UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

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MEMORANDUM

SUBJECT: **Primisulfuron-methyl** Toxicology Chapter for RED

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TXR No: 0050792
PC Code: 128973
DP Barcode: 283427
Submission: S610273

Attached is the Toxicology Chapter for the **Primisulfuron-methyl** reregistration eligibility decision (RED). There were sufficient data for selecting dietary, dermal, and inhalation endpoints for risk assessment. Based on currently available information, twenty eight (28)-day inhalation study in rats is required for **Primisulfuron-methyl**.

PRIMISULFURON-METHYL: TOXICOLOGY CHAPTER FOR RED

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1.0 HAZARD CHARACTERIZATION

The toxicity data indicate that primisulfuron-methyl (CGA-136872) does not appear to be acutely toxic by acute oral and inhalation exposures (Toxicity Category IV) and moderately toxic by acute dermal exposure (Toxicity Category III). It is an eye irritant (Toxicity Category III) but not a skin sensitizer, nor a dermal irritant (Toxicity Category IV).

The 21-day dermal toxicity study in rabbits showed that primisulfuron-methyl did not produce any dermal or systemic toxicity at the limit dose (1000 mg/kg/day). In a 90-day oral toxicity study in rats, decreased body weight, body weight gain, and food consumption/efficiency were observed at the lowest observed adverse effect level (LOAEL) of 150 mg/kg. In a chronic toxicity/carcinogenicity study in rats, overall decreased body weight gain was founded at the LOAEL (150 mg/kg), and no treatment-related increase in tumor incidence was observed in any treated groups when compared to controls.

In a 90-day study in dogs, the systemic toxicity observed were decreases in body weight, body weight gain, food consumption/efficiency, hematological parameters (erythrocytes, hemoglobin, and hematocrit) and thyroid/parathyroid weight at 250 mg/kg/day. There were increased platelets and prothrombin time. In addition, primisulfuron-methyl produced mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia in the thyroid. In a 1-year chronic study in dogs, decreases in hematological parameters (erythrocytes, hemoglobin, and hematocrit) and increases in platelets, relative liver weight, pale liver, vaculolar liver and thyroid hyperplasia were observed at 250 mg/kg/day.

In a carcinogenicity study in mice, the systemic toxicity observed were (i) increased mortality; (ii) decreased body weight gains; and (iii) kidney, liver, testes, teeth, and bone toxicity. Primisulfuron-methyl produced hepatocellular adenoma, carcinomas, and adenomas/carcinomas combined in both sexes at 2 highest doses (408 and 1156 mg/kg/day). These doses were considered to be excessively toxic by Cancer Peer Review Committee and the Committee classified primisulfuron-methyl as a Group D carcinogen.

Primisulfuron-methyl produced delayed ossification in fetal rats at 500 mg/kg/day in the absence of maternal toxicity. The developmental toxicity includes increased incidence in incomplete or absence of ossification of several bones (hyoids, interparietals, ischium, os pubis and bipartite centrum/vertebrae). Primisulfuron-methyl did not produce developmental toxicity in rabbits, but, treatment-related maternal toxicity, abortion, was observed at 300 mg/kg/day and 600 mg/kg/day.

Primisulfuron-methyl affected reproductive parameters in rats including decreases in testicular/spermatic function (F1 generation) at 250 mg/kg/day. In addition, offspring toxicity manifested as decreased pup weight was also evident.

At higher dose, the testicular effects were found in the rats and mice, and the thyroid effects were found in the dogs. These observations suggested a possible effect on the endocrine system.

Primisulfuron-methyl was not mutagenic in three assays: the Ames test (S. typhimurium strains TA1535, 1537, 98 and 100), unscheduled DNA synthesis (UDS) in rat hepatocytes, and a bone marrow micronucleus assay using Chinese hamsters.

In a metabolism study in rats, primisulfuron-methyl was rapidly absorbed, metabolized and eliminated in the urine [23-31% (males) and 35-77% (females)] and feces [46-67% (males) and 13-48% (females)]. No tissue accumulation was observed. There appears to be several metabolic pathways for primisulfuron-methyl: The main pathway is hydroxylation of the pyrimidine ring to give rise to the 5-hydroxy-primidinyl-CGA-136872 (i.e. CGA-239769) followed by isomerization of the pyrimidinyl moiety. Bridge cleavage results in the formation of 2-carboxymethyl-benzene-sulfonamide in the feces and saccharin (a cyclization product) in the urine. The corresponding pyrimidinyl moiety is further metabolized.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food and non-food uses for primisulfuron-methyl are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	Y	Y
870.1200 Acute Dermal Toxicity	Y	Y
870.1300 Acute Inhalation Toxicity	Y	Y
870.2400 Primary Eye Irritation	Y	Y
870.2500 Primary Dermal Irritation	Y	Y
870.2600 Dermal Sensitization	Y	Y
870.6100 Acute Delayed Neurotox. (Hen)	N	-
870.6200a Acute Neurotox. Screening Battery (Rat)	N	-
870.3100 Oral Subchronic (Rodent)	Y	Y
870.3150 Oral Subchronic (Non-Rodent)	Y	Y
870.3200 21-Day Dermal	Y	Y
870.3250 90-Day Dermal	N	-
870.3465 90-Day Inhalation	N	-
870.3700a Developmental Toxicity (rodent)	Y	Y
870.3700b Developmental Toxicity(non-rodent)	Y	Y
870.3800 Reproduction	Y	Y
870.4100a Chronic Toxicity (Rodent)	Y	Y
870.4100b Chronic Toxicity (Non-rodent)	Y	Y
870.4200a Oncogenicity (Rat)	Y	Y
870.4200b Oncogenicity (Mouse)	Y	Y
870.4300 Chronic/Oncogenicity	Y	Y
870.5100 Mutagenicity—Gene Mutation - bacterial	Y	Y
870.5395 Mutagenicity—Structural Chromosomal Aberrations	Y	Y
870.5550 Mutagenicity—Unscheduled DNA Synthesis in Rat Hepatocytes	Y	Y
870.6100 90-Day Neurotoxicity (hen)	N	-
870.6200b 90 Day Neuro. Screening Battery (Rat)	N	-
870.6300 Develop. Neuro	N	-
870.7485 General Metabolism	Y	Y
870.7600 Dermal Penetration	N	N, 1
870.7200 Companion Animal Safety	N	-
Special Studies for Ocular Effects		
Acute Oral (Rat)	N	-
Subchronic Oral (Rat)	N	-
Six-month Oral (Dog)	N	-

Y - Yes; **N** - no 1. The HIARC extrapolated a dermal absorption factor of 30% for primisulfuron-methyl (HIARC Report, TXR NO. 0050694).

3.0 DATA GAP(S)

Twenty eight (28)-day inhalation study in rats (abbreviated 90-day protocol) is required. The HIARC is requiring this study due to the concern for the potential occupational exposure via this route based on the current use pattern. The registrant is recommended to follow all the procedures stipulated in the Subdivision F Guidelines for the 90-day inhalation toxicity study (870.3465) except that the exposure duration can be reduced to 28 days.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time. The toxicity data indicate that primisulfuron-methyl does not appear to be acutely toxic by acute oral and inhalation exposures (Toxicity Category IV) and moderately toxic by acute dermal exposure (Toxicity Category III). It is an eye irritant, but its effects are reversible within 72 hours. It is not a skin sensitizer nor a dermal irritant (Toxicity Category IV).

The acute toxicity data on the primisulfuron-methyl technical is summarized in Table 2.

Table 2. Acute Toxicity of Primisulfuron-methyl Technical

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral - Rat	40331206	LD_{50} > 5050 mg/kg	IV
870.1200	Acute Dermal - Rabbit	40331207	LD_{50} > 2010 mg/kg	III
870.1300	Acute Inhalation - Rat	40331208	LC_{50} > 4.81 mg/L	IV
870.2400	Acute Eye Irritation - Rabbit	40331209	No corneal opacity, conjunctivitis reversible by 72 hours	III
870.2500	Acute Dermal Irritation - Rabbit	40331210	Not a dermal irritant	IV
870.2600	Skin Sensitization - Guinea Pig	40331211	Not a skin sensitizer	N/A

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time. The subchronic feeding study in rats showed decrease in body weight and body weight gain at LOAEL (150 mg/kg). In a 90-day study in dogs, the systemic toxicity observed were decreases in body weight, body weight gain, food consumption/efficiency, hematological parameters (erythrocytes, hemoglobin, and hematocrit) and thyroid/parathyroid weight at 250 mg/kg/day. There were increased platelets and prothrombin time. In addition, primisulfuron-methyl produced mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia in the thyroid. In a 1-year chronic study in dogs, decreases in hematological parameters (erythrocytes, hemoglobin, and hematocrit) and increases in platelets, relative liver weight, pale liver, vaculolar liver and thyroid hyperplasia were observed at 250 mg/kg/day.

870.3100 90-Day Oral Toxicity - Rat

In a 90-day oral toxicity study (MRID 40331218), primisulfuron-methyl (94% a.i.; Lot No. FL-851407) was administered to 15 CD (Sprague Dawley) rats/sex/dose in the diet at dose levels of 0, 10, 300, 3000, 10,000, or 20,000 ppm (equivalent to 0, 0.5, 15, 150, 500, or 1000 mg/kg/day based on 1 ppm = 0.05 mg/kg/day).

No treatment-related effects were observed on mortality, hematology, clinical chemistry, ophthalmology, or urinalysis. No adverse effect was noted at 10 and 300 ppm.

Systemic toxicity was evident in the 3000-20,000 ppm males and the 10,000-20,000 ppm females. Food consumption was generally decreased ($p<0.05$) throughout the study, and food efficiency was decreased during the first three weeks (except for the 10,000 ppm females). Body weights were decreased from Weeks 8-13 in 10,000 ppm females and throughout the study in 3000-20,000 ppm males and 20,000 ppm females (decr 9.2-19.8%; $p<0.05$). Terminal body weights in 3000-20,000 ppm males were also decreased ($p<0.05$).

Increases in the incidences of tooth abnormalities were observed (treated/15 vs controls/15) grossly in the 20,000 ppm males as discolored (1 vs 0), pitted (2 vs 0), and shortened/broken (10 vs 1) teeth. In addition, the 10,000 ppm males also had shortened/broken teeth (4 treated). These signs were also noted during clinical observations.

The 20,000 ppm males had soft skull caps (3/15 treated vs 0/15 controls).

The testes were a target organ. At 20,000 ppm, testes were small (5/15 treated vs 0/15 controls), and weighed less ($p<0.05$; absolute). Microscopic examination confirmed mild to moderate atrophy and degeneration of the testes in 10,000 (2/15) and 20,000 (5/15) ppm.

The LOAEL is 3000 ppm (150 mg/kg/day) based on decreased body weights, body weight gain, food consumption, and food efficiency in males. The NOAEL for this study is 300 ppm (15 mg/kg/day).

This study is **acceptable/guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

870.3150 90-Day Oral Toxicity - Dog

In a 90-day oral toxicity study (MRID 40331219), primisulfuron-methyl (94% a.i.; Lot No. FL-851407) was administered to 4 beagle dogs/sex/dose in the diet at dose levels of 0, 25, 1000, or 10,000 ppm (equivalent to 0, 0.6, 25, or 250 mg/kg/day based on 1 ppm = 0.025 mg/kg/day).

No treatment-related effects were observed on mortality or ophthalmology. No adverse effect was noted at 25 and 1000 ppm.

In the 10,000 ppm group, decreased average mean food consumption (decr 20.1-42.5%) and decreased food efficiency (data not provided) were reported. Body weight was severely affected as 2 males and all females lost 12.8-36.7% of their initial weight. The other two males essentially maintained their initial weight (one gained 0.6 kg and one lost 0.2 kg). During clinical observations, a slight thinness in 2 males and all females, and a loss of appetite in 1 male and 3 females were noted, corroborating the body weight and food consumption/efficiency data.

In the 10,000 ppm group, the absolute and relative (to body and brain) thyroid/parathyroid weights decreased (data not reported; not statistically significant). Mild to severe colloid depletion in the small follicles of the thyroid (all dogs) and moderate to severe parafollicular cell hyperplasia in all males and 3 females were observed.

In the 10,000 ppm group, decreased ($p<0.05$) erythrocytes, hemoglobin, and hematocrit were observed. Platelets and prothrombin time were increased ($p<0.05$) in the 10,000 ppm males. Thus, the dogs were suffering a slight anemia. These effects may have been influenced by the poor nutritional status of the dogs.

In the gall bladder at 10,000 ppm, all animals had a thickened mucosa, with distention in two females and one male. At 10,000 ppm, trace-to-mild epithelial hyperplasia was observed in 2 males and 3 females. At 1000 ppm, one male and 3 females had trace-to-mild epithelial hyperplasia. Additionally, one 1000 ppm female had a thickened mucosa. However, during the chronic oral toxicity study in dogs (MRID 40512008), an adverse effect on the gall bladder was not observed when the animals were treated with 10,000/5000 ppm for 52 weeks (reduced from 10,000 to 5000 ppm during Week 11). Consequently, it is unclear whether the compound has an effect on the gall bladder, particularly at 1000 ppm.

The LOAEL is 10,000 ppm (250 mg/kg/day) based on the following: (i) decreased body

weights, body weight gain, food consumption, and food efficiency; (ii) thinness and inappetence; (iii) decreased erythrocytes, hemoglobin, and hematocrit; (iv) increased platelets and prothrombin time; (v) decreased thyroid/parathyroid weights; and (vi) in the thyroid, mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia. The NOAEL for this study is 1000 ppm (25 mg/kg/day).

This study is acceptable/guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 21-day dermal toxicity study (MRIDs 41135302 and 41337601), CGA-136872 (primisulfuron methyl, 98.2% a.i.; Lot/Batch #: FL-872675), moistened with sterilized water, was applied to the shaved intact skin (120-240 cm^2) of 5 New Zealand White rabbits/sex/group at dose levels of 0, 10, 100, or 1000 mg/kg bw/day, 6 hours/day for 7 days/week during a 21-day period.

There were no compound-related effects on mortality, clinical signs, body weight, body weight gains, food consumption, ophthalmology, hematology, clinical chemistry, gross pathology, organ weight, or histopathological data observed at any dose level in either sex. There were no signs of dermal irritation at any dose.

The LOAEL was not observed. The NOAEL is 1000 mg/kg/day (limit dose) for males and females.

This 21-day dermal toxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3200; OECD 410) for a 21-day dermal toxicity study in rabbits.

870.3465 90-Day Inhalation – Rat

Twenty eight (28)-day inhalation study in rats (abbreviated 90-day protocol) is required. The HIARC is requiring this study due to the concern for the potential occupational exposure via this route based on the current use pattern. The registrant is recommended to follow all the procedures stipulated in the Subdivision F Guidelines for the 90-day inhalation toxicity study (870.3465) except that the exposure duration can be reduced to 28 days.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. Primisulfuron-methyl produced delayed ossification in fetal rats at 500 mg/kg/day in the absence of maternal toxicity. The developmental toxicity includes increased incidence in incomplete or

absence of ossification of several bones (hyoids, interparietals, ischium, os pubis and bipartite centrum/vertebrae). Primisulfuron-methyl did not produce developmental toxicity in rabbits, but, treatment-related maternal toxicity, abortion, was observed at 300 mg/kg/day and 600 mg/kg/day.

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 40874701), primisulfuron-methyl (Batch # FL851407; purity not reported) was administered in 3% aqueous corn starch containing 0.5% Tween 80, orally via gavage, in a dosing volume of 10 mL/kg, to 24 female Crl: COBS CD (SD) BR rats/group, at dose levels of 0, 100, 500, or 1000 (limit dose) mg/kg/day, on gestation days (GD) 6 through 15. All surviving dams were sacrificed on GD 20 and their fetuses were removed by cesarean and examined.

No mortalities occurred during the study. When compared to concurrent controls, no treatment-related changes were observed in clinical signs; body weights; food consumption; group mean numbers of corpora lutea, implantation sites, resorptions, live or dead fetuses; post-implantation loss; or maternal gross pathology.

Slight decreases ($p < 0.05$) in maternal body weight gains were observed in all treated groups during GDs 8-12 (↓17-35%). These decreases were not dose-related since the greatest decrease in body weight gain was seen in the 100 mg/kg/day group. Body weight gains for the overall (GDs 6-16) treatment interval were comparable between treated animals and controls. The only statistically significant group mean body weight differences between treated and control dams were observed only at the low dose (100 mg/kg/day) and only on weighing days 12 and 20. Increased salivation was noted in the 1000 mg/kg dams (5/24) during GDs 1-3 only, however, this finding was considered not to be toxicologically important because increased salivation occurred prior to dosing. **The maternal LOAEL was not observed. The maternal NOAEL is 1000 mg/kg/day (limit dose).**

At 500 and 1000 mg/kg/day, there appeared to be a **slight delay** in fetal skeletal development as characterized by incomplete or lack of ossification of the hyoids, interparietals, ischium, os pubis and bipartite centrum/vertebrae. For the hyoid historical data of 4 studies (1983-1985), the mean % of fetuses/litters was 11.5%/48% with ranges of 9-16%/36-58%. The incidence of hyoids at 500 mg/kg/day (16%/54%; not statistically significant) was within the historical control ranges and the mean values at 1000 mg/kg/day (21%/68%; $p<0.05$) slightly exceeded the historical control ranges. For the bipartite centrum/vertebrae historical data of 19 studies (1983-1985), the mean % of fetuses/litters was 1.65/12.4% with ranges of 0-4%/0-27%. The incidence of bipartite centrum/vertebrae at 500 mg/kg/day (5%/21%; $p<0.05$) slightly exceeded the historical control ranges and mean values at 1000 mg/kg/day (2%/14%; not statistically significant) were within the historical control ranges. **The developmental toxicity LOAEL is 500 mg/kg/day based on incomplete ossification of several bones. The developmental toxicity NOAEL is 100 mg/kg/day.** It was not clear whether or not a slight decrease in body weight gains in maternal

animals during GD 8-12 would influence this observation.

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the guideline data requirement for a developmental study (83-3a) in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40331220), primisulfuron-methyl (Batch # FL851407; 94% a.i.) was administered in 3% aqueous cornstarch containing 0.5% Tween 80, orally via gavage, in a dosing volume of 10 mL/kg, to 19 female New Zealand White rabbits/group, at dose levels of 0, 10, 300, or 600 mg/kg/day, on gestation days (GD) 7 through 19. All surviving does were sacrificed on GD 29 and their fetuses were removed by cesarean section and examined. When compared to concurrent controls, no treatment-related changes were observed in numbers of corpora lutea, implantation sites, resorptions, live or dead fetuses; post-implantation loss; fetal weights, or maternal gross pathology.

At 600 mg/kg/day, two treatment-related mortalities occurred on GD 25 and 26. One doe was aborting at the time of death. Both animals exhibited decreased food consumption, weight loss, and stool abnormalities prior to death.

Abortions occurred on GD 19 and GD 24 at 300 mg/kg (2/18) and on GD 24 and GD 27 at 600 mg/kg (3/14). One 300 mg/kg and both 600 mg/kg animals displayed decreased food consumption, weight loss, and stool abnormalities. One 300 mg/kg animal showed stool abnormalities only. Body weight gains were decreased in the 600 mg/kg animals during GDs 7-20, 14-20, and 20-24 and in the 300 mg/kg animals during GDs 7-14 (30% decrease; not statistically significant). Stool abnormalities were present in 6/19 and 8/19 does in the 300 and 600 mg/kg groups, respectively. **The maternal LOAEL is 300 mg/kg/day based on abortion, decreased body weight gains, and stool abnormalities. The maternal NOAEL is 10 mg/kg/day.** No treatment-related developmental findings were noted. **The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 600 mg/kg/day (HDT).**

This study is classified as ACCEPTABLE/GUIDELINE and satisfies the guideline data requirement for a developmental study (83-3b) in rabbits.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. Primisulfuron-methyl affected reproductive parameters in rats including decreases in testicular/spermatic function (F1

generation) at 250 mg/kg/day. In addition, offspring toxicity manifested as decreased pup weight was also evident at dose that produced parental toxicity.

870.3800 Reproduction and Fertility Effects - Rat

4. <u>Reproductive Toxicity Study Conclusions</u>

In a 2-generation reproduction toxicity study (MRID 40512009), primisulfuron-methyl (Batch # P505003; 94% a.i.) was administered continuously in the diet to Crl:COBS®CD®(SD)BR rats (30/sex/dose) at nominal dose levels of 0, 10, 1000, or 5000 ppm (equivalent to 0, 0.5, 50, or 250 mg/kg/day based on 1 ppm = 0.05 mg/kg/day). The P animals were given test article diet formulations for approximately 70 days prior to mating to produce the F_1 litters. After weaning, F_1 animals (30/sex/dose) were randomly selected to become the F_1 parents of the F_2 generation and were given the same concentration test formulation as their dam. F_1 animals were given test formulations for at least 84 days.

No treatment-related parental mortalities occurred. Clinical signs, food consumption, and reproductive performance were unaffected by the test substance. No treatment related findings were noted at 10 and 1000 ppm.

At 5000 ppm, decreased ($p<0.05$) body weights were observed in the F0 (decr. 7-9%) and F1 males (decr. 7-15%). Gross pathological examination revealed an increased incidence of small testes (13 treated vs. 1 control) in the F1 males. Similarly, group mean testicular weights (absolute and relative) were decreased ($p<0.01$) relative to controls in these animals (decr. 27-28%). Histologically, an increased incidence of seminiferous tubule atrophy and aspermatogenesis (21 treated vs. 5 controls) with a relative aspermia in the epididymides (11 treated vs. 3 controls) was observed in the F1 males.

The LOAEL for parental toxicity is 5000 ppm (250 mg/kg/day) based on decreased body weight (both generations). The LOAEL for reproduction toxicity is 5000 ppm (250 mg/kg/day) based on an increased incidence of seminiferous tubule atrophy and aspermatogenesis with a relative aspermia in the epididymides (F1 generation) in the males. The NOAEL is 1000 ppm (50 mg/kg/day).

Pup viability, implantation sites, sex ratios, live and dead fetuses, litter size, birth index, weaning index, sexual maturation and developmental parameters were unaffected by treatment. No treatment-related findings were noted at 10 and 1000 ppm. At 5000 ppm, decreased ($p<0.05$) pup weights were observed in the F1 males and females on post-natal days 14 and 21 (decr. 7-12%). **The LOAEL for offspring toxicity is 5000 ppm (250 mg/kg/day) based on decreased pup weight in the F1 generation. The NOAEL for offspring toxicity is 1000 ppm (50 mg/kg/day).**

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a

multi-generation reproduction study (83-4) in rats.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. In a chronic toxicity/carcinogenicity studies in rats, decreased body weigh gain was observed. No treatment-related increase in tumor incidence was seen in any treated groups when compared to controls.

In a 1-year chronic study in dogs, decreases in hematological parameters (erythrocytes, hemoglobin, and hematocrit) and increases in platelets, relative liver weight, pale liver, vaculolar liver and thyroid hyperplasia were observed at 250 mg/kg/day.

870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic/carcinogenicity study (MRID 40856502), primisulfuron-methyl (92.7-94% a.i.; Lot No. 8525D-H) was administered to 70 CD rats/sex/dose in the diet at dose levels of 0, 10, 300, 3000, 10,000 (equivalent to 0, 0.5, 15, 150, or 500 mg/kg/day based on 1 ppm = 0.05 mg/kg/day) (reduced to 8000 after 13 weeks), or 20,000 ppm (sacrificed and discontinued after 13 weeks) for 24 months. An interim sacrifice group (10 rats/sex/dose) was treated similarly for 12 months and sacrificed. Also,10 rats/sex were treated at 0, 3000, and 10,000/8000 ppm for 12 months, and then received control diet for another month before sacrifice. No treatment-related effects were observed on mortality, food consumption, water consumption, food efficiency, hematology, clinical chemistry, urinalysis, organ weights, or the incidence of neoplasms. No adverse effect was noted at 10 and 300 ppm.

Decreased ($p<0.05$) body weights were observed in the 10,000/8000 ppm treated group throughout the study, in the 3000 ppm treated males at Weeks 13 and 52, and in the 3000 ppm females at Week 104. Overall body weight gains (Weeks 0-104; calculated by the reviewers) were decreased in the 3000 ppm males (decr 12%) and the 10,000/8000 ppm males (decr 41%) and females (decr 65%).

At 10,000/8000 ppm, soft testes were observed grossly in 22/90 treated males vs 14/90 controls. An effect on the testes at this dose was corroborated by the microscopic finding of atrophic testes (42/70 treated vs 24/69 controls).

Increases in the incidences of tooth abnormalities were observed (treated vs controls) in the 10,000/8000 ppm group including the following: (i) chipped/irregular incisors (12-49 vs 0); (ii) white incisors (11-14 vs 0); (iii) malocclusion (20-35 vs 14-15); and (iv) missing incisors (10-15 vs 5-6).

Findings at 13 months in the recovery groups were similar to those at the 12-month sacrifice for

all parameters.

The LOAEL is 3000 ppm (150 mg/kg/day in males) based on decreased overall (Weeks 0-104) body weight gains. The NOAEL for this study is 300 ppm (15 mg/kg/day).

Under the conditions of this study, there was not a treatment-related increase in tumor incidence in any treated groups when compared to controls. Dosing was considered adequate based on decrease in body weight and overall body weight gains, and increased incidence of testicular atrophy.

This study is **acceptable/guideline** and satisfies the guideline requirement for a chronic/ carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRID 40512008), primisulfuron-methyl (94% a.i.; Lot No. FL 851407) was administered to 4 beagle dogs/sex/dose in diet at dose levels of 0, 25, 1000, or 10,000/5000 ppm (equivalent to 0, 0.6, 25, or 250/125 mg/kg/day based on 1 ppm = 0.025 mg/kg/day) (reduced to 5000 ppm after Week 10 due to body weight depression for 52 weeks).

No treatment-related effects were observed on mortality, clinical signs, body weight, food consumption, ophthalmology, urinalysis, or the incidence of neoplasms. No adverse effect was noted at 25 and 1000 ppm.

In the 10,000/5000 ppm males, decreased (decr 15-25%; $p<0.01$) erythrocytes, hemoglobin, and hematocrit were observed at 3, 6, and 12 months. Platelets were increased (incr 65-95%; $p<0.01$) in the 10,000/5000 ppm group at months 3 and 12. Thus, the males were suffering a slight anemia.

Slight effects were also seen in the liver at 10,000/5000 ppm. Pale livers were observed grossly in 3/4 treated males vs 0/4 controls. Relative (to body) liver weights were increased in males (incr 22%; $p<0.05$) and females (incr 23%; NSS). Vacuolar liver changes (trace to moderate) were observed in males and females (2-3/4 treated vs 0/4 controls). In addition, cholesterol levels were decreased in both sexes throughout the study (decr 27-46%), and was significant ($p<0.05$) in males at Month 3 and females at Months 3 and 12.

Thyroid hyperplasia (trace to moderate) was also observed in the 10,000/5000 ppm group (4/4 treated each sex vs 0/4 controls).

The LOAEL is 10,000/5000 ppm (250/125 mg/kg/day) based on: (i) decreased erythrocytes, hemoglobin, and Hematocrit; (ii) increased platelets; (iii) increased relative (to body) liver weights; (iv) increased incidence of pale livers; (v) vacuolar liver changes; and (vi) thyroid hyperplasia. The NOAEL for this study is 1000 ppm (25 mg/kg/day).

This study is **acceptable/guideline** and satisfies the guideline requirements for a chronic oral study [OPPTS 870.4100, OECD 452] in dogs.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. The carcinogenicity data showed that Primisulfuron-methyl did not produce an increase in tumor incidence in rats. In a carcinogenicity study in mice, the systemic toxicity observed were (i) increased mortality; (ii) decreased body weight gains; and (iii) kidney, liver, testes, teeth, and bone toxicity. Primisulfuron-methyl produced hepatocellular adenoma, carcinomas, and adenomas/carcinomas combined in both sexes at 2 highest doses (408 and 1156 mg/kg/day). These doses were considered to be excessively toxic by Cancer Peer Review Committee, and the Committee classified primisulfuron-methyl as a Group D carcinogen (May 3, 1990).

870.4200a Carcinogenicity Study - rat

See two-year chronic toxicity and carcinogenicity study described above.

870.4200b Carcinogenicity - Mouse

In a combined chronic/carcinogenicity study (MRIDs 40856503 and 41337602), primisulfuron-methyl (Lot No. 851407, 861201, and 861923; 92.7-95.5% a.i.) was administered to 50 CD-1 mice/sex/dose in diet at dose levels of 0, 10, 300, 3000, 10,000 (reduced to 7000 during Week 23) ppm (1.35, 40.2, 408, and 1156 mg/kg/day in males; and 1.72, 50.8, 512, and 1386 mg/kg/day in females) for 80 weeks.

There were no compound-related effects on food consumption or blood cell differential counts. No adverse effect was observed in the 10 and 300 ppm groups. Toxicity was observed at 3000 ppm and increased at 10,000/7000 ppm, except when noted.

Signs of general toxicity were observed. Survival at 80 weeks was decreased (treated vs controls) in males at 3000 (58% vs 80%) and 10,000/7000 (26%) ppm, and in females at 3000 (73% vs 80%) and 10,000/7000 (62%) ppm. Decreased ($p<0.05$) body weights were observed in males at 3000 ppm during Weeks 64 and 80 and at 10,000/7000 ppm throughout the study, and in females at 10,000/7000 ppm beginning on Week 28 and persisting to the end of the study. Overall body weight gains were decreased in males at 3000 (decr 29%) and 10,000/7000 (decr 36%) ppm, and in females at 10,000/7000 (decr 27%) ppm. Decreased defecation was noted during the first 13 weeks at 10,000/7000 ppm, but incidence was similar to controls after 13 weeks.

Kidney weights (absolute; relative to body; relative to brain) were decreased ($p<0.01$) in the 3000

ppm males (decr 22-28%) and the 10,000/7000 ppm males and females. Gross abnormalities in the kidney (granular/nodule/pale/hydronephrotic/small/irregular/pitted/foci, tan/red/black) were observed in the 3000 (30-71% treated vs 10-16% controls) ppm and 10,000/7000 ppm groups. Chronic nephritis was observed in the 3000 ppm (48-80% treated vs 32-42% controls) and 10,000/7000 ppm groups.

Liver weights (absolute; relative to body; relative to brain) in both sexes were increased ($p<0.01$) in the 3000 (incr 40-54%) ppm group and the 10,000/7000 ppm group. In the original review, liver weights (absolute; relative to body; relative to brain) were increased at 10 (11-13%; $p<0.05$) and 300 ppm (16-17%; $p<0.01$) females. However, there were no microscopic findings to corroborate the weight changes in the liver. Therefore, slight increases in liver weights in females at 10 and 300 ppm were not considered biologically significant. Grossly, liver masses were observed in males at 3000 (37% treated vs 14% controls) and 10,000/7000ppm, and females at 10,000/7000 ppm. Liver foci were observed in males at 3000 and 10,000/7000 (20% vs 0%, each) ppm, and in females at 10,000/7000 ppm. Microscopically, cytomegaly and karyomegaly in the liver were observed in the 3000 (56-92% vs 0%) ppm group and 10,000/7000 ppm group. Basophilic foci in the liver were observed in males at 3000 (18% vs 0%), and both sexes at 10,000/7000 ppm.

Testes weights (absolute; relative to body; relative to brain) were decreased ($p<0.01$) at 10,000/7000 ppm. Grossly, testes abnormalities (soft, small, discolored, or foci) were observed in the 10,000/7000 ppm animals. Testicular degeneration was observed at 3000 (37% treated vs 14% controls) and 10,000/7000 ppm. Mineralization in the testes was observed at 10,000/7000 ppm. Relative aspermia in the epididymis was observed at 10,000/7000 ppm.

Abnormalities were observed clinically in the teeth of the 3000 and 10,000/7000 ppm animals throughout the study (23-49 treated vs 0 controls, each sex and all time intervals). Malocclusion was noted at 3000 (3-6 vs 0, each sex and all time intervals) and 10,000/7000 ppm animals throughout the study. Hypoplasia in the teeth was observed in the 3000 and 10,000/7000 ppm groups (70-82%, each treated vs 0% controls). Hyperostosis was observed in the bone (femur, skull, and alveolar) of the 3000 and 10,000/7000 ppm groups. Hyperostosis in the femur was most extensive and was observed in the 3000 (48-86% vs 0-2%) ppm group and the 10,000/7000 ppm group.

The LOAEL is 3000 ppm (408 mg/kg/day), based on: (i) increased mortality; (ii) decreased body weight gains; and (iii) kidney, liver, testes, teeth, and bone toxicity. The NOAEL is 300 ppm (40.2 mg/kg/day).

Microscopically, an increased ($p<0.01$) incidence in hepatocellular adenoma was observed (treated vs controls) in males at 3000 (56% vs 10%) and 10,000/7000 (50%) ppm and females at 3000 (18% vs 0%) and 10,000/7000 (38%) ppm. These values are greater than the IRDC historical control ranges of 0-26.7% in males and 0-5% in females. Hepatocellular carcinoma was observed ($p<0.01$) in 10,000/7000 ppm females (26% treated vs 0% in all other doses and

controls), and this incidence exceeded the IRDC historical control range (0-2.9%). Hepatocellular carcinoma was also observed ($p<0.01$) in the males at > 300 ppm (6-8% treated vs 2% controls). This effect in males was not dose-dependent effect, and the incidence was within the IRDC historical control range (0-14.3%). Significant ($p<0.01$) positive trends were detected in the incidence of hepatocellular adenoma and carcinoma.

This study was evaluated by the HED Cancer Peer Review Committee in May 3, 1990. The Committee determined that primisulfuron-methyl produced hepatocellular adenoma, carcinomas, and adenomas/carcinomas combined in both sexes of mice at 2 highest doses (3,000 and 10,000/7,000 ppm). However, these doses were considered to be excessively toxic and above those considered to be adequate for evaluating carcinogenic activity. Although tumors were produced by primisulfuron-methyl at 2 lower doses (1.35 and 40.2 mg/kg/day), the committee considered these dose levels to be inappropriate in that they were not sufficiently high enough to properly evaluate primisulfuron-methyl. For these reasons, the Committee considered the entire primisulfuron-methyl mouse study to be inadequate, and thus selected the **Group D classification**. The Committee did not recommend that a repeat carcinogenicity study of primisulfuron-methyl be performed in mice at this time. The Committee felt that the use of dose levels between 300 ppm and 3,000 ppm would probably result only in the appearance of a marginal increase of liver adenomas in male mice. At best, this finding would raise the classification of primisulfuron-methyl Group C without quntification. On the other hand, a negative response in a repeat study would move the compound to the Group E category.

This study is **acceptable/guideline** and satisfies guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate based on pre-1991 mutagenicity guidelines. Primisulfuron-methyl was not mutagenic in three assays: the Ames test (S. typhimurium strains TA1535, 1537, 98 and 100), unscheduled DNA synthesis (UDS) in rat hepatocytes, and a bone marrow micronucleus assay using Chinese hamsters.

Gene Mutation

870.5100 Mutagenicity—Gene Mutation - bacterial MRID # 40331221. Classification: acceptable	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to primisulfuron methyl at concentrations of 1, 4, 16, 64, or 256 μg/plate. No treatment-related increases in the number of revertants/plate were observed in any bacterial strain at any dose level of primisulfuron methyl in the presence or absence of S9-activation

Cytogenetics

Guideline # 84-2/870.5395 Study type: *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in Chinese Hamsters MRID # 40331222. Classification: acceptable	Chinese hamsters (8/sex/dose/sample time) were dosed once via oral gavage (20 mL/kg) with primisulfuron methyl at doses of. 0, 1250, 2500, or 5000 mg/kg. Bone marrow cells were harvested at 16, 24, or 48 hours post-dosing.. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls in either trial.

Other Genotoxicity

Guideline # 84-4 / 870.5550 Study type: Unscheduled DNA Synthesis in Rat Hepatocytes/ Mammalian Cell Cultures MRID # 40331223. Classification: acceptable	In an unscheduled DNA synthesis assay, hepatocyte cultures from male RAIF (SPF) rats were exposed to primisulfuron methyl at concentrations of 2, 10, 50, 100, 200, or 400 μg/mL (Trial 1) and 0.4, 2, 10, 20, 40, 60, 80, 100, 200, or 400 μg/mL (Trial 2). There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: The available data base did not indicate that this chemical induced neurotoxicity. The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to Primisulfuron-methyl. The currently available data do not support a need for a developmental neurotoxicity study as indicated in the HIARC Report (HED Doc. 0050694, dated April 26, 2002). The reasons are the following:

- No evidence of increased susceptibility following in utero exposure or pre- and/or post-natal exposure in rats.
- No neurotoxic effects are seen in available studies.
- Doses selected for risk assessment were approximately 5-10X less than the dose that produced testicular and thyroid effects.
- In addition, the current developmental neurotoxicity study guideline may not be able to identify the observed effects on the endocrine system.

Based on the weight of evidence presented, the HIARC concluded that a developmental neurotoxicity study is not required for primisulfuron-methyl.

870.6100 Delayed Neurotoxicity Study - Hen

No delayed neurotoxicity study in hens is available nor is one required.

870.6200 Acute Neurotoxicity Screening Battery

No acute neurotoxicity study in rats is available nor is one required.

870.6200 Subchronic Neurotoxicity Screening Battery

No subchronic neurotoxicity study in rats is available nor is one required.

870.6300 Developmental Neurotoxicity Study

No developmental neurotoxicity study in rats is available nor is one required.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time. With gavage administration in rats, primisulfuron-methyl was rapidly absorbed, metabolized and eliminated in the urine [23-31% (males) and 35-77% (females)] and feces [46-67% (males) and 13-48% (females)]. No tissue accumulation was observed. There appeared to be several metabolic pathways for primisulfuron-methyl: The main pathway was hydroxylation of the pyrimidine ring to give rise to the 5-hydroxy-primidinyl-CGA-136872 (i.e. CGA-239769) followed by isomerization of the pyrimidinyl moiety. Bridge cleavage resulted in the formation of 2-carboxymethyl-benzene-sulfonamide in the feces and saccharin (a cyclization product) in the urine. The corresponding pyrimidinyl moiety was further metabolized.

870.7485 Metabolism - Rat

In a rat metabolism study (MRIDs 40856502 and 40856403), [Pyrimidinyl-2-^{14}C] CGA-136872 or [Phenyl-U-^{14}C] CGA-136872 (primisulfuron-methyl; Lot No. not reported; >99% radiochemical purity) was formulated in PEG-200/0.1 M $NaHCO_3$ (1:4 v/v) at 0.5 mg/kg, or in an aqueous solution of 7 M sodium carboxymethylcellulose at 500 mg/kg. Sprague-Dawley rats (5/sex) were treated with [^{14}C] CGA-136872 as follows: (i) Group 1 received a single gavage dose at 0.5 mg/kg; (ii) Group 2 received a single oral dose at 500 mg/kg; (iii) Group 3 received 14 daily oral doses of unlabeled CGA-136872 followed by an oral dose of [^{14}C] CGA-136872 (0.5 mg/kg) on Day 15; and (iv) Group 4 received an i.v. dose at 0.5 mg/kg. Additionally, Sprague-Dawley rats were fed diets containing 0, 100, 500, 1000, 5000, 10,000, or 20,000 ppm unlabeled CGA-136872 for up to 28 days. On Days 5, 12, 19, and 26, 5 rats/sex/dose received 0.5 mg/kg [^{14}C] CGA-136872 (radiolabel position unspecified).

Total urinary excretion in the oral treatment group relative to the i.v. treatment groups suggests that gastrointestinal absorption may have been 94-103% at 0.5 mg/kg and only 23-32% at 500 mg/kg. Plasma concentrations were not measured; therefore, bioavailability could not be

determined.

Recovery of radioactivity in the urine and feces was 71-95% within 2 days and 88.5-102% within 7 days. At 0.5 mg/kg, males excreted 23-31% dose in the urine and 46-67% dose in the feces; conversely, females excreted 35.3-77% dose in the urine and 13-48% dose in the feces. At 0.5 mg/kg, elimination followed first-order kinetics, and the average half-lives for urinary and fecal excretion were about 20.3 hours. The average half-life did not change due to sex or radiolabel position at 0.5 mg/kg. At 500 mg/kg, excretion in the feces accounted for 83-93% dose in both sexes (MRID 40856502).

Radioactivity in the tissues was highest in the liver. In rats receiving the 100 ppm diet, 2-3% of administered dose in females and 6-7% in males was found in the liver at 2 days post-dose. Length of dietary treatment did not affect the residue level; however, increased dietary concentrations led to decreased tissue levels (as % administered dose). Radioactivity in the liver was < 0.2% of administered dose (< 2.2 μg/g) in rats at 7 days post-dose. Total radioactivity in the tissues was only 0.5% of administered dose at 7 days post-dose (MRID 40856502).

About 95% of the total radioactivity elimination in the excreta has been characterized. Analysis of urine and feces indicated the presence of 11 metabolites and the parent compound. Each metabolite accounted for >3% of the radioactivity in at least one sample. The compound was metabolized to a greater extent at 0.5 mg/kg rather than 500 mg/kg and in males rather than females. The metabolism involved mainly hydroxylation of the pyrimidine ring to give rise to the 5-hydroxy-primidinyl-CGA-136872 (i.e. CGA-239769) followed by isomerization of the pyrimidinyl moiety. Bridge cleavage results in the formation of 2-carboxymethyl-benzene-sulfonamide in the feces and saccharin (a cyclization product) in the urine. The corresponding pyrimidinyl moiety is further metabolized. The concentration of parent compound in the urine decreased with increased dietary levels in males (30.2-39.7% radioactivity in the urine) and females (60.0-85.4% radioactivity in the urine). This sex difference is attributed to a preferential renal elimination of the unchanged parent compound by female, whereas biliary excretion of metabolites is the predominant route in males.

This study (MRID 40856403) in rats, in conjunction with the other study (MRID 40856502), is classified as **acceptable/guideline** and satisfies the guideline requirement for a metabolism study (OPPTS 870.7485, OECD 417) in rats.

870.7600 Dermal Absorption - Rat

No dermal absorption study is available for primisulfuron-methyl and no other appropriate data are available for assessing the dermal absorption factor. As an alternative to assuming 100% dermal absorption by default, a conservative estimate was extrapolated by the HIARC as described below:

An upper bound estimation of 30% was calculated from the ratio of the LOAEL of 300 mg/kg/day established in the developmental toxicity study in rabbits to the NOAEL of >1000mg/kg (limit dose: assumed to be a LOAEL on a worst case scenario) in the 21-day dermal toxicity study in rabbits (MRID No. 41135302). (HIARC Report, TXR No. 0050694).

5.0 HAZARD ENDPOINT SELECTION

The Hazard Identification Assessment Review Committee (HIARC) met on April 16, 2002 to evaluate the entire toxicological data base, the information of the use patterns, and exposure of primisulfuron methyl. The Committee selected the relevant toxicity endpoints and doses for risk assessment for various exposure conditions. The details are presented in the appended HIARC report (TXR No. 0050694, dated April 26, 2002).

5.1 See Section 9.2 for Endpoint Selection Table for Use in Human Risk Assessment.

5.2 Dermal Absorption

Dermal Absorption Factor: 30%

There is no dermal absorption study available for primisulfuron-methyl. As an alternative to assuming 100% dermal absorption by default, a conservative estimate was extrapolated by the HIARC as shown below:

An upper bound estimation of 30% was calculated from the ratio of the LOAEL of 300 mg/kg/day established in the developmental toxicity study in rabbits to the NOAEL of >1000mg/kg (limit dose: assumed to be a LOAEL on a worst case scenario) in the 21-day dermal toxicity study in rabbits (MRID No. 41135302).

5.3 Classification of Carcinogenic Potential

5.3.1 Conclusions

No treatment-related increase in tumor incidence in any treated groups when compared to controls was seen in the combined chronic/carcinogenicity study rats.

Primisulfuron-methyl produced an increase in hepatocellular adenoma, carcinomas, and adenomas/carcinomas combined in both sexes of mice at 2 highest doses (3,000 and 10,000/7,000 ppm). However, the HED Cancer Peer Review Committee evaluated the available toxicology data and concluded that doses which produced tumors were considered to be excessively toxic and above those considered to be adequate for evaluating carcinogenic activity. Although tumors were not produced by primisulfuron-methyl at 2 lower doses (1.35 and 40.2 mg/kg/day), the committee considered these dose levels to be inappropriate in that they were not sufficiently high enough to properly evaluate primisulfuron-methyl. For these reasons, the Committee considered

the entire primisulfuron-methyl mouse study to be inadequate, and thus selected the **Group D classification**. The Committee did not recommend that a repeat carcinogenicity study of primisulfuron-methyl be performed in mice at this time because the Committee felt that the use of dose levels between 300 ppm and 3,000 ppm would probably result only in the appearance of a marginal increase of liver adenomas in male mice. At best, this finding would raise the classification of primisulfuron-methyl Group C without quntification. On the other hand, a negative response in a repeat study would move the compound to the Group E category.

5.3.2 Classification of Carcinogenic Potential

The Cancer Peer Review Committee has classified primisulfuron-methyl as a **Group D** carcinogen (not classifiable as to human carcinogen). This classification was based upon the belief of the Peer Review Committee that the mouse study where hepatocellular tumors occurred was inadequate.

5.3.3 Quantification of Carcinogenic Potential

No quantification is needed.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

The HIARC determined that a special FQPA safety factor can be removed (1X) because there was no evidence of increased susceptibility following pre/postnatal exposures to rabbits and rats and there are low levels of concerns with no residual uncertainties in the prenatal study in rats.

6.2 Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is not a concern for developmental neurotoxicity resulting from exposure to primisulfuron-methyl.

7.0 OTHER ISSUES

There are no other issues.

8.0 REFERENCES

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9.0 APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity in rats	40331218 (1987) Acceptable/guideline 0, 10, 300, 3000, 10,000, or 20,000 ppm (equivalent to 0, 0.5, 15, 150, 500, or 1000 mg/kg/day based on 1 ppm = 0.05 mg/kg/day)	NOAEL = 15 mg/kg/day LOAEL = 150 mg/kg/day based on decreased body weight gain and food consumption/efficiency.
870.3150 90-Day oral toxicity in dogs	40331219 (1987) Acceptable/guideline 0, 25, 1000, or 10,000 ppm (equivalent to 0, 0.6, 25, or 250 mg/kg/day)	NOAEL = 25 mg/kg/day. LOAEL = 250 mg/kg/day based on decreased body weight, body weight gain, food consumption/efficiency, erythrocytes, Hb, hematocrit, and thyroid/parathyroid weight. Platelets and prothrombin time were increased. In the thyroid, mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia were observed.
870.3200 21-day dermal-rabbit	41337601 and 41135302 (1989) acceptable/guideline 10, 100, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (limit dose). LOAEL = not observed
870.3700a Prenatal developmental in rats	40874701 (1988) acceptable/guideline 0, 100, 500, or 1000 mg/kg/day	maternal toxicity NOAEL > 1000 mg/kg/day. (HDT) developmental toxicity NOAEL = 100 mg/kg/day. LOAEL = 500 mg/kg/day based on incomplete or lack of ossification of several bones (hyoids, interparietals, ischium, os pubis and bipartite centrum/vertebrae)
870.3700b Prenatal developmental in rabbits	40331220 (1987) acceptable/guideline 0, 10, 300, or 600 mg/kg/day	maternal toxicity NOAEL = 10 mg/kg/day. LOAEL = 300 mg/kg/day based on abortion and decreased body weight gain developmental toxicity NOEL = 600 mg/kg/day (HDT)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects in rats	40512009 (1987) acceptable/guideline 0, 10, 1000, or 5000 ppm (equivalent to 0, 0.5, 50, or 250 mg/kg/day based on 1 ppm = 0.05 mg/kg/day)	Parental systemic toxicity NOAEL =50 mg/kg/day LOAEL =250 mg/kg/day based on decreased body weight (both generation) and increased seminiferous tubule atrophy and aspermatogenesis with a relative aspermia in the epididymides (F1 generation) Reproductive toxicity NOAEL =50 mg/kg/day LOAEL =250 mg/kg/day based on decreased pup weight (F1 generation)
870.4.300 Chronic toxicity and carcinogenicity in rats	40856502 (1988) acceptable/guideline 0, 10, 300, 3000, 10,000 (reduced to 8000 after 13 weeks) (equivalent to 0, 0.5, 15, 150, or 500 mg/kg/day based on 1 ppm = 0.05 mg/kg/day)	NOAEL = 15 mg/kg/day LOAEL= 150 mg/kg/day based on decreased body weight gain At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate.
870.4100b Chronic toxicity dogs	40512008 (1987) acceptable/guideline 0, 25, 1000, or 10,000/5000 ppm (equivalent to 0, 0.6, 25, or 250/125 mg/kg/day)	NOAEL = 25 mg/kg/day LOAEL= 250/125 mg/kg/day based on decreased erythrocytes, Hb, and hematocrit and increased platelets, relative liver weight, pale liver, vaculolar liver, and thyroid hyperplasia.
870.4300 Chronic toxicity and carcinogenicity in mice	40856503 and 41337602 (1988) acceptable/guideline 0, 1.35, 40.2, 408, and 1156 mg/kg/day in males 1.72, 50.8, 512, and 1386 mg/kg/day in females	NOAEL = 40.2 mg/kg/day LOAEL= 408 mg/kg/day based on (i) increased mortality; (ii) decreased body weight gains; and (iii) kidney, liver, testes, teeth, and bone toxicity. Hepatocellular adenoma, carcinomas, and adenomas/carcinomas combined in both sexes at 2 highest doses (408, and 1156 mg/kg/day). These doses were considered to be excessive toxic by Cancer Peer Review Committee. cancer classification: Group D
870.5100 Gene Mutation - bacterial	40331221 (1983) acceptable/guideline *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to primisulfuron methyl at concentrations of 1, 4, 16, 64, or 256 μg/plate in the presence or absence of S9-activation.	The test was negative. No treatment-related increases in the number of revertants/plate were observed in any bacterial strain at any dose level of primisulfuron methyl in the presence or absence of S9-activation

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5395 Cytogenetics *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in Chinese Hamsters	40331222 (1987) acceptable/guideline Chinese hamsters (8/sex/dose/sample time) were dosed once via oral gavage (20 mL/kg) with primisulfuron methyl at doses of. 0, 1250, 2500, or 5000 mg/kg.	The test was negative. Bone marrow cells were harvested at 16, 24, or 48 hours post-dosing. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.
Other Genotoxicity study 870.5550 Unscheduled DNA Synthesis in Rat Hepatocytes/ Mammalian Cell Cultures	40331223 (1987) acceptable/guideline Hepatocyte cultures from male RAIF (SPF) rats were exposed to primisulfuron methyl at concentrations of 2, 10, 50, 100, 200, or 400 μg/mL (Trial 1) and 0.4, 2, 10, 20, 40, 60, 80, 100, 200, or 400 μg/mL (Trial 2).	The test was negative. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.
870.7485 Metabolism and pharmacokinetics	40856502 and 40856403 (1988) acceptable/guideline Rats were treated with [Pyrimidinyl-2-^{14}C] CGA-136872 or [Phenyl-U-^{14}C] CGA-136872 as follows: (i) Group 1 received a single gavage dose at 0.5 mg/kg; (ii) Group 2 received a single oral dose at 500 mg/kg; (iii) Group 3 received 14 daily oral doses of unlabeled CGA-136872 followed by an oral dose of [^{14}C] CGA-136872 (0.5 mg/kg) on Day 15; and (iv) Group 4 received an i.v. dose at 0.5 mg/kg.	Recovery of radioactivity in the urine and feces: 88.5-102% within 7 days. At 0.5 mg/kg, (M: 23-31% dose in urine; 46-67% in feces) (F: 35.3-77% dose in urine; 13-48% in feces). At 500 mg/kg, 83-93% dose in feces in both sexes Tissues: 0.5% of dose at 7 days post-dose (highest in the liver) Metabolic Pathway: Mainly hydroxylation of the pyrimidine ring to give rise to the 5-hydroxy-primidinyl-CGA-136872 (i.e. CGA-239769) followed by isomerization of the pyrimidinyl moiety. Bridge cleavage results in the formation of 2-carboxymethyl-benzene-sulfonamide in the feces and saccharin (a cyclization product) in the urine. The corresponding pyrimidinyl moiety is further metabolized.

9.2 Summary of Toxicological Dose and Endpoints for **primisulfuron-methyl** for Use in Human Risk Assessment[1]

Exposure Scenario	Dose used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary	Not Applicable	No toxicological effects attributable to a single dose (exposure) were observed in oral toxicity studies.	
Chronic Dietary	NOAEL= 25 mg/kg/day UF = 100 **Chronic RfD** = 0.25 mg/kg/day	FQPA SF = 1 **cPAD** = chronic RfD / FQPA SF = 0.25 mg/kg/day	Chronic toxicity study in dogs. LOAEL = 125 mg/kg/day based on (i) decreased erythrocytes, hemoglobin, and hematocrit; (ii) increased platelets; (iii) increased relative (to body) liver weights; (iv) increased incidence of pale livers, vacuolar liver changes, and thyroid hyperplasia.
Short-Term (1 - 30 Days)	oral study NOAEL= 50 mg/kg/day	**LOC for MOE** = 100 (Occupational)[c]	2-Generation reproduction study in rats LOAEL = 250 mg/kg/day based on decreased pup weight in the F1 generation
Intermediate-Term (1 - 6 Months)	oral study NOAEL= 25 mg/kg/day	**LOC for MOE** = 100 (Occupational)	90-day toxicity study in dogs LOAEL = 250 mg/kg/day based on (i) decreased body weights, body weight gain, food consumption, and food efficiency; (ii) thinness and inappetence; (iii) decreased erythrocytes, hemoglobin, and hematocrit; (iv) increased platelets and prothrombin time; (v) decreased thyroid/parathyroid weights; and (vi) in the thyroid, mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia.
Dermal Intermediate-Term[a] (1 - 6 Months)	Oral study NOAEL= 25 mg/kg/day	**LOC for MOE** = 100 (Occupational)	90-day toxicity study in dogs LOAEL = 250 mg/kg/day based on (i) decreased body weights, body weight gain, food consumption, and food efficiency; (ii) thinness and inappetence; (iii) decreased erythrocytes, hemoglobin, and hematocrit; (iv) increased platelets and prothrombin time; (v) decreased thyroid/parathyroid weights; and (vi) in the thyroid, mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia.
Dermal Long-Term [a] (> 6 Months)	Oral study NOAEL= 25 mg/kg/day	**LOC for MOE** = 100 (Occupational)	Chronic toxicity study in dogs. LOAEL = 125 mg/kg/day based on (i) decreased erythrocytes, hemoglobin, and hematocrit; (ii) increased platelets; (iii) increased relative (to body) liver weights; (iv) increased incidence of pale livers, vacuolar liver changes, and thyroid hyperplasia.

Exposure Scenario	Dose used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Inhalation Short-Term [b] (1 - 30 days)	Oral study NOAEL= 50 mg/kg/day	**LOC for MOE** = 100 (Occupational)	2-Generation reproduction study in rats LOAEL = 250 mg/kg/day based on decreased pup weight in the F1 generation
Inhalation Intermediate-Term [b] (1 - 6 Months)	Oral study NOAEL= 25 mg/kg/day	**LOC for MOE** = 100 (Occupational)	90-day toxicity study in dogs LOAEL = 250 mg/kg/day based on (i) decreased body weights, body weight gain, food consumption, and food efficiency; (ii) thinness and inappetence; (iii) decreased erythrocytes, hemoglobin, and hematocrit; (iv) increased platelets and prothrombin time; (v) decreased thyroid/parathyroid weights; and (vi) in the thyroid, mild to severe colloid depletion in the small follicles and moderate to severe parafollicular cell hyperplasia.
Inhalation Long-Term [b] (>6 Months)	Oral NOAEL= 25 mg/kg/day	**LOC for MOE** =100 (Occupational)	Chronic toxicity study in dogs. LOAEL = 125 mg/kg/day based on (i) decreased erythrocytes, hemoglobin, and hematocrit; (ii) increased platelets; (iii) increased relative (to body) liver weights; (iv) increased incidence of pale livers, vacuolar liver changes, and thyroid hyperplasia.
Cancer	**Classification: Group D**		

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure

a = Since an oral NOAEL was selected, a dermal absorption factor of 30% should be used in route-to-route extrapolation.

b = Absorption via the inhalation route is assumed to be equivalent to oral absorption.

c = There are no **residential** uses.

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