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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0051700

DATE: **March 26, 2003**

MEMORANDUM

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

FROM: Guruva B. Reddy
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

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

PC Code: 129081

On February 25, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for sulfentrazone 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. The potential for increased susceptibility of infants and children from exposure to sulfentrazone 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.

Committee Members in Attendance

Members present were: Jess Rowland, Elizabeth Doyle, Brenda Tarplee, Paula Deschamp, Ayaad Assaad, William Burnam, Jonathan Chen, Pamela Hurley, John Liccione, Elizabeth Mendez, P.V. Shah, William Dykstra

Member(s) in absentia: Susan Makris

Data evaluation prepared by: Guruva B. Reddy

Also in attendance were: Donna Davis, Karen Whitby, Jessica Kidwell, Mark Dow, George Kramer, and J. Herndon

Data Evaluation / Report Presentation

Guruva B. Reddy
Toxicologist

INTRODUCTION

On February 25, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for sulfentrazone 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. The potential for increased susceptibility of infants and children from exposure to sulfentrazone was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for sulfentrazone is adequate for FQPA assessment. The following acceptable studies were available:

- Developmental toxicity studies in rats and rabbits
- Two generation reproduction toxicity studies in rats
- Acute and subchronic neurotoxicity studies in rats

2. Evidence of Neurotoxicity

The HIARC concluded that there is no concern for neurotoxicity resulting from exposure to sulfentrazone.

In the acute neurotoxicity study increased incidence of clinical signs in males and females at 750 and 2000 mg/kg/day were observed including staggered gait, splayed hind limbs and abdominal gripping. In this study Functional Observation Battery (FOB) parameters and motor activity were decreased at 750 and 2000 mg/kg/day, however, these findings were of short duration, complete recovery was observed in 14 days and there was no evidence of neuropathology. In the subchronic neurotoxicity study systemic toxicity was seen at 2500 (M/F; 150/180 mg/kg/day) and 5000 ppm (M/F; 265/292 mg/kg/day) evidenced by increased incidence of clinical signs. FOB testing revealed reduced hind limb grip strength and increased tail flick latency among 5000 ppm males at week 8. Also at week 8, the one surviving female at 5000 ppm displayed an abnormal posture and gait, lack of auditory response, and an uncoordinated landing during righting reflex evaluation. Motor activity levels in females at 2500 ppm increased during week 13 of testing. There was no evidence of neuropathology due to treatment.

Acute Neurotoxicity Study in Rats

Executive Summary: Sulfentrazone (F6285 Technical, 93.8%) was administered via a single gavage dose in corn oil at levels of 0, 250, 750, or 2000 mg/kg to Sprague-Dawley rats

(10/sex/group; MRID 43651002). The rats were observed for 14 days; clinical observation, body weight, functional observation battery, and motor activity data were collected. Neurohistopathological evaluations were performed on 5 rats/sex/group.

Treatment-related effects included death in three females at 2000 mg/kg, increased incidences of clinical signs in males and females at 750 and 2000 mg/kg (most notably, staggered gait, splayed hind limbs, abdominal gripping, and abdominogenital staining and/or reddish-brown staining under the cage), and significantly decreased mean body weight gain for males at 2000 mg/kg. In addition, significant effects were noted in FOB parameters and motor activity was decreased among males and females at 750 and 2000 mg/kg. However, these findings were of short duration, and recovery was complete within 14 days of dosing. Neuropathological evaluation of rats killed at study termination confirmed the reversibility of the systemic effects noted, and demonstrated that acute administration of F6285 Technical did not result in lesions of the nervous system.

NOAEL = 250 mg/kg

LOAEL = 750 mg/kg, based upon increased incidences of clinical signs of toxicity, FOB findings, and decreased motor activity which were reversed by Day 14 postdose. Additional findings at 2000 mg/kg included decreased male body weight gains. There was no evidence of neuropathology.

This study is classified as **ACCEPTABLE/Guideline** and satisfies the §81-8 guideline requirement for an acute neurotoxicity study in rats.

Subchronic Neurotoxicity Study in Rats

Executive Summary: Sulfentrazone (F6285 Technical, 93.5%) was administered in the diet for approximately 90 days at levels of 0, 500, 2500, or 5000 ppm (for males/females: 30/37, 150/180, or 265/292 mg/kg/day, respectively) to Sprague-Dawley rats (10/sex/group)(MRID 43651002). Clinical observation, body weight, food consumption, functional observation battery, and motor activity data were collected. Neurohistopathological evaluations were performed on 5 rats/sex from the control and 2500 ppm treatment levels, and on the surviving 3 male rats at the 5000 ppm treatment level.

Treatment-related effects included death in seven males and ten females at 5000 ppm; increased incidences of clinical signs in males and females at 2500 and 5000 ppm; and decreased mean body weight, body weight gain, and food consumption for males at ≥5000 ppm and females at ≥2500 ppm. FOB testing revealed reduced hind limb grip strength and increased tail flick latency among 5000 ppm males at Week 8. Also at Week 8, the one surviving female at 5000 ppm displayed an abnormal posture and gait, lack of auditory response, and an uncoordinated landing during righting reflex evaluation. Motor activity levels in females at 2500 ppm were increased during the Week 13 testing. Treatment-related gross pathological findings in both sexes at 5000 ppm included enlarged spleens and distended bladders filled with red fluid. Neuropathological evaluation revealed no treatment-related lesions.

NOAEL = 500 ppm (30/37 mg/kg/day for M/F)

LOAEL = 2500 ppm (150/180 mg/kg/day for M/F), based upon increased incidences of clinical signs; decreased body weight, body weight gains, and food consumption in females; and increased motor activity in females at Week 13. Additional findings at 5000 ppm included increased mortality; decreased body weight and body weight gains in males; decreased hind limb grip strength and increased tail flick latency in males at Week 8; and gross pathological lesions (bladders distended with red fluid, enlarged spleens). There was no evidence of neuropathology at either 2500 or 5000 ppm.

This study is classified as **ACCEPTABLE/Guideline** and satisfies the §82-7 guideline requirement for a subchronic neurotoxicity study in rats.

3. Developmental Toxicity Study Conclusions

a) Developmental Toxicity Study in Rats

i) Executive Summary: Sulfentrazone (F6285 Technical), was administered by gavage to pregnant female Crl:CD®BR (Sprague-Dawley) rats on days 6-15 of gestation at dose levels of 0, 1.0, 10.0, 25.0, and 50.0 mg/kg/day (MRID 42932104). The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; spleen and uterine weights were recorded; spleens were examined histopathologically. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral and skeletal evaluation.

Evidence of treatment-related maternal toxicity at the 50.0 mg/kg/day dose level consisted of significantly increased mean spleen-to-brain weight ratio and a moderate increase in splenic extramedullary hematopoiesis, which was interpreted as being related to an increased physiological demand for erythrocyte production over and above that in the bone marrow. Clinical observations (fresh or dried blood observed around the vagina) and significant decreases in mean maternal body weight change values on days 15-20 and 0-20 were considered to result from treatment-related fetal loss.

Maternal LOAEL = 50.0 mg/kg/day, based upon increased relative spleen weight and splenic extramedullary hematopoiesis.
Maternal NOAEL = 25.0 mg/kg/day

Evidence of treatment-related developmental toxicity consisted of decreased fetal viability, decreased fetal body weight, and increased incidences of fetal alterations, comprised, for the most part, of skeletal malformations and variations.

Fetal viability: At the 50.0 mg/kg/day dose level, treatment-related decreases in mean litter size and in the percent of total fetuses and live fetuses were noted. In addition, treatment-related increases were noted for the percent of dead fetuses; mean number of resorptions; percent of early, late, and total resorptions; and percent of rats with any resorption.

Fetal body weight: Treatment-related decreases in mean fetal weight values (total and by sex) were observed for the 25.0 and 50.0 mg/kg/day dose groups.

Fetal alterations: In the high-dose group (50.0 mg/kg/day), the percent of litters with fetuses with any alteration was significantly increased (91.3%). At the same dose, significant increases occurred for the percent of fetuses with any alteration (25.8%) and the average percentage of fetuses with any alteration (30.24 per litter). The increased incidences of alterations at the high-dose were attributed to significant increases in the fetal and litter incidences of both malformations and variations at that dose. The percent of litters with fetuses with any malformation (30.4%) or variation (87.0%), the percent of fetuses with any malformation (4.8%) or variation (23.1%), and the mean percent of fetuses with any malformation (6.63) or variation (27.52) per litter were increased ($p \leq 0.01$). In addition, at the 25.0 mg/kg/day level, a significant increase ($p \leq 0.05$) in the percentage of litters with any variation was noted.

Treatment-related malformations (only at the 50.0 mg/kg/day dose level) included the following: 1) The fetal and litter incidences of edema (anasarca) were increased. Four fetuses (from four litters) were observed with anasarca at this dose, whereas no edematous fetuses were observed in the control or other treated groups. 2) The fetal incidence of short ribs was increased. Since this malformation was believed to be related to significantly increased skeletal variations of the ribs (hypoplasia and/or wavy ribs), it was attributed to treatment. 3) An increase in the number of fetuses with bent radius and ulna was noted, and an observation of bent fibula was noted in one fetus at that same dose level. These observations were not present in the control or other treated groups for this study, nor were they present in the historical control data from the performing laboratory (included with the study report).

Treatment-related variations included the following: 1) Increases in the fetal and/or litter incidences of skeletal variations occurred at the 50.0 mg/kg/day dose level in the vertebral arches (incompletely ossified), ribs (hypoplastic or wavy), sternebrae (incompletely ossified or unossified) and pelvis (incompletely ossified ischia or pubis). 2) A significant reduction in the mean numbers of caudal vertebral and metacarpal ossification sites was noted for both the 25.0 and 50.0 mg/kg/day dose groups. At 50.0 mg/kg/day, the ossification site averages were also significantly reduced for sternal centers, metatarsals, and hindpaw phalanges.

Developmental LOAEL = 25.0 mg/kg/day, based upon 1) decreased mean fetal weight and 2) retardation in skeletal development as evidenced by an increased number of litters with any variation and by decreased numbers of caudal vertebral and metacarpal ossification sites.
Developmental NOAEL = 10.0 mg/kg/day

The study is **classified as Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (§83-3a) in the rat.

ii) Executive Summary: The test substance, F6285 Technical (Sulfentrazone, 94.2%), was administered by gavage to pregnant female Crl:CD®BR (Sprague-Dawley) rats (10/group) on days 6-15 of gestation at dose levels of 0, 25.0 or 50.0 mg/kg/day (MRID 43651003). The rats were observed for signs of toxicity; body weight and food consumption values were recorded.

On day 20 of gestation, the rats were sacrificed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then examined by the Staple's dissection procedure for cardiac abnormalities. The HIARC on February 25, 2003, reevaluated the DER in the light of the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document and recommended that the maternal and developmental endpoints should be set; however, study classification remained unchanged.

All dams survived to cesarean section, and no compound-related clinical signs were observed. At 50.0 mg/kg/day, maternal body weight values were significantly decreased at Day 20 and body weight change values were significantly reduced for gestation days 15-20 and 0-20, although food consumption was not affected. These maternal weight changes were the result of decreased litter size and prenatal fetal death. Significant reductions in gravid uterine weight, without accompanying decreases in adjusted body weight change, occurred at 50.0 mg/kg/day. The **maternal LOAEL = 50 mg/kg/day, based on decreased body weight changes (gestation) and litter size and the NOAEL = 25 mg/kg/day.**

At 50.0 mg/kg/day, cesarean section revealed significant reductions in the number of implantations and the percentage of live fetuses, as well as a significant increase in the percentage of early resorptions. These factors all contributed to a significant decrease in litter size at 50.0 mg/kg/day. Additionally, mean fetal body weight at 50.0 mg/kg/day was reduced 22% as compared to control. No treatment-related cardiac abnormalities were observed in either treated group when fetuses were examined by the Staple's dissection technique. The **developmental LOAEL = 50 mg/kg/day, based on significant reductions in the number of implantations and percentage of live fetuses, increase in the percentage of early resorptions, and decreased fetal body weights and NOAEL = 25 mg/kg/day.**

This study is classified as **SUPPLEMENTARY** and provides additional information under guideline §83-3 for a prenatal developmental toxicity study in rats. The results of this study confirm the maternal and fetal findings of the previously-conducted study on F6285 Technical in rats (A91-3410; MRID No. 429321-04; HED Doc. No. 011176) and do not alter the study conclusions.

iii) Executive Summary: Sulfentrazone (F6285 Technical), was administered by 6-hour dermal application to pregnant female Crl:CD®BR (Sprague-Dawley) rats on days 6-15 of gestation at dose levels of 0, 5, 25, 50, 100, and 250 mg/kg/day (MRID 42932105). The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; spleen and uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral and skeletal evaluation.

There was no evidence of treatment-related maternal toxicity. All rats survived to cesarean section. Maternal body weight change, food consumption, gross pathological findings, and absolute and relative (to brain) spleen weight values were comparable between control and

treated groups. Vaginal bleeding between gestation days 13 and 17 was observed in rats of all groups (including control) and was judged by the study author to be related to the extrusion of Reichert's membrane, which has been shown to occur during this stage of pregnancy and is frequently observed in dermal studies because the rats cannot groom themselves (Long and Evans, 1920). This finding, although attributed to treatment, was not considered a toxic effect, since the incidence of this finding in the control animals was high (14/24), and no correlation to fetal loss was observed in any group.

Maternal LOAEL = Not determined
Maternal NOAEL ≥ 250 mg/kg/day

Evidence of treatment-related developmental toxicity consisted of decreased fetal body weight and increased incidences of fetal alterations, comprised primarily of skeletal variations and reductions in mean numbers of ossification sites.

At the high-dose level (250 mg/kg/day), significant treatment-related decreases in mean fetal body weight (males, females, and combined) were observed. In addition, the percent of fetuses with any alteration observed (9.8%) was increased ($p \leq 0.01$) from the control incidence (3.2%). The percent of litters containing fetuses with any alteration (68.0%) was also significantly increased as compared to the control (37.5%) at the high dose, and was primarily attributable to increased incidences of skeletal variations.

Fetal malformations noted were sporadic and not attributed to treatment. No external or visceral variations of concern were observed. Significant treatment-related increases in the fetal and litter incidences of incompletely ossified lumbar vertebral arches, hypoplastic or wavy ribs, and incompletely ossified or nonossified ischia or pubes occurred at the high-dose (250 mg/kg/day). An additional significant increase in the high-dose fetal incidence of variations in the sternebrae (incompletely ossified or unossified) was not judged to be treatment-related. At 250 mg/kg/day, the mean numbers of thoracic vertebral and rib ossification sites were significantly decreased, a high-dose effect of treatment with F6285, consistent with the significant treatment-related hypoplasia observed in the skeletal evaluation of the ribs.

Developmental LOAEL = 250 mg/kg/day, based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites.
Developmental NOAEL = 100 mg/kg/day

The study is **classified as Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (§83-3a) in the rat.

b) Developmental Toxicity Study in Rabbits

Executive Summary: Sulfentrazone (F6285 Technical), was administered by gavage to pregnant

female New Zealand White rabbits (20/group) on days 7-19 of gestation (with the day of mating defined as gestation Day 0) at dose levels of 0,100, 250, and 375 mg/kg/day (MRID 42932106). The rabbits were observed for signs of toxicity; body weight and food consumption values were recorded. Cesarean section was performed on Day 28 of gestation; the does were necropsied, uterine weights were recorded, and uterine contents were examined. Fetal specimens were evaluated for external, visceral, and skeletal abnormalities by standard methodologies.

In the does, treatment-related incidences of decreased feces and hematuria were noted at the 250 mg/kg/day or greater. In addition, at the 375 mg/kg/day dose level, five rabbits aborted. Significant reductions in mean body weight change were observed for the dosing period (GD 7-19) and for the study duration (GD 0-29, both before and after adjustment for gravid uterine weight) at the 250 and 375 mg/kg/day dose levels.

Maternal LOAEL = 250 mg/kg/day, based upon increased abortions, clinical signs (hematuria and decreased feces), and reduced body weight gain
Maternal NOAEL = 100 mg/kg/day

At the 250 and 375 mg/kg/day dose levels, significant decreases in the percent live fetuses per litter, significant increases in the percent early resorptions per litter, and significantly decreased fetal body weight (8 and 15% below control, respectively) were observed. These decrements in litter size, survival, and weight were also observed as a significantly decreased mean gravid uterine weight value in does at the 375 mg/kg/day dose level.

No external or visceral findings in fetuses suggested a response to treatment; however, skeletal evaluation revealed dose- and treatment-related findings at the 375 mg/kg/day dose level. These included significant increases in both the fetal and litter incidences of fused caudal vertebrae (a malformation) and of partially fused nasal bones (a variation). In addition, at 375 mg/kg/day, significant treatment-related reductions in ossification site averages were observed for metacarpals and both fore- and hindpaw phalanges.

Developmental LOAEL = 250 mg/kg/day, based upon increased resorptions, decreased live fetuses per litter, and decreased fetal weight
Developmental NOAEL = 100 mg/kg/day

The study is **classified as Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (§83-3b) in the rabbit.

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

i) <u>Executive Summary</u>: Sulfentrazone (F6285 Technical, 94.2%) was administered at dietary levels of 0, 200, 500, or 700 ppm (equivalent to approximately 0, 14, 33, or 46 mg/kg/day in males and 0, 16, 40, or 56 mg/kg/day in females) to Sprague-Dawley rats (30/sex/group) over two consecutive generations of one litter each (MRID 43345408). Following a 14-week premating period, during which clinical observation, body weight, and food consumption data were collected, the rats were mated 1:1. The dams were monitored throughout the gestation and

lactation periods. Offspring from the resulting litters were examined; pups were weighed, and survival was monitored until weaning and sacrifice. Gross and histopathological evaluations were performed on all adults; offspring were necropsied at weaning.

At 500 and 700 ppm, treatment-related effects included decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males. Gestation body weight gain decrements were the result of prenatal litter loss. Reductions in F1 male premating body weight gain, although appearing systemic in nature, may have been secondary to developmental toxicity in these animals. For both generations, the following were noted: increased duration of gestation, reduced prenatal viability (fetal and litter), reduced litter size, increased number of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation.

Male fertility was reduced in the F1 generation at 500 and 700 ppm. Histopathological evaluation of the reproductive organs of the F1 males revealed degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degenerated seminal product in the epididymides.

No effects of treatment were observed at the 200 ppm dietary level.

Systemic NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Systemic LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males.

Reproductive NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Reproductive LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based upon increased duration of gestation in females, decreased F1 male fertility and degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degenerated seminal material in the epididymis of F1 males.

Offspring NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Offspring LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based upon reduced pre- and postnatal pup and litter survival, reduced litter size, increased number of stillborn pups, and decreased pup weight throughout lactation in both generations of offspring.

This study is classified as **ACCEPTABLE/Guideline** and satisfies the §83-4 guideline requirement for a two-generation reproductive toxicity study in rats.

ii) In a reproduction study (MRID 43869101), Sprague-Dawley rats (28/sex/dose F0; and 24/sex/dose F1) received either 0, 50, 100, 200, or 500 ppm of sulfentrazone Technical (93.5% a.i.) by dietary administration (equivalent to 0, 3.9, 7.8, 16, and 40 mg/kg/day for F0 males; 0,

4.1, 13.4, 16, and 43 mg/kg/day for F0 females; 0, 4.5, 9.2, 18, and 45 mg/kg/day for F1 males; 0, 5.0, 10.1, 20, and 51 mg/kg/day for F1 females, based upon premating intake values). F0 rats received treated diet for a 12-week premating period. Mating performance, gestation, and lactation parameters were evaluated. F1 pups were selected at weaning for the second generation. The age at sexual maturation (vaginal opening or balanopreputial separation) was recorded. F1 rats were mated following a 12-week premating period; the dams were killed on gestation day 20, and uterine contents were examined. Postmortem evaluation of adult rats of both generations included evaluation of weights and histopathology of selected organs (including quantification of oocytes), and epididymal sperm count, motility, and morphology assessments. Due to the absence of second generation lactation data, this study was designated as a one-generation reproduction study.

No mortalities or clinical signs appeared associated with administration of the test material at any dose level. No effects upon mean body weights or weight gain were apparent for F0 males and females, or for F1 males. The mean body weight gain for F1 females during weeks 4-16 was decreased 11% from control values ($p \leq 0.01$). **The LOAEL for parental (systemic) toxicity is 500 (51 mg/kg/day) based upon a decrease in F1 female body weight gain the parental (systemic) toxicity NOAEL is 200 ppm (20 mg/kg/day).**

There were no effects of treatment on mating performance or fertility in males or females of either generation.

Decreased survival was noted in F1 pups at 500 ppm, as evidenced by a decreased number of live pups per litter, an increased number of litters losing more than one pup, and a 2-fold increase in the overall incidence of postnatal pup mortality as compared to controls. Also at 500 ppm, F1 mean pup weights per litter were significantly decreased at postnatal days 1, 4, and 7; and F2 fetal weights were significantly decreased at gestation day 20. Vaginal opening was delayed by approximately 4 days in F1 female offspring at 500 ppm, accompanied by evidence of vaginal threads. In F1 males, significant reductions in mean epididymides, prostate and testes weights were apparent at the 500 ppm treatment level; histopathological evaluation of the reproductive organs did not identify any treatment-related findings. No effects on epididymal sperm count motility or morphology were noted at any treatment level.

In conclusion, offspring/reproductive toxicity is apparent at the high dose level based upon effects in F1 offspring. **The Offspring/Reproductive Toxicity LOAEL is at 500 ppm (40 mg/kg/day)** based upon reduced gestation day 20 fetal weights; decreased postnatal day 0, 4, and 7 pup weights; decreased pup survival; delayed vaginal patency; and reduced epididymides, prostate and testes weights and **the Offspring/Reproductive. NOAEL is at 200 ppm (16 mg/kg/day).**

The study is classified as **Acceptable/Non-guideline** and does not satisfy the guideline requirement for a reproduction study (OPPTS 870.3800; §83-4). However, the study data supports the conclusions of the two-generation reproduction study in rats with sulfentrazone (MRID 43345408; FMC Study A92-3545).

5. Additional Information from Literature Sources

A literature search was conducted and no neurotoxicity, developmental or reproduction toxicity studies were found.

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is a low concern for pre- and/or postnatal toxicity resulting from exposure to sulfentrazone.

A. Determination of Susceptibility

There is evidence of increased quantitative susceptibility following *in utero* exposure in the developmental toxicity studies in rats via the oral and dermal routes. The NOAELs for developmental toxicity in the these studies were lower than the maternal toxicity NOAELs. The developmental effects seen in the dermal study (decreased fetal body weights and increased skeletal variations), occurred at doses that were not maternally toxic. In an unacceptable/guideline developmental study in rats no increased susceptibility was evident.

There is evidence of qualitative increased susceptibility following *in utero* exposure in the developmental toxicity study in rabbits. In this study, the developmental effects (decreased pup viability) were observed at the maternally toxic (clinical signs, increased abortions and decreased body weight gain) dose.

There is evidence for qualitative increased susceptibility following pre-and/or postnatal exposure in the 2-generation reproduction study in rats. In this study, offspring effects (decreased litter survival) were observed at the slightly maternally toxic dose (slightly decreased body weight gain) indicating, increased qualitative susceptibility. In addition, reproductive effects (increased duration of gestation in females, decreased F1 male fertility, degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degenerated seminal material in the epididymis of F1 males) were observed at doses that resulted in decreased body weights in both generations and premating body weight in F1 males (at the same dose that produced maternal toxicity). In the 1-generation reproduction study similar effects as seen in 2-generation reproduction study were observed. In this acceptable/non-guideline study, severe offspring effects (decreased fetal survival) was observed in the presence of maternally toxic dose (significantly decreased body weight gain), indicating slight qualitative susceptibility. In addition, reproductive effects (delayed vaginal opening and presence of vaginal threads, and decreased epididymides, prostrate, and testicular weights) were observed in F1 generation animals at doses that resulted decreased body weight gains in F1 generation females.

B. Degree of Concern Analysis and Residual Uncertainties

Since there is qualitative and quantitative evidence of increased susceptibility of the young following exposure to Sulfentrazone in the rat and rabbit developmental studies and in the rat reproduction studies, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual uncertainties are identified, HIARC examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analysis for Sulfentrazone follow.

The concerns are low for the quantitative susceptibility of rat fetuses observed following oral and dermal exposures, the qualitative susceptibility of rabbit fetuses seen via the oral route, and the qualitative susceptibility seen in the 1- and 2-generation reproduction studies since in all these studies, the dose-response was well characterized; there were clear NOAELs and LOAELs for developmental, offspring, maternal and parental toxicities; the developmental effects in rabbits and the offspring effects in the rats were seen in the presence of maternal and parental toxicities, respectively; and the parental reproductive and offspring effects were reproducible between the two reproductive studies. There is no confidence in the quantitative susceptibility demonstrated in one oral rat developmental study (MRID No. 42932104) since the results were not replicated in the second study (MRID No. 43651003). In the first study, the developmental NOAEL was 10 mg/kg/day and the LOAEL was 25 mg/kg/day, which were lower than the maternal NOAEL 25 and LOAEL 50 mg/kg/day. However, in the second study when tested at the same doses, the 25 mg/kg/day was a NOAEL for developmental toxicity.

There are no residual uncertainties for pre and/or post natal toxicities via the oral route since the doses selected for overall risk assessments would address the concerns for the developmental and offspring toxicities seen in the above mentioned studies. Although the developmental NOAEL of 10 mg/kg/day in the oral pre-natal rat study is lower than the NOAEL of 25 mg/kg/day selected for establishing the acute RfD for Females 13-50, the lower value was not chosen because as noted above the fetal effects were not replicated in the second study and also because the fetal effects (decrease in fetal weight and skeletal retardation) are not attributable to a single exposure and thus not appropriate for acute dietary risk assessments. The offspring NOAEL of 14 mg/kg/day selected for the incidental oral, chronic dietary and long-term inhalation exposure risk assessments is comparable to the developmental NOAEL of 10 mg/kg/day and this "numerical" difference is an artifact of dose selection in these studies. Similarly, there are no residual uncertainties for pre and/or post natal toxicities via the dermal route since the dose/endpoint/study/species of concern was used for dermal risk assessment.

Therefore, there are no residual uncertainties for pre-/post-natal toxicity study.

C. Special FQPA Safety Factor(s):

The special FQPA Safety Factor can be reduced to 1X because, there are low concerns and no residual uncertainties for pre- and post-natal toxicity as explained under section 6 A&B.

Note: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

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

A. Evidence that **support requiring** a Developmental Neurotoxicity study:

- Neurobehavioral effects were observed in the acute and subchronic neurotoxicity studies in adult rats (See Section I.2).

B. Evidence that **support not requiring** a Developmental Neurotoxicity study:

- Effects seen in the acute neurotoxicity study were only observed at the high dose, were of short duration, and were reversed within 14 days. There was no evidence of neuropathology following perfusion of central and peripheral nervous system in both acute and subchronic neurotoxicity studies in rats.

- No evidence of neurotoxicity (clinical signs or neuropathology) was observed in any of the other studies. The increased pre- and post-natal susceptibility due to toxicity of the chemical at the high dose which does not include neurotoxicity or apparent alterations of nervous system development.

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

II HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - Females 13 - 50 years old

Study Selected: Developmental Toxicity Study - Rat (2 separate studies) §870.3700a

MRID No.: 43651003 & 42932104

i) Executive Summary: The test substance, F6285 Technical (Sulfentrazone, 94.2%), was administered by gavage to pregnant female Crl:CD®BR (Sprague-Dawley) rats (10/group) on days 6-15 of gestation at dose levels of 0, 25.0 or 50.0 mg/kg/day (MRID 43651003). The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then examined by the Staple's dissection procedure for cardiac abnormalities. Previously this study did not establish the NOAELs and LOAELs. Therefore, the HIARC on February 25, 2003, reevaluated the DER in the light of the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document and recommended that maternal and developmental NOAELs/LOAELs should be set; however, study classification remained unchanged.

All dams survived to cesarean section, and no compound-related clinical signs of toxicity were observed. At 50.0 mg/kg/day, maternal body weight values were significantly decreased at Day 20 and body weight change values were significantly reduced for gestation days 15-20 and 0-20, although food consumption was not affected. These maternal weight changes were the result of decreased litter size and prenatal fetal death. Significant reductions in gravid uterine weight, without accompanying decreases in adjusted body weight change, occurred at 50.0 mg/kg/day. The **maternal NOAEL = 25 mg/kg/day and LOAEL = 50 mg/kg/day, based on decreased body weight changes (gestation) and litter size.**

At 50.0 mg/kg/day, cesarean section revealed significant reductions in the number of implantations and the percentage of live fetuses, as well as a significant increase in the percentage of early resorptions. These factors all contributed to a significant decrease in litter size at 50.0 mg/kg/day. Additionally, mean fetal body weight at 50.0 mg/kg/day was reduced 22% as compared to control. No treatment-related cardiac abnormalities were observed in either treated group when fetuses were examined by the Staple's dissection technique. The **developmental NOAEL = 25 mg/kg/day and LOAEL = 50 mg/kg/day, based on significant reductions in the number of implantations and percentage of live fetuses, increase in the percentage of early resorptions, and decreased fetal body weights.**

This study is classified as **SUPPLEMENTARY** and provides additional information under guideline §83-3 for a prenatal developmental toxicity study in rats. The results of this study confirm the maternal and fetal findings of the previously-conducted study on F6285 Technical in rats (A91-3410; MRID No. 42932104; HED Doc. No. 011176) and do not alter the study conclusions.

ii) Executive Summary: Sulfentrazone (F6285 Technical), was administered by gavage to pregnant female Crl:CD®BR (Sprague-Dawley) rats on days 6-15 of gestation at dose levels of 0, 1.0, 10.0, 25.0, and 50.0 mg/kg/day (MRID 42932104). The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the

rats were sacrificed and necropsied; spleen and uterine weights were recorded; spleens were examined histopathologically. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral and skeletal evaluation.

Evidence of treatment-related maternal toxicity at the 50.0 mg/kg/day dose level consisted of significantly increased mean spleen-to-brain weight ratio and a moderate increase in splenic extramedullary hematopoiesis, which was interpreted as being related to an increased physiological demand for erythrocyte production over and above that in the bone marrow. Clinical observations (fresh or dried blood observed around the vagina) and significant decreases in mean maternal body weight change values on days 15-20 and 0-20 were considered to result from treatment-related fetal loss.

Maternal LOAEL = 50.0 mg/kg/day, based upon increased relative spleen weight and splenic extramedullary hematopoiesis.
Maternal NOAEL = 25.0 mg/kg/day

Evidence of treatment-related developmental toxicity consisted of decreased fetal viability, decreased fetal body weight, and increased incidences of fetal alterations, comprised, for the most part, of skeletal malformations and variations.

Fetal viability: At the 50.0 mg/kg/day dose level, treatment-related decreases in mean litter size and in the percent of total fetuses and live fetuses were noted. In addition, treatment-related increases were noted for the percent of dead fetuses; mean number of resorptions; percent of early, late, and total resorptions; and percent of rats with any resorption.

Fetal body weight: Treatment-related decreases in mean fetal weight values (total and by sex) were observed for the 25.0 and 50.0 mg/kg/day dose groups.

Fetal alterations: In the high-dose group (50.0 mg/kg/day), the percent of litters with fetuses with any alteration was significantly increased (91.3%). At the same dose, significant increases occurred for the percent of fetuses with any alteration (25.8%) and the average percentage of fetuses with any alteration (30.24 per litter). The increased incidences of alterations at the high-dose were attributed to significant increases in the fetal and litter incidences of both malformations and variations at that dose. The percent of litters with fetuses with any malformation (30.4%) or variation (87.0%), the percent of fetuses with any malformation (4.8%) or variation (23.1%), and the mean percent of fetuses with any malformation (6.63) or variation (27.52) per litter were increased ($p \leq 0.01$). In addition, at the 25.0 mg/kg/day level, a significant increase ($p \leq 0.05$) in the percentage of litters with any variation was noted.

Treatment-related malformations (only at the 50.0 mg/kg/day dose level) included the following: 1) The fetal and litter incidences of edema (anasarca) were increased. Four fetuses (from four litters) were observed with anasarca at this dose, whereas no edematous fetuses were observed in the control or other treated groups. 2) The fetal incidence of short ribs was increased. Since this malformation was believed to be related to significantly increased skeletal variations of the ribs

(hypoplasia and/or wavy ribs), it was attributed to treatment. 3) An increase in the number of fetuses with bent radius and ulna was noted, and an observation of bent fibula was noted in one fetus at that same dose level. These observations were not present in the control or other treated groups for this study, nor were they present in the historical control data from the performing laboratory (included with the study report).

Treatment-related variations included the following: 1) Increases in the fetal and/or litter incidences of skeletal variations occurred at the 50.0 mg/kg/day dose level in the vertebral arches (incompletely ossified), ribs (hypoplastic or wavy), sternebrae (incompletely ossified or unossified) and pelvis (incompletely ossified ischia or pubis). 2) A significant reduction in the mean numbers of caudal vertebral and metacarpal ossification sites was noted for both the 25.0 and 50.0 mg/kg/day dose groups. At 50.0 mg/kg/day, the ossification site averages were also significantly reduced for sternal centers, metatarsals, and hindpaw phalanges.

Developmental LOAEL = 25.0 mg/kg/day, based upon 1) decreased mean fetal weight and 2) retardation in skeletal development as evidenced by an increased number of litters with any variation and by decreased numbers of caudal vertebral and metacarpal ossification sites.
Developmental NOAEL = 10.0 mg/kg/day

The study is **classified as Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (§83-3a) in the rat.

Dose and Endpoint for Establishing aRfD: The Developmental NOAEL of 25 mg/kg/day based on decreased live fetuses and increased early resorptions seen at the LOAEL of 50 mg/kg/day.

Uncertainty Factor (UF): 100 (10X to account for interspecies extrapolation and 10X for intraspecies variability).

Comments about Study/Endpoint/Uncertainty Factor: Decreased live fetuses and increased early resorptions observed were attributed to a single exposure. Decreased live fetuses and increased early resorptions were seen in two developmental toxicity studies in rats at the same dose levels (50 mg/kg/day). The developmental NOAEL of 10 mg/kg/day in the one study (MRID No.42932104) was not selected since the effects (decreased mean fetal weights and skeletal retardations) were judged to be not attributable to single exposure.

Acute RfD (Females 13 - 50 years old) = $\frac{25 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.25 mg/kg**

2. Acute Reference Dose (aRfD) - General Population (including infants and children)

Study Selected: Acute Neurotoxicity Study - Rat § 870.6200

MRID No.: 43345405

Executive Summary: The test substance, F6285 Technical (Sulfentrazone, 93.8%) was administered via a single gavage dose in corn oil at levels of 0, 250, 750, or 2000 mg/kg to Sprague-Dawley rats (10/sex/group). The rats were observed for 14 days; clinical observation, body weight, functional observation battery, and motor activity data were collected. Neurohistopathological evaluations were performed on 5 rats/sex/group.

Treatment-related effects included death in three females at 2000 mg/kg, increased incidences of clinical signs in males and females at 750 and 2000 mg/kg (most notably, staggered gait, splayed hindlimbs, abdominal gripping, and abdominogenital staining and/or reddish-brown staining under the cage), and significantly decreased mean body weight gain for males at 2000 mg/kg. In addition, significant effects were noted in FOB parameters and motor activity was decreased among males and females at 750 and 2000 mg/kg. However, these findings were of short duration, and recovery was complete within 14 days of dosing. Neuropathological evaluation of rats killed at study termination confirmed the reversibility of the systemic effects noted, and demonstrated that acute administration of F6285 Technical did not result in lesions of the nervous system.

NOAEL = 250 mg/kg

LOAEL = 750 mg/kg, based upon increased incidences of clinical signs of toxicity, FOB findings, and decreased motor activity which were reversed by Day 14 postdose. Additional findings at 2000 mg/kg included decreased male body weight gains. There was no evidence of neuropathology.

This study is classified as **ACCEPTABLE/Guideline** and satisfies the §81-8 guideline requirement for an acute neurotoxicity study in rats.

Dose and Endpoint for Establishing aRfD: NOAEL = 250 mg/kg/day, based upon increased incidence of clinical signs, FOB findings, and decreased motor activity which were reversed by Day 14 postdose observed at the LOAEL of 750 mg/kg/day.

Uncertainty Factor (UF): 100 (10X to account for interspecies extrapolation and 10X for intraspecies variability).

Comments about Study/Endpoint/Uncertainty Factor: Increased incidences of clinical signs (staggered gait, splayed hindlimbs, and abdominal gripping), FOB parameters and decreased motor activity were seen after a single exposure.

Acute RfD (General Population) = $\frac{250 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **2.5 mg/kg**

3. Chronic Reference Dose (cRfD)

Study Selected: 2-Generation Reproduction Study - Rat § 870.3800

MRID No.: 43345408

Executive Summary: Sulfentrazone (Technical, 94.2% a.i) was administered at dietary levels of 0, 200, 500, or 700 ppm (equivalent to approximately 0, 14, 33, or 46 mg/kg/day in males and 0, 16, 40, or 56 mg/kg/day in females) to Sprague-Dawley rats (30/sex/group) over two consecutive generations of one litter each. Following a 14-week premating period, during which clinical observation, body weight, and food consumption data were collected, the rats were mated 1:1. The dams were monitored throughout the gestation and lactation periods. Offspring from the resulting litters were examined; pups were weighed, and survival was monitored until weaning and sacrifice. Gross and histopathological evaluations were performed on all adults; offspring were necropsied at weaning.

At 500 and 700 ppm, treatment-related effects included decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males. Gestation body weight gain decrements were the result of prenatal litter loss. Reductions in F1 male premating body weight gain, although appearing systemic in nature, may have been secondary to developmental toxicity in these animals. For both generations, the following were noted: increased duration of gestation, reduced prenatal viability (fetal and litter), reduced litter size, increased number of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation.

Male fertility was reduced in the F1 generation at 500 and 700 ppm. Histopathological evaluation of the reproductive organs of the F1 males revealed degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degenerated seminal product in the epididymides.

No effects of treatment were observed at the 200 ppm dietary level.

Systemic NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Systemic LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males.

Reproductive NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Reproductive LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based upon increased duration of gestation in females, decreased F1 male fertility and degeneration and/or atrophy of the germinal epithelium of the testes, oligospermia and intratubular degenerated seminal material in the epididymis of F1 males.

Offspring NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females)

Offspring LOAEL = 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females), based upon reduced pre- and postnatal pup and litter survival, reduced litter size, increased number of stillborn pups, and decreased pup weight throughout lactation in both generations of offspring.

This study is classified as **ACCEPTABLE/Guideline** and satisfies the §83-4 guideline requirement for a two-generation reproductive toxicity study in rats.

Dose and Endpoint for Establishing cRfD: Systemic toxicity NOAEL = 14 mg/kg/day, based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males seen at the LOAEL of 33 mg/kg/day.

Uncertainty Factor(s): 100 (10X to account for interspecies extrapolation and 10X for intraspecies variability).

Comments about Study/Endpoint/Uncertainty Factor: This study has the lowest NOAEL in the database for chronic toxicity studies, and is appropriate for the route and duration of exposure. The dose is protective of testicular effects seen in two reproduction studies (MRIDs 43345408 & 43869101). The HIARC commented that the NOAEL 10 mg/kg/day (with a LOAEL of 25 mg/kg/day) from the developmental toxicity study in the rat and the NOAEL of 14 mg/kg/day (with a LOAEL of 33 mg/kg/day) in the 2-generation reproduction study are essentially the same and that the apparent difference between the 2 NOAELs (10 vs 14 mg/kg/day) is an artifact of dose selection in these studies.

Chronic RfD = $\frac{\text{14 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ = **0.14 mg/kg/day**

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: 2-Generation Reproduction Study - Rat § 870.3800

MRID No.: 43345408

Executive Summary: see Section 3.3, Chronic RfD

Dose and Endpoint for Risk Assessment: Offspring NOAEL of 14 mg/kg/day, based upon decreased pup weight throughout lactation in both generations of offspring.

Comments about Study/Endpoint: The study/endpoint is appropriate for the population of concern (infants and children) and the duration of exposure (1 - 30 days).

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: 2-Generation Reproduction Study - Rat § 870.3800

MRID No.: 43345408

Executive Summary: see Section 3.3, Chronic RfD

Dose and Endpoint for Risk Assessment: Offspring NOAEL of 14 mg/kg/day, based upon decreased pup weight throughout lactation in both generations of offspring.

Comments about Study/Endpoint: The study/endpoint is appropriate for the population of concern (infants and children) and the duration of exposure (1 to 6 months).

6. Dermal Absorption

A dermal absorption study was not available. A dermal absorption value of 10% was calculated based on the comparison of the dermal developmental LOAEL of 250 mg/kg/day from the dermal developmental toxicity study in rats (MRID43004603) and the oral developmental LOAEL of 25 mg/kg/day in an oral prenatal developmental toxicity study in rats (MRID 42932104). This dermal absorption value of 10% will be used for all dermal exposure risk assessment scenarios. The same end points (decreased fetal weights) were observed via both routes.

Dermal Absorption Factor: 10%

7. Dermal Exposure: Short-Term (1- 30 days) Exposure

Study Selected: Dermal Developmental Toxicity Study - Rat § 870.3700

MRID No.: 42932105

Executive Summary: Sulfentrazone (F6285 Technical), was administered by 6-hour dermal application to pregnant female Crl:CD®BR (Sprague-Dawley) rats on days 6-15 of gestation at dose levels of 5, 25, 50, 100, and 250 mg/kg/day. The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were sacrificed and necropsied; spleen and uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral and skeletal evaluation.

There was no evidence of treatment-related maternal toxicity. All rats survived to cesarean section. Maternal body weight change, food consumption, gross pathological findings, and absolute and relative (to brain) spleen weight values were comparable between control and treated groups. Vaginal bleeding between gestation days 13 and 17 was observed in rats of all groups (including control) and was judged by the study author to be related to the extrusion of Reichert's membrane, which has been shown to occur during this stage of pregnancy and is frequently observed in dermal studies because the rats cannot groom themselves (Long and Evans, 1920). This finding, although attributed to treatment, was not considered a toxic effect,

since the incidence of this finding in the control animals was high (14/24), and no correlation to fetal loss was observed in any group.

Maternal LOAEL = Not determined
Maternal NOAEL ≥ 250 mg/kg/day

Evidence of treatment-related developmental toxicity consisted of decreased fetal body weight and increased incidences of fetal alterations, comprised primarily of skeletal variations and reductions in mean numbers of ossification sites.

At the high-dose level (250 mg/kg/day), significant treatment-related decreases in mean fetal body weight (males, females, and combined) were observed. In addition, the percent of fetuses with any alteration observed (9.8%) was increased ($p \leq 0.01$) from the control incidence (3.2%). The percent of litters containing fetuses with any alteration (68.0%) was also significantly increased as compared to the control (37.5%) at the high dose, and was primarily attributable to increased incidences of skeletal variations.

Fetal malformations noted were sporadic and not attributed to treatment. No external or visceral variations of concern were observed. Significant treatment-related increases in the fetal and litter incidences of incompletely ossified lumbar vertebral arches, hypoplastic or wavy ribs, and incompletely ossified or nonossified ischia or pubes occurred at the high-dose (250 mg/kg/day). An additional significant increase in the high-dose fetal incidence of variations in the sternebrae (incompletely ossified or unossified) was not judged to be treatment-related. At 250 mg/kg/day, the mean numbers of thoracic vertebral and rib ossification sites were significantly decreased, a high-dose effect of treatment with F6285, consistent with the significant treatment-related hypoplasia observed in the skeletal evaluation of the ribs.

Developmental LOAEL = 250 mg/kg/day, based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites.
Developmental NOAEL = 100 mg/kg/day

The study is **classified as Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (§83-3a) in the rat.

Dose and Endpoint for Risk Assessment: Developmental NOAEL of 100 mg/kg/day, based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites seen at the LOAEL of 250 mg/kg/day.

Comments about Study/Endpoint: This route specific study examines the most sensitive endpoints of concern (developmental effects) in the most sensitive species following appropriate

duration of exposure (1-30 days).

8. Dermal Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: Dermal Developmental Toxicity Study - Rat § 870.3700

MRID No.: 42932105

Executive Summary: See short-term dermal

Dose and Endpoint for Risk Assessment: Developmental NOAEL of 100 mg/kg/day, based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites seen at the LOAEL of 250 mg/kg/day.

Comments about Study/Endpoint: This study is appropriate for the route and duration of exposure (1-6 months). Since, decrease in fetal body weights were seen in 2-generation reproduction study (LOAEL 33 mg/kg/day; NOAEL 14 mg/kg/day) and developmental toxicity study in rats at a LOAEL of 25 mg/kg/day and NOAEL of 10 mg/kg/day, indicating that the effect of concern is the same irrespective of duration of exposure. Therefore, this dose and endpoint is appropriate for this exposure period.

9. Dermal Exposure Long-Term (> 6 Months)

Study Selected: Dermal Developmental Toxicity Study - Rat §870.3700

MRID No.: 42932105

Executive Summary: see short-term dermal

Dose and Endpoint for Risk Assessment: Developmental NOAEL of 100 mg/kg/day, based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites seen at the LOAEL of 250 mg/kg/day.

Comments about Study/Endpoint: The dermal developmental toxicity study is appropriate for the route and duration of exposure, since, decreases in fetal body weights were seen in the 2-generation reproduction study (LOAEL 33 mg/kg/day; NOAEL 14 mg/kg/day) and the developmental toxicity study in rats at a LOAEL of 25 mg/kg/day and NOAEL of 10 mg/kg/day, indicating that the effect of concern is the same irrespective of duration of exposure. Therefore, this dose and endpoint is appropriate for this exposure period. In addition, the dermal NOAEL of 100 mg/kg/day is supported by the NOAEL of 14 mg/kg/day established in a 2-generation oral reproduction study with a 10% dermal absorption rate i.e., the comparable dermal dose is

approximately 140 mg/kg/day (oral NOAEL of 14 mg/kg/day adjusted by 10% dermal absorption = 140 mg/kg/day).

10. Inhalation Exposure: Short -Term (1- 30 days)

Study Selected: 2-Generation Reproduction Toxicity Study - Rat §870.3800

MRID No.: 43345408

Executive Summary: see Chronic RfD

Dose/Endpoint for Risk Assessment: Systemic toxicity NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females) based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males seen at the LOAEL of 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females).

Comments about Study/Endpoint: With the exception of an acute inhalation study in which sulfentrazone was placed in Toxicity Category III (LC_{50} > 4.13 mg/L), no other inhalation studies are available. Therefore, an oral study was chosen for the short-term inhalation endpoint. This study/endpoint is appropriate for the population of concern (general population, including infants and children) and the duration of exposure (1 - 30 days). Since the dose identified for the short-term inhalation exposure is from an oral study, route-to-route extrapolation should be used. Decrease in fetal body weights were seen in the 2-generation reproduction study (LOAEL 33 mg/kg/day; NOAEL 14 mg/kg/day) and the developmental toxicity study in rats at a LOAEL of 25 mg/kg/day with a NOAEL of 10 mg/kg/day. These findings demonstrate that the effect of concern is consistently observed irrespective of duration of exposure. Absorption via the inhalation route is assumed to be comparable to oral absorption (i.e., use 100% default inhalation absorption values).

11. Inhalation Exposure: Intermediate-Term (1- 6 Months)

Study Selected: 2-Generation Reproduction Toxicity Study - Rat § 870.3800

MRID No.: 43345408

Executive Summary: see Chronic RfD

Dose/Endpoint for Risk Assessment: Systemic toxicity NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females) based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males seen at the LOAEL of 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females).

Comments about Study/Endpoint: With the exception of an acute inhalation study in which

sulfentrazone was placed in Toxicity Category III (LC_{50} > 4.13 mg/L), no other inhalation studies are available for risk assessment. Therefore, an oral study was chosen for the intermediate-term inhalation endpoint. This study/endpoint is appropriate for the population of concern (general population, including infants and children) and the duration of exposure (1 - 6 months). Since the dose identified for the intermediate-term inhalation exposure is from an oral study, route-to-route extrapolation should be used. Since, decrease in fetal body weights were seen in 2-generation reproduction study (LOAEL 33 mg/kg/day; NOAEL 14 mg/kg/day) and developmental toxicity study in rats at a LOAEL of 25 mg/kg/day and NOAEL of 10 mg/kg/day, indicating that the effect of concern is the same irrespective of duration of exposure. Absorption via the inhalation route is assumed to be comparable to oral absorption (i.e., use 100% default inhalation absorption values).

12. Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: 2-Generation Reproduction Toxicity Study - Rat §87.3800

MRID No.: 43345408

Executive Summary: see Chronic RfD

Dose/Endpoint for Risk Assessment: Systemic toxicity NOAEL = 200 ppm (14 mg/kg/day for males, 16 mg/kg/day for females) based on decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), and reduced premating body weight gains in the second generation (F1) males seen at the LOAEL of 500 ppm (33 mg/kg/day for males, 40 mg/kg/day for females).

Comments about Study/Endpoint: With the exception of an acute inhalation study in which sulfentrazone was placed in Toxicity Category III (LC_{50} > 4.13 mg/L), no other inhalation studies are available. Therefore, an oral study was chosen for the long-term inhalation endpoint. This study/endpoint is appropriate for the population of concern (general population, including infants and children) and the duration of exposure (> 6 months). Since the dose identified for the long-term inhalation exposure is from an oral study, route-to-route extrapolation should be used. Since, decrease in fetal body weights were seen in 2-generation reproduction study (LOAEL 33 mg/kg/day; NOAEL 14 mg/kg/day) and developmental toxicity study in rats at a LOAEL of 25 mg/kg/day and NOAEL of 10 mg/kg/day, indicating that the effect of concern is the same irrespective of duration of exposure. Absorption via the inhalation route is assumed to be comparable to oral absorption (i.e., use 100% default inhalation absorption values).

13. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	
Dermal	100	100	100
Inhalation	100	100	100

14. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows:

The incidental oral, dermal and inhalation exposure scenarios can be combined for assessing aggregate risk because the toxicity endpoints selected for these scenarios are the same (i.e., body weight decreases in fetuses and as well as in maternal animals) following oral, dermal and inhalation (oral equivalents) routes.

III CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43345409

Executive Summary: In a chronic toxicity/oncogenicity study, groups of 60 male Sprague-Dawley rats were given diets containing 0, 600, 1000, 2000, or 3000 ppm of Sulfentrazone (94.2%) and groups of 60 females were given diets containing 0, 300, 600, 1000, or 2000 ppm of Sulfentrazone (94.2%) for 2 years. The female rats were initially given the same diets as male rats, the concentrations were reduced on day 162 because of adverse effects on body weights. These dietary concentrations resulted in doses of 0, 24.3, 40.0, 82.8, or 123.5 mg/kg/day for males and 0, 20.0, 36.4, 67.0, or 124.7 mg/kg/day for females. A total of ten animals per group per sex were selected for interim evaluations, which included animals dying before week 52 and those expected to die before termination.

There were no treatment-related effects on survival, clinical signs of toxicity or serum chemistry and urinalysis parameters in either male or female rats at any dose.

In female rats at 1000 and 2000 ppm, statistically significant, dose-related decreases in body weights (up to 11 and 19%, respectively), body weight gain (13 and 26%), and food consumption (up to 13 and 16%) were observed. Hemoglobin concentrations were decreased up to 13-18%, respectively, in male rats receiving 2000 and 3000 ppm of the test material, and up to 15-25%, respectively, in female rats receiving 1000 and 2000 ppm. Corresponding statistically significant decreases in hematocrit, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) occurred at the same doses in both sexes. Statistically significant increases in the nucleated red blood cell (NRBC) count in peripheral blood and in the reticulocyte count in bone marrow occurred in female rats receiving 2000 ppm and in the red blood cell (RBC) count in male and female rats receiving the two highest doses. The clinical pathology findings were consistent with the reported mechanism of action of Sulfentrazone: inhibition of protoporphyrinogen oxidase and disruption of heme synthesis.

A significant increase in the incidence of cataracts was noted among high-dose male (3000 ppm) and female (2000 ppm) rats, at histopathological evaluation. There were no other organ toxicities noted.

At 600 and 1000 ppm in male rats and 300 and 600 ppm in female rats, body weights, body weight gain, and food consumption values were similar to those of controls. The hemoglobin concentrations, hematocrit, MCV, and MCH were slightly decreased, compared with controls, but the magnitude of the decrease (<10%) suggested that the effects were not biologically significant.

Based upon these findings, the lowest-observed-effect level (LOAEL) for F6285 technical is 2000 ppm (82.8 mg/kg/day) for male rats and 1000 ppm (67.0 mg/kg/day) for female rats. The corresponding no-observed-effect level (NOAEL) is 1000 ppm (40.0 mg/kg/day) for male rats and 600 ppm (36.4 mg/kg/day) for female rats.

This study showed no evidence of carcinogenicity in male and female rats administered F6285 technical for 2 years.

The study is classified as **ACCEPTABLE/Guideline** and satisfies the §83-5 guideline for a chronic/oncogenicity study in rats.

Discussion of Tumor Data: Administration of sulfentrazone in the diet to Charles River CD:BR (Sprague-Dawley) rats at doses up to 3000 ppm for 2 years did not increase the incidence of tumors of any kind and at any dose (Memo, G. Ghali, May 7, 1996, RfD/Peer Review Report of Sulfentrazone).

Adequacy of the Dose Levels Tested: The highest dose in this study was considered to be adequate, but not excessive, in both sexes based on statistically significant, dose-related

decreases in body weight (3 to 20%), body weight gain (5 to 30%), and food consumption (7 to 16%). Additionally, at the HDT, hemoglobin concentration, hematocrit levels, and mean corpuscular volume decreased. There was an increase in the nucleated red blood cells in both sexes. These clinical pathology findings were consistent with the reported mechanism of action of sulfentrazone i.e., inhibition of protoporphyrinogen oxidase and disruption of heme syntheses (Memo, G. Ghali, May 7, 1996, RfD/Peer Review Report of Sulfentrazone).

2. Carcinogenicity Study in Mice

MRID No. 43345407

Executive Summary: Groups of 50 male and 50 female CD-1 mice were fed diets containing 0, 300, 600, 1000, or 2000 ppm Sulfentrazone (94.2%) for 18 months. The intake of test material was equivalent to 0, 46.6, 93.9, 160.5, or 337.6 mg/kg/day for male mice and 0, 58.0, 116.9, 198.0, or 407.1 mg/kg/day for female mice in the control through high-dose groups, respectively.

Mean body weights of all male treated groups were 6 to 8% less than controls at study termination. In 2000 ppm males at termination, body weight gain was decreased 27% as compared to control. Female body weights were not affected, nor were food consumption or clinical observations for either sex.

Treatment with Sulfentrazone induced dose-dependent decreases in HGB and HCT for both sexes. Statistically significant HBG decreases (18-22% less than control) were observed in 1000 and 2000 ppm males and females at study termination. Decreases in HGB or HCT values noted at 300 and 600 ppm were less severe, and often did not exhibit a dose response relationship. Treatment-related decreases in MCV, MCH, and MCHC were also observed, and slight increases in platelet counts, observed in high-dose males, may have also been related to treatment. The clinical hematology findings were consistent with the reported mechanism of action of Sulfentrazone: inhibition of protoporphyrinogen oxidase and disruption of heme synthesis.

Histopathological examination revealed treatment-related increases in the incidences of extramedullary hematopoiesis of the splenic red pulp in treated mice of both sexes. Increased incidences of amyloid deposition in the kidney, spleen, adrenal, liver, and thyroid in both sexes may have been promoted by treatment; however, a clear dose-response was not apparent.

No treatment-related neoplastic lesions were observed.

The study **LOAEL = 1000 ppm** (160.5 mg/kg/day in males and 198.0 mg/kg/day in females), based upon treatment-related decreases in hemoglobin and hematocrit. The **NOAEL = 600 ppm** (93.9 mg/kg/day in males and 116.9 mg/kg/day in females).

The study is classified as **ACCEPTABLE/Guideline** and satisfies the §83-2 guideline for an oncogenicity study in mice.

Discussion of Tumor Data: Administration of sulfentrazone in the diet to Swiss Crl:CD-1 (ICR) BR mice at doses up to 2000 ppm for 78 weeks was not associated with any increase in tumor incidence in any tissue (Memo, G. Ghali, May 7, 1996, RfD/Peer Review Report of Sulfentrazone).

Adequacy of the Dose Levels Tested : The highest dose was considered to be adequate, but not excessive, based on decreased body weights (6 to 8%), and body weight gain (27%) in males and hemoglobin levels (18 - 22%) in males and females. The hematology findings were consistent with the reported mechanism of action of sulfentrazone which was known to disrupt heme syntheses.

3. **Classification of Carcinogenic Potential**: Sulfentrazone was reviewed by the HED RfD/Peer Review Committee on 2/15/1996 and 4/4/1996. In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), sulfentrazone was classified as **"not likely to be carcinogenic to humans".**

IV. MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to sulfentrazone. The available mutagenicity studies clearly indicate that sulfentrazone is weakly clastogenic in the *in vitro* mouse lymphoma assay in the absence of S9 activation, however, the response was not evident in the presence of S9 activation. Sulfentrazone is neither mutagenic in bacterial cells nor clastogenic in male and female mice in vivo.

The acceptable studies satisfy both the pre-1991 and the new mutagenicity initial testing battery guidelines. No additional testing is necessary at this time.

Mutagenicity Testing of Technical Grade Sulfentrazone

Study	Results
Gene Mutation-Ames MRID 41911601	Negative for reverse mutation in S. typhimurium strains up to highest dose level tested of 10,000 µg/plate, both in the presence and in the absence of activations system (+/- S9)
Gene Mutation-Mouse lymphoma Chinese hamster MRID 43004604	In a forward gene mutation assay, sulfentrazone at precipitating levels (2400 to 3000 µg/mL) were **equivocally, dose-related positive in the absence of S9 activation.** This response was not repeated at doses up to 1800 µg/mL in the presence of S9 activation.
In vivo micronucleus assay MRID 43004605	The test was negative in mice administered single intraperitoneal doses of 85-340 mg/kg. The 340 mg/kg dose was estimated to be approximately 80% of the $LD_{50/7}$. No evidence of a cytotoxic effect on the target organ and no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow cells.

Study	Results
Dominant Lethal Assay - Rats MRID 44248302	In dominant lethal assay male rats were dosed po at 0, 100, 225, or 450 mg/kg/day for 5 days, and mated to untreated females sequentially for 10 weeks to determine the level of fetal deaths due to dominant lethal mutations. There were no significant difference from negative controls in the proportion of early dead: total implants, and (total) dead: total implants. Based on the results, **sulfentrazone is considered negative for inducing dominant lethal mutations in pre-meiotic, meiotic, and post-meiotic germ cells of male rats under conditions of this assay up to the estimated MTD.**

V. HAZARD CHARACTERIZATION

Sulfentrazone is an aryl triazolinone herbicide used for controlling a variety of broadleaf weeds. Its mode-of-action for controlling emerging weeds is by protoporphyrinogen oxidase inhibition. Sulfentrazone has low acute toxicity via the oral, dermal and inhalation routes (Toxicity Category III). It is a mild eye irritant (Toxicity Category III), but not a dermal irritant or sensitizer.

No dermal toxicity was seen at the limit dose in a 28-day dermal toxicity in rabbits. Subchronic and chronic toxicity studies in rats, mice and dogs identified the hematopoietic system as the target organ. Protoporphyrinogen oxidase inhibition in the mammalian species may result in disruption of heme synthesis. In these studies disturbed heme synthesis was seen at about the same dose levels (LOAELs of 57 to 83 mg/kg/day) across species, except in the case of mice, where the effects were seen at a little higher dose (LOAELs of 94 - 108 mg/kg/day). In a 90-day toxicity study in dogs, altered red cell indices and increased liver weights, including liver and splenic microscopic changes were seen at 57 - 73 mg/kg/day. At similar doses in the chronic dog study hematopoietic effects and liver changes were seen with similar severity. In a 90-day rat study altered red cell indices were observed at doses of 62 mg/kg/day and effects were reversible following a 4-week recovery period. In the mouse subchronic toxicity study, altered red cell parameters and splenic changes were seen at 108 mg/kg/day. The red cell effects were reversible following a 4-week recovery period, however, the splenic changes were not completely reversed. In the rat and mouse oncogenicity studies similar hematological effects as seen in subchronic and chronic toxicity studies were also evident, indicating that systemic toxicity (hematopoietic effects) occurs around the same dose level from short-through long-term exposure without increasing the severity.

Carcinogenicity studies in rats and mouse showed no evidence of increased incidence of tumor formation due to treatment with sulfentrazone. The HED RfD/Peer Review Committee on 2/15/1996 and 4/4/1996, in accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), classified sulfentrazone as a **"not likely to be carcinogenic to humans".**

The available mutagenicity studies indicate that sulfentrazone is weakly clastogenic in the *in vitro* mouse lymphoma assay in the absence of S9 activation, however, the response was not evident in the presence of S9 activation. Sulfentrazone is neither mutagenic in bacterial cells nor clastogenic in male and female mice in vivo. The acceptable studies satisfy both the pre-1991 and the new mutagenicity initial testing battery guidelines.

In the acute neurotoxicity study an increased incidence of clinical signs (staggered gait, splayed hind limbs and abdominal gripping) and decreased FOB parameters and motor activity were observed at 750 and 2000 mg/kg/day, however, these findings were of short duration. Complete recovery was observed in 14 days and there was no evidence of neuropathology. In the subchronic neurotoxicity study systemic toxicity was seen at 2500 (M/F; 150/180 mg/kg/day) and 5000 (M/F; 265/292 mg/kg/day) ppm; however, there was no evidence of neuropathology due to treatment. There is evidence of increased quantitative susceptibility following *in utero* exposure in the developmental toxicity studies in rats via the oral and dermal routes. There is evidence of increased qualitative susceptibility following *in utero* exposure in the developmental toxicity study in rabbits. There is evidence for increased qualitative susceptibility following pre-and/or postnatal exposure in the 2-generation reproduction study in rats. The developmental effects seen in the oral and dermal studies occurred at a dose that did not cause maternal toxicity, indicating increased quantitative susceptibility. The developmental effects seen in dermal study, such as decreased fetal body weights and increased skeletal variations occurred at doses that were not maternally toxic, indicating increased quantitative susceptibility. In the developmental toxicity study in rabbits, the developmental effects, such as decreased pup viability, were observed at the maternally toxic dose (clinical signs, abortions and decreased body weight gains), indicating increased qualitative susceptibility. In a 2-generation reproduction toxicity study, offspring effects such as decreased litter survival (more severe than maternal effects) were observed at the slightly maternally toxic dose (slightly decreased body weight gain), indicating increased qualitative susceptibility. In addition, reproductive effects such as increased duration of gestation in females, decreased F1 male fertility, degeneration and/or atrophy of the germinal epithelium of the testes, and oligospermia and intratubular degenerated seminal material in the epididymis of F1 males (more severe than the maternal effects) were observed at a dose in dams that resulted in decreased body weights in both generations and decreased premating body weight in F1 males (maternally toxic dose), indicating increased qualitative susceptibility.

Sulfentrazone is readily absorbed from the G.I. tract of rats following oral dosing and nearly all radioactivity was recovered in the urine (84 - 104% of the dose) and feces within 72 hours. There were no major sex related differences in the pattern of excretion.

VI. DATA GAPS / REQUIREMENTS

The HIARC identified 28-Day inhalation toxicity study as a data gap due to the concern for toxicity by the inhalation route based on the current use pattern. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with exposure (treatment) ending after 28 days, instead of 90 days.

VII. ACUTE TOXICITY

Acute Toxicity Profile of Sulfentrazone

GDLN	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	41911605	LD_{50} = 2855 (M & F) mg/kg	III
81-2	Acute Dermal (mice)	41911606	LD_{50} = 711 (M & F) mg/kg	III
81-2	Acute Dermal	41911606 42286400	LD_{50} > 2000 mg/kg/day	III
81-3	Acute Inhalation	42471002	4-hour, whole body exposure; LC_{50} > 4.13 mg/L	III
81-4	Primary Eye Irritation	41911608	Corneal opacity, iritis, diffuse irritation within 24, clearing by day 4	III
81-5	Primary Skin Irritation	41911609	No erythema or edema after 4-hour exposure	IV
81-6	Dermal Sensitization	41911610	Not a dermal sensitizer	N/A

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR SULFENTRAZONE

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = **25** mg/kg/day UF = 100 **Acute RfD = 0.25** mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **0.25** mg/kg/day	**Developmental Toxicity Study - Rat** LOAEL = 50 mg/kg/day, based on decreased live fetuses, and increased early resorptions
Acute Dietary (General population including infants and children)	NOAEL = 250 mg/kg/day UF = 100 **Acute RfD** = 2.5 mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **2.5** mg/kg/day	**Acute neurotoxicity Study - Rat** LOAEL = **750** mg/kg/day based on increased incidence of clinical signs and FOB parameters and decreased motor activity
Chronic Dietary (All populations)	Systemic NOAEL= **14** mg/kg/day UF = **100** **Chronic RfD** = **0.14** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.14** mg/kg/day	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased body weight and body weight gains
Short-Term Incidental Oral (1-30 days)	Offspring NOAEL= **14** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased pup body weights during lactation in both generations
Intermediate-Term Incidental Oral (1- 6 months)	Offspring NOAEL= **14** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased pup body weights during lactation in both generations

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1 to 30 days)	Dermal study NOAEL= 100 mg/kg/day (dermal absorption rate = 10%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Dermal Developmental Study - Rat** LOAEL = **250** mg/kg/day based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites
Intermediate-Term Dermal (1 to 6 months)	Dermal study NOAEL= **100** mg/kg/day (dermal absorption rate = **10%**)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Dermal Developmental Study - Rat** LOAEL = **250** mg/kg/day based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites
Long-Term Dermal (>6 months)	Dermal study NOAEL= **100** mg/kg/day (dermal absorption rate = **10%**)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**Dermal Developmental Study - Rat** LOAEL = **250** mg/kg/day based on decreased fetal body weight; increased incidences of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites
Short-Term Inhalation (1 to 30 days)	Oral study systemic NOAEL= **14** mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased body weight and body weight gains

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (1 to 6 months)	Oral study systemic NOAEL= **14** mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased body weight and body weight gains
Long-Term Inhalation (>6 months)	Oral study systemic NOAEL= **14** mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	**2-Generation Reproduction Study** LOAEL = **33** mg/kg/day based on decreased body weight and body weight gains
Cancer (oral, dermal, inhalation)	sulfentrazone classified as **"not likely to be carcinogenic to humans"**		

UF = uncertainty factor, FQPA SF = Special 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, LOC = level of concern, NA = Not Applicable

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.