the study up to 500 mg/kg/day. The significant increase in maternal deaths at the 700 mg/kg/day (HDT) precluded a meaningful evaluation of this dose level, since only 7 litters and 47 fetuses were available for examination.

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

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

7 **DATA GAPS**

The HIARC requires a 28-day inhalation toxicity study in rats (OPPTS Guideline No. 870.3465) [The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline No. 3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.] This 28-day inhalation toxicity study will provide a basis from which to determine more reliable route-specific MOEs for worker inhalation risks rather than the less reliable route-to-route MOE calculations currently being used.

8 ACUTE TOXICITY

Acute Toxicity of Imazapic

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	42711407	LD ₅₀ > 5,000 mg/kg	IV
81-2	Acute Dermal	42711408	LD ₅₀ > 2,000 mg/kg	III
81-3	Acute Inhalation	42711409	LC ₅₀ > 5.52 mg/L	IV
81-4	Primary Eye Irritation	42711410	minimally irritating	III
81-5	Primary Skin Irritation	42711411	non-irritating	IV
81-6	Dermal Sensitization	42711412	not a dermal sensitizer	
81-8	Acute Neurotoxicity		no study available	

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary		An acute dietary endpoint was not selected based on the absence of an appropriate endpoint attributable to a single dose	
	Acute RfD = not established		
Chronic Dietary	LOAEL = 137 mg/kg/day UF = 300	Increased incidence of minimal degeneration and/or necrosis of skeletal muscle	One-year feeding toxicity study in dogs
		Chronic RfD = 0.5 mg/kg/day	
Incidental Oral, Short-Term	NOAEL= 350 mg/kg/day	decrease in body weight gain and food consumption during dosing period.	Rabbit developmental toxicity study
Incidental Oral, Intermediate-Term	NOAEL= 350 mg/kg/day	decrease in body weight gain and food consumption during dosing period.	Rabbit developmental toxicity study
Dermal, Short- and Intermediate-Term		No systemic toxicity was seen following repeated dermal application at 1,000 mg/kg/day over a 3-week period. Since no hazard was identified, quantification is not required	
Dermal, Long-Term*	Oral LOAEL= 137 mg/kg/day	increased incidence of minimal degeneration and/or necrosis of skeletal muscle.	One-year feeding toxicity study in dogs
Inhalation, Short-Term*	Oral NOAEL= 350 mg/kg/day	decrease in body weight gain and food consumption during dosing period.	Rabbit developmental toxicity study
Inhalation, Intermediate-Term*	Oral NOAEL= 350 mg/kg/day	decrease in body weight gain and food consumption during dosing period.	Rabbit developmental toxicity study

Inhalation, Long-Term*	Oral LOAEL= 137 mg/kg/day	increased incidence of minimal degeneration and/or necrosis of skeletal muscle.	One-year feeding toxicity study in dogs
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* Appropriate route-to-route extrapolation should be performed for these risk assessments. Exposure values using absorption factors of 50% for dermal and 100% for inhalation should be converted to equivalent oral doses and compared to the oral NOAEL or LOAEL.