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

FEB 10 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: HED Risk Assessment for Use of the New Chemical Herbicide **Sulfentrazone** (F6285) on Soybeans and Rotational Crops; PP# 4F4407; PC Code **129081**; CAS 122836-35-5; PRATS Case Number 285935; DP Barcode numbers D211074, D215963, D226429, and D226833.

FROM: Steve Robbins, Chemical Manager SR 1/31/97
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Michael Metzger, Acting Chief M. Metzger for
Risk Characterization and Analysis Branch
Health Effects Division (7509C)
and
Margaret J. Stasikowski, Director Stephanie L. Irene 2/10/97
Health Effects Division (7509C)

TO: Joanne Miller, Product Manager Team 23
Fungicide-Herbicide Branch
Registration Division (7505C)

As requested, the Health Effects Division (HED) has completed a risk assessment for use of sulfentrazone on soybeans. The Hazard Assessment is from Susan L. Makris in Toxicology Branch II, the Dietary Exposure Assessment, Product Chemistry and Tolerance Assessment is from George F. Kramer in Chemistry Branch I, Tolerance Support, the Occupational/Residential Exposure Assessment is from Bruce Kitchens in the Occupational and Residential Exposure Branch, and the Dietary Risk Assessment from Brian Steinwand in the Science Analysis Branch. All the studies described below have been found acceptable except as noted.

I. EXECUTIVE SUMMARY

The Health Effects Division (HED) has reviewed toxicology and residue chemistry data submitted by the registrant in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR § 158 to support the use of sulfentrazone on soybeans and rotational crops. The toxicology data requirements for a food-use registration have been satisfied. **The residue chemistry data requirements remain**

outstanding (see section VII of this document). Because of these outstanding data requirements, the registrant has proposed that time-limited tolerances be established. HED has determined that sulfentrazone is a Group E chemical with an RfD of 0.014 mg/kg/day. The RfD Committee determined that sulfentrazone contains clear, unequivocal evidence of developmental and reproductive toxicity and that an additional modifying factor of 10X will be necessary to modify both the dietary and occupational endpoints. Therefore, HED's level of concern is 1000 and MOE's greater than 1000 will not be of concern. The aggregate risk, through food and water, was determined to be 25% of the RfD for the general U.S. population and 64% of the RfD for children 1 to 6 years old (the subgroup with the highest exposure). This risk should be considered very conservative since the exposure assumptions used in both the food (tolerance level residues and 100% crop treated) and water dietary exposure assessment were conservative in nature. The lowest Margins of Exposure (MOE) for workers was 1,700 for mixer/loader applicators using an open pour-dry flowable product (the subgroup with the highest worker exposure). **Therefore, HED does not consider the risk of registering sulfentrazone for use on soybeans and rotational crops to exceed the level of concern.**

II. BACKGROUND

FMC has submitted an application for permanent tolerances for the combined residues of the herbicide sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]methanesulfonamide) and its major metabolite 3-hydroxymethyl sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl] methanesulfonamide). The end use products, Authority 75DF Herbicide and Authority 4F Herbicide, are proposed to be registered for use on soybeans. To cover use on the primary crop, the petitioner has proposed the following tolerances (expressed as parent plus the metabolite 3-hydroxymethyl sulfentrazone):

Soybean Seed	--	0.05 ppm

For residues in rotational crops (inadvertent residues), the petitioner has proposed the following tolerances (expressed as parent plus the metabolites 3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone [N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]methanesulfonamide]):

Cereal Grains (excluding sweet corn), Forage	--	0.2 ppm
Cereal Grains (excluding sweet corn), Straw	--	0.6 ppm
Cereal Grains (excluding sweet corn), Hay	--	0.2 ppm
Cereal Grains (excluding sweet corn), Grain	--	0.1 ppm
Cereal Grains (excluding sweet corn), Stover	--	0.1 ppm

Cereal Grains (excluding sweet corn), Bran	--	0.1 ppm
Cereal Grains (excluding sweet corn), Hulls	--	0.2 ppm

III. USE PATTERN

Sulfentrazone is applied pre-emergence, at-plant or pre-plant soil incorporated (PPI) by ground equipment in a volume of 10-40 gal/A. The application rate is 0.3125-0.375 lbs. ai/A and only one application may be made per season.

The labels contains the following rotational crop restrictions: winter wheat, 4 months; spring wheat, 9 months; field corn, 10 months; barley, peanuts, rice and tobacco, 12 months; canola, corn (pop, seed and sweet), cotton and sorghum, 18 months; all other crops, 24 months.

Sulfentrazone may be tank-mixed with Command, Commence, Dual, Frontier, Lasso, Prowl, Sonalan and trifluralin-containing products. Tolerances on soybeans are established for the a.i.s of all of these products.

IV. PRODUCT CHEMISTRY

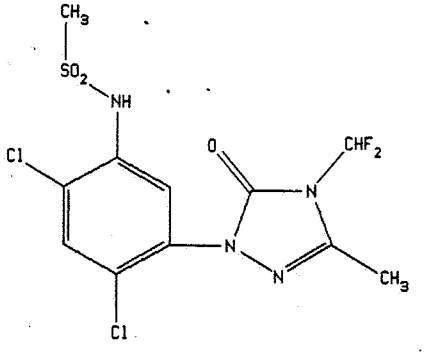
Common Name: Sulfentrazone (ISO)

Code Number: F6285

Chemical Name: N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1H-1,2,4-triazol-1-yl]phenyl]methanesulfonamide

PC Code: 129081

Structural Formula:



Sulfentrazone

Molecular Formula: $C_{11}H_{10}N_4O_3Cl_2F_2S$

Molecular Weight: 389.02

Chemical Family: Aryl Triazolinone

Color: Tan

Physical State: Solid

Melting Point: 120-122°C

Specific Gravity: 1.21 g/ml at 20°C

Solubility: Soluble in water at 25°C
in Acetone at 64% w/w
in Acetonitrile at 18.6% w/w
in Toluene at 0.66% w/w
in Hexane at 0.01% w/w

V. HAZARD ASSESSMENT

A. Acute Toxicity

Table 1: Acute Toxicity of Sulfentrazone

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral (rats)	41911605	LD_{50} = 2855 (M&F)	3
81-1	Acute Oral (mice)	41911606	LD_{50} = 711 (M&F)	3
81-2	Acute Dermal	41911607 42286400	LD_{50} > 2000 mg/kg	3
81-3	Acute Inhalation	42471002	4-hour, whole body exposure; LC_{50} > 4.13 mg/L	3
81-4	Primary Eye Irritation	41911608	Corneal opacity, iritis, diffuse irritation within 24 hr, clearing by day 4	3
81-5	Primary Skin Irritation	41911609	No erythema or edema after 4-hr exposure	4
81-6	Dermal Sensitization	41911610	Not a sensitizer	N/A
81-8	Acute Neurotoxicity	43345405	NOEL = 250 mg/kg; LOEL = 750 mg/kg, based on increased incidences of clinical signs and FOB findings, decreased motor activity, reversible by day 14	N/A

B. Subchronic Toxicity

In a subchronic toxicity study in rats (MRID# 43004601; HED# 011176) sulfentrazone was administered to Fischer 344 rats (10/sex/group) for 90 days at dietary levels of 0, 50, 100, 300, 1000, 3000, or 7000 ppm (0, 3.3, 6.7, 19.9, 65.8, 199.3, or 534.9 mg/kg/day for males and 0, 4, 7.7, 23.1, 78.1, 230.5, or 404.3

mg/kg/day for females respectively). Ten additional rats per sex per group at the control, 1000, and 3000 ppm levels were maintained an additional 4 weeks to assess recovery.

Administration of the test substance caused severe anemia complicated by inanition. The anemia was postulated to result from the interference of heme biosynthesis through the inhibition of protoporphyrin oxidase and the accumulation of protoporphyrin IX. As a result of the anemia and inanition, all high-dose (7000 ppm) rats died before Week 6 of study and one 3000 ppm female died during Week 2. Treatment-related clinical observations in all 7000 ppm animals and all 3000 ppm females included decreased or brownish-red feces, red abdominogenital staining, decreased locomotion, hypersensitivity to touch, dehydration, pale eyes and ears, shedding fur, unthriftiness, and walking on toes. At 3000 and 7000 ppm, mean body weight values for both sexes were significantly decreased through the periods of treatment and recovery. Food consumption was decreased for all animals that died on study and at 3000 ppm for some measured intervals. During the treatment phase, blood clinical chemistry changes attributed to anemia were also noted in the 1000 and 3000 dose groups and some of these effects remained through the recovery period.

Gross and microscopic pathological treatment-related findings in the spleen (increased absolute and relative weights) were attributed to the observed anemia in the 3000 and 7000 dose groups. After 4-weeks of recovery, only 1 female exhibiting enlarged spleen was noted at 3000 ppm. Significantly increased liver weight for males and females following treatment and significantly decreased liver weight for females following the recovery period were noted at 3000 ppm. These changes may be related to treatment. Other significant organ weight findings, in the adrenals, heart, brain, kidneys, and testes of animals in the 3000 ppm dose group and in the heart and testes of males at 1000 ppm were considered to be secondary toxic effects resulting from the treatment-related body weight depression and anemia.

Following the treatment period, histopathological findings were observed in both sexes at the 3000 and 7000 ppm dose groups; no treatment-related lesions were observed following the recovery period. For both the 3000 and 7000 ppm treatment groups, anemia was directly associated with microscopic alterations in the bone marrow and spleen and with related lesions in the heart, liver, lungs, and kidneys. Effects were more severe in females, resulting in earlier mortality at 7000 ppm (average time to mortality was 18 days for females, as compared to 32 days for males); in the males, the longer exposure time prior to death resulted in increased severity of erythroid hyperplasia in the bone marrow. The anemia resulted in a loss of mature erythrocytes and accumulations of large numbers of nucleated erythrocyte precursors (reticulocytes) in the bone marrow and spleen. Splenic effects also included increased extramedullary

hematopoiesis. Other microscopic changes noted in both sexes at 3000 and 7000 ppm were associated with inanition.

Based upon findings following a 4-week recovery period, the effects of dietary administration of sulfentrazone appear to be reversible. The NOEL is 19.9 mg/kg/day in males and 23.1 mg/kg/day in females (300 ppm) and the LOEL is 65.8 mg/kg/day in males and 78.1 mg/kg/day in females (1000 ppm) based on clinical anemia.

In a subchronic 90-day feeding study in mice (MRID# 43004602; HED# 011176) sulfentrazone was administered by dietary admix to Charles River B6C3F1 mice (10/sex/group) at doses of 0, 50, 100, 300, 550, 1000, or 3000 ppm (0, 10.3, 17.8, 60.0, 108.4, or 194.4 mg/kg/day for males and 0, 13.9, 29.0, 79.8, 143.6, or 257.0 mg/kg/day for females respectively; all 3000 ppm mice died by study day 9). There was a 4-week recovery period (10/sex/group) for 0, 550, and 1000 ppm animals of both sexes.

Histopathological evaluation revealed erythroid hypoplasia of the bone marrow and evidence of inanition. The following test article effects were observed at 550 and 1000 ppm: decreases in body weights and/or gains; decreased erythrocytes, hemoglobin and hematocrit values; and splenic microscopic pathology (increased incidence and severity of extramedullary hematopoiesis). A 4-week recovery period reversed all of the test article effects with the exception of the splenic hematopoietic findings in females only. However, only the post-recovery splenic alterations in 1000 ppm females were reduced in severity. The NOEL is 60.0 mg/kg/day for males and 79.8 mg/kg/day for females (300 ppm) and the LOEL is 108.4 mg/kg/day for males and 143.6 mg/kg/day for females (550 ppm).

In a subchronic 90-day feeding study in dogs (MRID# 42932102; HED# 011176) sulfentrazone was administered by dietary admix to Marshall Farms beagle dogs (4/sex/group) at doses of 0, 300, 800, or 2000 ppm (0, 10, 28, or 57 for males and 0, 10, 28, or 73 for females, respectively) for 13 weeks. The highest dose tested (2000 ppm) caused: lower body weights and lower weight gains in males and females mostly during the first 5 weeks of the study; decreases in hemoglobin and hematocrit (as well as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)); elevated alkaline phosphatase levels; increased liver weights; and microscopic liver as well as splenic changes. The NOEL is 28 mg/kg/day (800 ppm) and the LOEL is 57 mg/kg/day for males and 73 mg/kg/day for females (2000 ppm).

The HED RfD/Peer Review Committee (meeting on February 15, 1996 and April 4, 1996) recommended that an acceptable subchronic (21-day) dermal toxicity study be submitted by the registrant.

C. Chronic Toxicity and Carcinogenicity

In a one year feeding study in dogs (MRID# 43345406; HED# 011834), groups of four male and four female beagle dogs were fed diets containing 0, 300, 800, or 1800 ppm sulfentrazone for one year. The intake of test material was equivalent to 0.0, 9.9, 24.9, or 61.2 mg/kg/day for male dogs and 0.0, 10.4, 29.6, or 61.9 mg/kg/day for female dogs in the control through high-dose groups, respectively. Because of the death of one dog and the poor food consumption and body weight losses of survivors within the 1800 ppm female dog treatment group, the diet of this group was supplemented with canned dog food from Day 119 through the remainder of the study. After dietary supplementation began, the food intake, body weight and body weight gain of female dogs in this group increased and no further effects on body weight were noted for the remainder of the study. No treatment-related effects on body weight were found in the male dog groups or in the remaining female dog groups.

Treatment with the test material induced a compensated red blood cell (RBC) normochromic microcytosis in both male and female dogs receiving the highest dose. The microcytosis developed within the first three months of treatment and persisted through the remainder of the study, although its severity did not appear progressive. In addition, the serum alkaline phosphatase activity of male and female high dose dogs and female dogs treated with 800 ppm test material was increased 2-6 fold. However, due to variability of findings at 800 ppm and lack of supportive evidence for toxicity at that dose, the increased alkaline phosphatase activity was not considered to be adverse. The only microscopic treatment-related effects were found in the liver and gallbladder and consisted primarily of cytoplasmic pigmentation (minimal at 800 ppm, but with increased severity at 1800 ppm). The biological significance of pigmentation was questioned by the RfD/Peer Review Committee. The Committee first considered the pigmentation to be a marker of other toxic effects but not a toxic effect by itself. However, the Committee determined that further investigation might be necessary.

The induction of normochromic microcytosis in animals fed diets containing 1800 ppm test material, although compensated by increased red cell production, reflects an adverse treatment-related effect. The microcytosis may have arisen from the inhibition of heme synthesis as indicated by the presence of brown to yellow/brown pigmentation in hepatocytes and reticuloendothelial cells of the liver. The microcytosis induced by sulfentrazone justifies an oral LOEL of 61.2 mg/kg/day for males and 61.9 mg/kg/day for females (1800 ppm). The NOEL is 24.9 mg/kg/day for males and 29.6 mg/kg/day for females (800 ppm).

In a 18-month feeding/carcinogenicity study in mice (MRID# 43345407; HED# 011834) groups of 50 male and 50 female CD-1 mice were fed diets containing 0, 300, 600, 1000, or 2000 ppm (equivalent to 0, 46.6, 93.9, 160.5, or 337.6 mg/kg/day for males and 0, 58.0, 116.9, 198.0, or 407.1 mg/kg/day for females, respectively). Mean body weights of all male treated groups were less than controls at study termination. In 2000 ppm males body weight gain was decreased 27% as compared to control at termination. Female body weights were not affected, nor were food consumption or clinical observations for either sex.

Treatment with sulfentrazone induced dose-dependent decreases in hemoglobin (HGB) and hematocrit (HCT) for both sexes. Statistically significant HGB decreases were observed in 1000 and 2000 ppm males and females at study termination. Decreases in HGB or HCT values noted at 3000 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 LOEL is 160.5 mg/kg/day in males and 198.0 mg/kg/day in females (1000 ppm) based upon treatment-related decreases in hemoglobin and hematocrit. The NOEL is 93.9 mg/kg/day in males and 116.9 mg/kg/day in females (600 ppm).

In a 2-year feeding/carcinogenicity study in rats (MRID# 43345409; HED# 011834) groups of 60 male Sprague-Dawley rats were given diets containing 0, 600, 1000, 2000, or 3000 ppm (0, 24.3, 40.0, 82.8, or 123.5 mg/kg/day, respectively) of sulfentrazone and groups of 60 females were given diets containing 0, 300, 600, 1000, or 2000 ppm (0, 20.0, 36.4, 67.0, or 124.7 mg/kg/day respectively) of sulfentrazone 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 concentration 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.

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, body weight gain, and food consumption were observed. Hemoglobin concentrations were decreased in male rats receiving 2000 and 3000 ppm of the test material, and in female rats receiving 1000 and 2000 ppm. Corresponding statistically significant decreases in hematocrit, MCV, and MCH occurred at the same doses in both sexes. Statistically significant increases in the reticulocyte count occurred in female rats receiving 2000 ppm and in the 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 LOEL for sulfentrazone is 82.8 mg/kg/day for male rats and 67.0 mg/kg/day for female rats. The NOEL is 40.0 mg/kg/day for male rats and 36.4 mg/kg/day for female rats.

The RfD/Peer Review Committee considered the carcinogenicity phases of the combined chronic toxicity/carcinogenicity studies in rats (MRID# 43345409) and mice (MRID# 43345407) to be acceptable and the data evaluation records (HED Doc. No. 011834) were considered adequate. The highest dose levels tested in both the rat (3000 ppm) and mouse (2000 ppm) studies were considered to be adequate for carcinogenicity testing in these strains of rats and mice.

In both rat and mouse studies, there were no treatment-related increases in tumors of any kind observed at any dose level. The Committee concluded that the treatment did not alter the spontaneous tumor profile in these strains of rat and mouse.

D. Developmental Toxicity

In a developmental toxicity study in rats (MRID# 42932103; HED# 011176) sulfentrazone 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, or 50.0 mg/kg/day. 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. Therefore, the maternal (systemic) LOEL is 50.0 mg/kg/day based upon increased relative spleen weight and splenic extramedullary hematopoiesis. The maternal (systemic) NOEL is 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.

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. 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. In the 50.0 mg/kg/day dose group, 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.

The developmental (fetal) LOEL is 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. The developmental (fetal) NOEL is 10.0 mg/kg/day.

In a supplementary prenatal oral developmental toxicity study in rats (MRID# 43651003; HED Doc. 011834), sulfentrazone was administered by gavage to pregnant Sprague-Dawley rats (10/group) on days 6-15 of gestation at dose levels of 25.0 or 50.0 mg/kg/day. 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. 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 results of this study confirm the maternal and fetal findings of the previously-conducted developmental study on sulfentrazone in rats (MRID No. 42932103) and do not alter the study conclusions.

In a dermal developmental toxicity study in rats (MRID#s 43004603 [Range-finding] and 42932105; HED# 011176) sulfentrazone

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, or 250 mg/kg/day. There was no evidence of treatment-related maternal toxicity. Maternal survival, 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. 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. Therefore, the Maternal (systemic) LOEL was not determined and the Maternal (systemic) NOEL is greater than or equal to 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 sulfentrazone consistent with the significant treatment-related hypoplasia observed in the skeletal evaluation of the ribs. Therefore, the Developmental (fetal) LOEL is 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. The Developmental (fetal) NOEL is 100 mg/kg/day.

In a developmental toxicity study in rabbits (MRID# 42932106; HED# 011176) sulfentrazone was administered by gavage to pregnant female New Zealand White rabbits (20/group) on days 7-19 of gestation at dose levels of 0, 100, 250, or 375 mg/kg/day. Treatment-related incidences of decreased feces and hematuria were noted at 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. Therefore, the Maternal (systemic) LOEL is 250 mg/kg/day, based upon increased abortions, clinical signs (hematuria and decreased feces), and reduced body weight gain. The Maternal (systemic) NOEL is 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. Therefore, the Developmental (fetal) LOEL is 250 mg/kg/day, based upon increased resorptions, decreased live fetuses per litter, and decreased fetal weight. The Developmental (fetal) NOEL is 100 mg/kg/day.

E. Reproductive Toxicity

In a two-generation reproductive toxicity study in rats (MRID# 43345408; HED# 011834), sulfentrazone 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.

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 pre-mating 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 pre-mating 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. Therefore, the systemic and reproductive/developmental NOEL is 14 mg/kg/day for males and 16 mg/kg/day for females (200 ppm). The systemic and reproductive/developmental LOEL is 33 mg/kg/day for males and 40 mg/kg/day for females (500 ppm), based upon reduced pre-mating body weight gain in F1 males; histopathological findings in the testes and epididymides of F1 males; decreased F1 male fertility; increased gestation duration; and reduced litter size, pre- and postnatal pup and litter survival, and pup weight throughout lactation in both generations of offspring.

In an additional 2-generation reproduction study in rats (MRID# 43869101; review in progress and study was not peer reviewed), sulfentrazone was administered at dietary levels of 50, 100, 200, or 500 ppm. F1 estrous cyclicity and sperm parameters were tested, and sexual maturation was examined. Toxicity was observed at 500 ppm and included slight decreases in body weight gain with statistical significance only for F1 females; slightly increased pup/fetal mortality and reduced pup weights; and decreased testes, epididymides, and prostate weights in F1 males. This study confirms the reproductive/developmental effects observed in the first 2-generation reproductive toxicity study (MRID# 43345408) reviewed by the Committee.

It was the conclusion of the RfD/Peer Review Committee that, under the conditions of the studies reviewed, sulfentrazone caused developmental and reproductive toxicity. The results of these studies elicited a high level of concern by the Committee, since the developmental toxicity studies demonstrated embryo/fetal toxicity at treatment levels that were not maternally toxic, and significant toxic effects were observed primarily in the second generation animals of the reproduction study. Because these animals had been exposed to sulfentrazone in utero, the possibility that the observed reproductive toxicity resulted from a developmental and/or genotoxic mechanism was suggested.

F. Mutagenicity

Reverse gene mutation assay in Salmonella typhimurium (MRID No. 41911601, Doc. No. 009263): The test was negative in all strains up to the highest dose level tested of 10,000 μg/plate in the presence and absence of metabolic activation system (+/-S9).

Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay (MRID No. 43004604, Doc. No. 011176): Equivocal but dose-related positive results were recorded at precipitating levels (2400, 2700 and 3000 μg/ml in the absence of S9). Increased mutation frequencies (to 4-fold over control) were accompanied by an increase in total mutant colonies and an increased frequency of small colony mutants; suggestive of clastogenic activity. The response was neither confirmed nor seen in the S9-activated phase of testing at doses up to 1800 μg/mL. It is not known if the test material would have induced a positive effect in the presence of S9 activation had higher precipitating levels been assayed.

Mouse micronucleus assay (MRID No. 43004605, Doc. No. 011176): The test was negative in ICR mice up to 340 mg/kg (estimated to be ≈ 80% of the $LD_{50/7}$) administered once by intraperitoneal injection. Minimal toxicity was reported, but no bone marrow cytotoxicity was observed.

When considered in isolation, the equivocal results from the mouse lymphoma assay provide weak evidence of possible mutagenic activity. In light of the evidence from the 2-generation reproduction study and developmental toxicity studies, discussed above, which suggest a potential concern for germ cell genotoxicity, the in vitro data, suggesting a potential for clastogenicity, assume greater importance. In the 2-generation reproduction study, major indicators of germ cell genotoxicity were apparent at the highest dose tested, 700 ppm (i.e., gonadal pathology--F1 generation, reduced pregnancies--F1 generation; and reduced litter sizes--both generations). Similarly, post-implantation loss was markedly increased in the P generation and to a lesser extent in the F1 generation at the highest dose tested. Increased post-implantation loss was also observed in the P generation at the mid-dose of 500 ppm. The RfD/Peer Review Committee indicated that the increased incidence of post-implantation loss in the F1 generation is of particular concern since the possibility exists that genetic defects could have been inherited by viable progeny. Crude estimates of the dominant lethality index (DLI) derived from dead implants per total implants indicate such a possibility. The estimated DLI for the parental high-dose generation was 0.54. This value is ≈7-fold higher than the expected spontaneous rate of dominant lethal in rats (0.08) and indicative of a powerful effect. The ≈2.4-fold increase in DLI for the high-dose F1 generation would also be

considered a positive response.

In the two developmental oral gavage studies conducted with rats, reproducible and significant decreases in total implants and live fetuses and significant increases in early resorptions were seen at the highest dose level of 50 mg/kg/day. Dose-related decreases in live fetuses and increases in early resorptions also occurred at the mid and high dose (250 and 375 mg/kg/day) in the rabbit developmental study.

Given all of the above considerations, the RfD/Peer Review Committee concluded that the weight-of-evidence supports a justifiable concern for a potential mutagenic risk to germinal cells. Since the overall findings suggest that highly proliferating tissue is a target for sulfentrazone, the RfD/Peer Review Committee recommended that a rat dominant lethal assay should be conducted to determine if the effects noted in the reproduction and developmental studies are associated with genetic damage to male germinal cells. The Registrant has recently completed a dominant lethal assay in rats, and has forwarded a summary (the complete study has not yet been submitted) of the results to the Agency. According to this summary, administration of sulfentrazone to male rats did not result in early prenatal loss that could be attributed to germ cell mutagenesis. A final determination of study results awaits receipt and review of the study data by the Agency.

G. Neurotoxicity

In an acute neurotoxicity study in rats (MRID# 43345405; HED# 0011834), sulfentrazone 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). 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 sulfentrazone did not result in lesions of the nervous system.

Due to the findings above the NOEL is 250 mg/kg. The LOEL of 750 mg/kg/day is based upon increased incidences of clinical signs, FOB findings, and decreased motor activity which were reversed by Day 14 post-dose. Additional findings at 2000 mg/kg

included decreased male body weight gains. There was no evidence of neuropathology.

In a subchronic neurotoxicity study in rats (MRID# 43651002; HED# 0011834) sulfentrazone 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). 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 hindlimb 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. Additional findings at 5000 ppm included increased mortality; decreased body weight and body weight gains in males; decreased hindlimb 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. Therefore the NOEL is 30 mg/kg/day for males and 37 mg/kg/day for females (500 ppm). The LOEL is 150 mg/kg/day for males and 180 mg/kg/day for females (2500 ppm), 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.

H. Metabolism

In a metabolism study in rats (MRID# 43345410) the absorption, distribution, elimination and biotransformation of sulfentrazone were studied in 3 groups of 5 Sprague-Dawley rats/sex. Groups A and C received a single oral dose of phenyl-^{14}C-sulfentrazone at dose levels of 50 and 500 mg/kg, respectively. Animals in Group B received a single oral dose of 50 mg/kg of phenyl-^{14}C-sulfentrazone after 14 days of dosing with 50 mg/kg of non-radioactive sulfentrazone.

Urine and feces were collected from Groups A, B and C at specific intervals until sacrifice (72 hours for Groups A and B and 96 hours for Group C). Nearly all radioactivity was excreted in the urine in all groups, indicating nearly complete absorption of sulfentrazone. No differences between the sexes existed. Only the carcass, liver and bone (Group B, females only) showed

detectable amounts of radioactivity (<0.5% of the dose) in all groups.

In all groups, the pooled urinary radioactivity consisted almost entirely (84 to 104% of the administered dose) of 3-hydroxy-methyl-sulfentrazone. A small amount (<1% of the administered dose) of 3-carboxylic acid-sulfentrazone was found in the urine of males from Groups A (50 mg/kg) and B (50 mg/kg, repeat).

Pooled fecal radioactivity showed that the major metabolite consisted of 3-hydroxymethyl-sulfentrazone (1.26 to 2.55% of the administered dose), except for the high dose males Group C (5.57% of the administered dose). The other major component was unchanged sulfentrazone(0.09 to 0.19% of the administered dose), except for the 500 mg/kg females (Group C) which contained 1.54% of the administered dose. In all groups, small amounts (0.02 to 0.10% of the administered dose) of 3-carboxylic acid were seen.

The proposed metabolic pathway appeared to be conversion of the parent compound mainly to 3-hydroxymethyl-sulfentrazone (excreted in urine and feces). A small amount of 3-hydroxymethyl-sulfentrazone was also converted to 3-carboxylic acid-sulfentrazone (excreted in the urine and feces). Feces also contained minor amounts of the parent compound and 4 unknown metabolites. The overall mean recovery for radioanalysis validation was 99.2%.

VI. DOSE RESPONSE ASSESSMENT

A. Reference Dose

The RfD/Peer Review Committee met concerning this chemical on two separate occasions. In the first meeting on April 4, 1996 the Committee recommended that a provisional RfD be established based upon the reproductive toxicity study in rats with a reproductive/developmental toxicity NOEL of 14 mg/kg/day in males and 16 mg/kg/day in females. At the next higher dose level of 33 mg/kg/day in males and 44 mg/kg/day in females the following effects were observed: decreased maternal body weight and/or body weight gain during gestation in both generations (P and F1), reduced pre-mating body weight gains in the second generation (F1 adults), increased duration of gestation in both P and F1 dams, 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, with degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degeneration of seminal product in the epididymides.

In the first meeting an uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability and an additional modifying factor (MF) of 3 was applied to account for the nature and severity of effects noted in the study and the high level of concern regarding potential mutagenic concern and other reproductive and developmental toxicity effects observed. On this basis, a provisional RfD was established at 0.05 mg/kg/day.

Under the directive of the Food Quality Protection Act (FQPA) of 1996, amending FIFRA, the RfD/Peer Review Committee reconvened for a second meeting on November 14, 1996 to reevaluate its position on the Reference Dose (RfD) for sulfentrazone. In this second meeting, the additional uncertainty factor for sulfentrazone was discussed, under the directive of FQPA, which requires that pesticide regulatory review incorporate an assessment of potential hazards to infants and children and include additional safety factors, of up to 10X when warranted, for the protection of these sensitive subpopulations.

In the second meeting (November 14, 1996), the Committee determined that the toxicology data profile for sulfentrazone contains clear, unequivocal evidence that this chemical causes developmental and reproductive toxicity. Therefore, the additional modifying factor was increased from 3 to 10. On this basis, the RfD was calculated to be 0.014 mg/kg/day. The Committee's conclusion was based on the results of the following studies: oral prenatal developmental toxicity study in New Zealand White rabbits (MRID# 42932106); oral prenatal developmental toxicity study in Sprague-Dawley rats (MRID# 42932103); dermal prenatal developmental toxicity study in Sprague-Dawley rats (MRID# 43004603); 2-generation reproduction study in rats Sprague-Dawley rats (MRID# 43345408).

The results of these studies elicited a high level of concern by the Committee, since the developmental toxicity studies in rats demonstrated embryo/fetal toxicity at treatment levels that were not maternally toxic, and significant toxic effects were observed primarily in the second generation animals of the reproduction study. Because these animals had been exposed to sulfentrazone *in utero*, the possibility that the observed reproductive toxicity resulted from a developmental and/or genotoxic mechanism was suggested.

B. Carcinogenicity Classification

The RfD/Peer Review Committee recommended that the chemical be classified as **"Group E"**, no evidence of carcinogenicity for humans; i.e. the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposure. This weight of the evidence judgment is largely based on the absence of significant

tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that the designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

C. Other Toxicity Endpoints

Dermal Absorption

No dermal absorption study is available for sulfentrazone. However, based upon a comparison of the maternal NOEL of 250 mg/kg/day in a dermal developmental toxicity study in rats (MRID 43004603) and the maternal NOEL of 25 mg/kg/day in an oral prenatal developmental toxicity study in rats (MRID 42932104), an estimate of dermal absorption was calculated as 10%.

Acute Dietary Endpoint (One Day)

The study selected was the oral prenatal developmental toxicity study in rats (MRID# 42932103). In this study the endpoint and dose chosen for use in risk assessment is 10 mg/kg/day, this is the NOEL for developmental toxicity following oral administration of sulfentrazone to the dams; while the developmental LOEL is 25 mg/kg/day based on decreased fetal weight and retarded skeletal development. The fetal effects observed were considered to have resulted from acute exposure and occurred at a dose which was not maternally toxic. It should be noted that since the RfD Committee determined that sulfentrazone contains clear, unequivocal evidence of developmental and reproductive toxicity. The additional modifying factor of 10X will also be used to modify this acute dietary endpoint.

Short (1-7 days), Intermediate (7 days to several months) and Chronic (Non-Cancer) Term Occupational or Residential Exposure

The endpoint and dose chosen for use in the risk assessment is 100 mg/kg/day, the NOEL from the dermal prenatal developmental toxicity study in rats (MRID# 43004603). The developmental LOEL is 250 mg/kg/day, based on decreased fetal weight, and delays/alterations in skeletal development. In this study the developmental NOEL is less than the maternal NOEL. It should be noted that since the RfD Committee determined that sulfentrazone contains clear, unequivocal evidence of developmental and reproductive toxicity. The additional modifying factor of 10X will also be used to modify these short- and intermediate-term, and chronic endpoints.

Acute Dietary, Short, Intermediate and Chronic Term Occupational or Residential **Inhalation Exposure:**

These are not applicable, exposure via this route

(inhalation) is not a concern. Acute (LC_{50}) studies for the technical and formulation materials resulted in Category 3 and 4 toxicity, respectively so risk assessments are NOT required.

VII. DIETARY EXPOSURE AND RISK CHARACTERIZATION

A. Dietary Exposure From **Food** Sources

i. Plant Metabolism

Soybeans: Sulfentrazone, radiochemically labelled in the aromatic ring (phenyl-UL-^{14}C) or in the triazole ring (carbonyl-^{14}C) was applied to outdoor plots in a single preemergence broadcast application at a rate of 0.5 lbs. ai/A (1.3X). The plants were grown to maturity and harvested for seed and hay. Immature plants were also harvested for forage. The maximum residues observed in forage were 1.057 ppm; in hay, 1.073 ppm; and in seed, 0.171 ppm. Metabolites were resolved on HPLC and compared with reference standards of sulfentrazone and possible metabolites. The major metabolites are 3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone, accounting for 38-50% and 13% of the total radioactive residue (TRR) in forage, 9-23% and 26-27% of the TRR in hay and 30-35% and 4% of the TRR in seed, respectively. Other metabolites identified include sulfentrazone carboxylic acid, desmethylsulfonyl sulfentrazone, desdifluoromethyl desmethyl sulfentrazone, desdifluoromethyl sulfentrazone and methyl triazole. The Metabolism Committee, which met on May 20, 1996, decided that a soybean tolerance based on the parent and 3-hydroxymethyl sulfentrazone is appropriate.

Rotational Crops: In a confined crop rotation study, sulfentrazone, radiochemically labelled in the aromatic ring (phenyl-UL-^{14}C) or in the triazole ring (carbonyl-^{14}C), was applied to soil at a rate of 0.5 lbs. ai/A (1.3X) in a greenhouse. Crops (lettuce, radishes and barley) were seeded 30, 122, 245 and 364 days after treatment (DAT) of the soil with sulfentrazone. The highest residue levels were seen in barley straw (2.98-3.36 ppm at 30 DAT and 0.67-1.83 at 364 DAT). The nature of the residue in soybeans and rotational crops is understood (MRID# 436565-01). Sulfentrazone is metabolized via four different pathways: 1) Oxidation of the 3-methyl group to form 3-hydroxymethyl sulfentrazone, followed by further oxidation to form sulfentrazone carboxylic acid which is decarboxylated to 3-desmethyl sulfentrazone. 2) Hydrolysis of the trifluoromethyl group to form desdifluoromethyl sulfentrazone which is oxidized and decarboxylated to form desdifluoromethyl desmethyl sulfentrazone. 3) Hydrolysis of the sulfonamide group to form desmethylsulfonyl sulfentrazone. and 4) Scission of the phenyl and triazole rings to produce methyl triazole. The corresponding phenyl metabolites are believed to remain bound.

ii. Animal Metabolism

Ruminants: In the ruminant metabolism study (MRID# 43345415), [phenyl(U)-^{14}C]- and [triazole(carbonyl)-^{14}C]-sulfentrazone were administered orally to lactating goats at a rate of 4.9 ppm (phenyl) or 6.0 ppm (triazole). Of the administered radioactivity, 78-94% was recovered in urine. Another 4.5-7.4% was recovered in the feces and <0.04% was recovered in the milk, blood and tissues. The total recovery was over 85%. The greatest tissue residues were 0.013 ppm in kidney (phenyl). Sulfentrazone *per se* was the predominant component of the residue in kidney, accounting for 53.8% of the TRR. The metabolite 3-hydroxymethyl sulfentrazone (7.7% of the TRR) was also identified.

Poultry: In the poultry metabolism study (MRID# 43345414), [phenyl(U)-^{14}C]- and [triazole(carbonyl)-^{14}C]-sulfentrazone were administered orally to laying hens at a rate of 4.70 ppm (phenyl) or 4.73 ppm (triazole). Doses were administered once daily for 12 consecutive days. Of the administered radioactivity, 94-106% was recovered in excreta. The TRR in tissues and eggs is shown in Table 9. The greatest tissue residues were 0.030 ppm in kidney (phenyl). Sulfentrazone *per se* was the predominant component of the residue, accounting for 27-70% of the TRR (Table 10). The metabolites 3-hydroxymethyl sulfentrazone (18-33% of the TRR) and 3-desmethyl sulfentrazone (14% of the TRR in liver only) were also identified.

iii. Residue Analytical Method - Plants

The petition method validation (PMV) for soybeans was successful, but the PMV for rotational crops was unsuccessful (Memo, G. Kramer 3/13/96). However, the petitioner has developed a streamlined method (P-3063M, MRID# 44005601) which simultaneously measures all three analytes in all crop matrices. The previously submitted method has been modified to include a more stringent hydrolysis step and by use of a more specific GC detector (ELCD instead of ECD). All three analytes are resolved in a single chromatographic separation. The method was validated in cereal grain RACs over a range of 0.025-0.50 ppm. The average recovery for sulfentrazone was 90 ± 9% (n=28); for 3-desmethyl sulfentrazone, 92 ± 18% (n=25); and for 3-hydroxymethyl sulfentrazone, 84 ± 14% (n=28). An ILV of this method was performed by Centre Analytical Labs. The method was validated by the independent lab in wheat forage.

Acceptable recoveries were obtained by the independent laboratory. The method and ILV have been sent to Beltsville for PMV. HED concludes that the revised method is adequate for data gathering purposes. A conclusion on the adequacy of the method for enforcement of the proposed tolerances will be withheld pending satisfactory Agency validation.

Samples from six trials for each crop were reanalyzed with the new method. When reanalyzed with the revised method, the total residues of sulfentrazone and its metabolites were generally 2-3X higher in soybean seed, 1.5-6X higher in cereal grain forage, 2-5X higher in cereal grain hay, 3-6X higher in cereal grain straw, 1.5-3X higher in cereal grain stover and unchanged in grain. The results presented in the Magnitude of the Residue - crops (vii) section below reflect this reanalysis.

The registrant has proposed that time-limited tolerances be established while the new enforcement method is validated by the Agency. This proposal was supported by a DRES run performed by the petitioner in which "10X" and "50X" scenarios produced dietary risks well below the RfD in the most highly exposed subgroup. In the 10X scenario, residues were assumed to be 10X the level of the proposed tolerances and meat and milk were assumed to be at the projected level of an analytical enforcement method (0.025 ppm). In the 50X scenario, residues were assumed to be 50X the level of the proposed tolerances and meat and milk were assumed to be at twice the level of an analytical enforcement method (0.050 ppm). Levels in drinking water were assumed to be 0.05 ppm in both scenarios.

iv. Residue Analytical Method - Animals

Since no tolerances have been proposed for animal RACs, an analytical enforcement method for animals is not required at this time. If, however, the required ruminant feeding studies (see below) demonstrate a potential for transfer of residues to meat or milk, then the registrant will be required to propose tolerances for these RACs and develop the appropriate analytical enforcement methodology. Any required enforcement methods for meat and milk will need successful ILVs and PMVs before being judged to be acceptable by HED/CBTS.

v. Storage Stability

Residues of sulfentrazone and its metabolites have been shown to be stable during storage for up to 38 months is soybeans and for up to 24 months in cereal grain RACs. The maximum storage intervals for the samples prior to reanalysis was 47 months for soybeans and 35 months for cereal grain RACs. CBTS is willing to extend the results of the storage stability studies to cover the actual storage intervals. Additional storage stability data are thus not required.

vi. Magnitude of the Residue - Meat, Milk, Poultry and Eggs

HED/CBTS has determined that, <u>based on the proposed tolerances</u>, the results of the metabolism studies preclude the need for conventional feeding studies (see below). Meat and milk tolerances and analytical enforcement methodology for animal RACs

are thus not required at this time. However, if in the future, the registrant wishes to propose tolerances for soybean forage and hay this conclusion will be reevaluated.

HED/CBTS has also determined that a conventional feeding study for poultry is not required. However, for any future petition which results in a higher dietary burden, the Agency may require that a poultry feeding study be performed.

vii. Magnitude of the Residue - Crop Field Trials/Processed Commodities

Soybeans: The registrant has submitted a total of 22 soybean residue trials, conducted in Regions 2 (5 trials), 4 (6 trials), and 5 (11 trials). The maximum 3-hydroxymethyl sulfentrazone residue in soybeans was 0.036 ppm and residues of sulfentrazone *per se* were <0.005 ppm in all samples.

viii. Field Rotational Crops

Wheat: The petitioner has provided the results of 23 wheat trials, conducted in Regions 2 (5 trials), 4 (5 trials), 5 (11 trials), 6 (1 trial) and 8 (1 trial). This regional distribution does not correspond to that required for wheat as a primary crop (i.e., a total of 12 trials are required in Regions 7, 8 and 11), but does correlate well with the areas where soybeans are grown. HED/CBTS thus concludes that the number and location of trials are adequate to set tolerances on wheat RACs when planted in rotation with the primary crop soybeans. The total of sulfentrazone and its metabolites was a maximum of 0.132 ppm in forage, 0.174 ppm in hay, 0.012 ppm in grain, and 0.599 ppm in straw.

The petitioner had requested a data waiver for the wheat processing study. As residues of sulfentrazone and its metabolites were nondetectable in grain samples from the first five limited field trials, HED/CBTS conditionally recommended in favor of this data waiver request pending resolution of all deficiencies related to the proposed wheat tolerances (Memo, G. Kramer 7/26/95). However, in the residue data submitted with a more resent amendment, detectable residues were found in grain in over one half of the trials. HED/CBTS thus concludes that a wheat processing study is to be required for the permanent petition. If concentration of residues is observed in bran, then residue data should also be provided for wheat aspirated grain fractions.

Corn: The petitioner has provided the results of 22 field corn trials, conducted in Regions 2 (2 trials), 4 (3 trials) and 5 (17 trials). This regional distribution does not correspond to that required for field corn as a primary crop (i.e., 2 trials are required in Regions 1 and 6), but does correlate well with the

areas where soybeans are grown. HED/CBTS thus concludes that the number and location of trials are adequate to set tolerances on field corn RACs when planted in rotation with the primary crop soybeans. The total of sulfentrazone and its metabolites was a maximum of 0.041 ppm in forage, 0.060 ppm in fodder and non-detectable in grain.

Rice: The petitioner has provided the results of 9 rice trials, conducted in Regions 4 (8 trials) and 6 (1 trial). The number and regional distribution does not correspond to that required for rice as a primary crop (i.e., 16 trials are required in Regions 4, 5, 6 and 10). Total residues of sulfentrazone and its metabolites were found to concentrate in rice hulls (3.9X) and bran (1.9X) (Memo, G. Kramer 7/1/96). Based on these concentration factors and the current highest average field trial value for cereal grain (0.068 ppm, rice), the appropriate tolerances for cereal grain hulls and bran would be 0.15 ppm and 0.30 ppm, respectively. A final conclusion on the appropriate tolerances for these commodities will be made once the additional rice residue data (see below) and wheat processing study are submitted. A revised Section F will be required. HED/CBTS thus concludes that an additional 4 rice field trials are required. Conclusions on the adequacy of the proposed permanent tolerances will be withheld pending submission and review of additional residue data.

Sorghum: A total of nine rotational field trials were conducted in the states of VA, LA, MO, TX (2), NE, KS, SD and IA in 1994/95. HED/CBTS thus concludes that the number and location of grain sorghum trials are adequate to set tolerances on cereal grain RACs when planted in rotation with the primary crop soybeans. In grain sorghum, the total of sulfentrazone and its metabolites was a maximum of 0.084 ppm in forage, 0.058 ppm in fodder, and 0.009 ppm in grain.

B. Dietary Exposure From Ground Water

A ground water exposure estimate for sulfentrazone is based on findings from a voluntary prospective ground water study conducted in a sandy (worst case) site in North Carolina. Although this single ground water monitoring study was incomplete, enough data were collected to confirm that sulfentrazone leaches substantially to ground water in areas with sandy soils. Sulfentrazone was found in ground water at concentrations as high as 37 ppb in shallow wells and 19 ppb in deeper wells. Residues in shallow ground water were highly persistent and only slowly dissipated, with little change in concentrations over a 1-year period, at which sampling was terminated. The use of 37 ppb in estimating dietary exposure through ground water represents the worst case. The worst case is based on soil type (sandy) and a limited population that would obtain their drinking water from wells in this type of soil.

However, HED feels that due to sulfentrazone's mobility (Koc = 43; Kd = 0.2-0.8) and persistence (≈9 year half life), over time the worst case values may be approached in more typical ground water settings. Using 37 ppb the dietary exposure calculation are as follows:

Adult Exposure = (chemical concentration in μg/L in consumed water) (10^{-3} mg/μg) (2 L/day) ÷ (70 kg body weight)

Adult Exposure = (37 ppb) (10^{-3}) (2 L/day) / (70 kg)

Adult Exposure = 1.05×10^{-3} mg/kg/day

Kids Exposure = (chemical concentration in μg/L in consumed water) (10^{-3} mg/μg) (1 L/day) ÷ (10 kg body weight)

Kids Exposure = (37 ppb) (10^{-3}) (1 L/day) / (10 kg)

Kids Exposure = 3.7×10^{-3} mg/kg/day

Therefore, the %RfD taken up by ground water exposure is calculated as follows:

%RfD = (Exposure mg/kg/day) ÷ (RfD mg/kg/day) X 100

%RfD Adults = 1.05×10^{-3} mg/kg/d ÷ 0.014 mg/kg/d X 100

%RfD for Adults = 8

%RfD Kids(1-6 yrs) = 1.05×10^{-3} mg/kg/d ÷ 0.014 mg/kg/d X 100

%RfD for Kids(1-6 yrs) = 26

C. Dietary Risk Characterization

i. Chronic Dietary Risk

A DRES chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. The chronic analysis showed that exposure from the proposed new tolerance, in/on soybeans, on cereal grains (excluding sweet corn), on bran of cereal grains, milk, eggs, and meat for children 1 to 6 years old (the subgroup with the highest exposure) would be 38.8% of the RfD. While the exposure for the general U.S. population would be 16.7% of the RfD.

The analysis for sulfentrazone is a worst case estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated with sulfentrazone. Even without refinements, the chronic dietary

risk exposure to sulfentrazone appears to be minimal for this petition on soybeans at 0.5 ppm, cereal grains at 1.0 ppm, milk, meat, and eggs at 0.025 ppm. If the new enforcement method is validated the chronic dietary risk exposure would be lower.

ii. Aggregate Dietary/Drinking Water Risk

The dietary and drinking water combined exposure to sulfentrazone would be 65% (39 + 26) of the RfD for children 1 to 6 years old. While the exposure for the general U.S. population would be 25% (8 + 17) of the RfD. HED does not consider the combined risk to exceed the level of concern.

iii. Acute Dietary Risk

The Margin of Exposure (MOE) is a measure of how close the high end exposure comes to the NOEL (the highest dose at which no effects were observed in the laboratory test), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). Generally, acute dietary margins of exposure greater than 100 tend to cause no dietary concern when results are compared to animal-derived data. Because the endpoint of concern was a developmental effect, the only analysis of concern is for females of child bearing age (high end exposure = 0.008 mg/kg/day).

Since the RfD Committee determined that sulfentrazone contains clear, unequivocal evidence of developmental and reproductive toxicity. This additional modifying factor increases HED's level of concern to 1000. The acute dietary MOE of 1,250 (MOE = 10 mg/kg/day ÷ 0.008 mg/kg/day) demonstrates no concern for females of child-bearing age considering the proposed tolerances.

VIII. DETERMINATION OF SAFETY FOR INFANTS AND CHILDREN

Under the directive of the Food Quality Protection Act (FQPA) recently enacted as an amendment to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Health Effects Division-RfD/Peer Review Committee reconvened on November 14, 1996 to reconsider its position on the Reference Dose (RfD) for Sulfentrazone. In this meeting, the appropriate uncertainty factor for Sulfentrazone was discussed, under the directive of the Food Quality Protection Act, which requires that pesticide regulatory review incorporate an assessment of potential hazards to infants and children and include additional safety factors, of up to 10X when warranted, for the protection of these sensitive subpopulations.

At this November 14, 1996 meeting, the Committee determined that the toxicology data profile for Sulfentrazone contains clear, unequivocal evidence that this chemical causes

developmental and reproductive toxicity. Based upon the available data and toxicity profile, the Committee considered sulfentrazone to be a relatively potent reproductive/developmental toxicant, and determined that an additional 10-fold modifying factor for the protection of infants and children was warranted.

This decision was based upon the data described above. The following facts were considered in reaching this conclusion:

1) The lowest NOEL (14 mg/kg/day) for chronic exposure, which is used to determine the RfD, is based upon severe, irreversible reproductive/developmental effects, observed in the two-generation reproduction study in rats at a LOEL of 33 mg/kg/day.

2) Developmental toxicity was observed in the absence of maternal effects in the prenatal developmental toxicity studies in rats (developmental NOELs were lower than maternal NOELs). This apparent increased sensitivity of the fetuses occurred following administration of sulfentrazone by either the dermal or as oral route, both of which are relevant to human exposure.

3) A steep dose-response curve exists for the reproductive and developmental endpoints of concern. The reproductive and/or developmental LOELs for the prenatal developmental toxicity studies in rats and the two-generation reproduction study are only approximately 2.5 times greater than the corresponding NOELS in each of these studies. The reproductive and developmental NOELs are extremely low (i.e., in the range of 10-13 mg/kg/day). Additionally, in the rat prenatal developmental toxicity and two-generation reproduction studies, the reproductive/developmental effects increase in incidence and/or severity at higher doses.

4) The reproductive/developmental toxicity profile is consistent and reproducible, providing a large measure of confidence in the endpoints and dose levels.

X. OTHER CONSIDERATIONS

A. Cumulative Effects

Sulfentrazone is structurally similar to four other pesticide products. These pesticides are Flumioxazin (PC Code 129034), Oxadiazon (PC Code 109001), LS 82-556 (FEBS Letters 245: 35-38, 1989), and M&B 39279 (FEBS Letters 245: 35-38, 1989). All these pesticides also produce protoporphyrin IX following inhibition of protoporphyrinogen oxidase.

Three of these chemicals (flumioxazin, oxadiazon, and M&B 39279) possess, like sulfentrazone, a phenyl ring attached to a

heterocyclic ring. However, because of the diversity of functional groups in these molecules it is not possible to determine whether properties other than protoporphyrinogen oxidase inhibition will be common to these compounds.

Oxadiazon, on the other hand, was associated with liver tumors in rats and mice and has been classified by the HED-CPRC as a "Group C(q)" carcinogen, and as a "Group C" carcinogen by the Agency Science Advisory Panel (SAP).

However the Agency has not made a determination whether sulfentrazone and any other pesticide have a common mode of toxicity and require cumulative risk assessment. For the purposes of this tolerance and registration application, the Agency has considered only risks from sulfentrazone. If required, cumulative risks will be assessed as part of Reregistration and tolerance reassessment, and when methodologies for determining common mode of toxicity and for performing cumulative risk assessment are finalized.

X.

OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

Sulfentrazone is formulated as the end use products, Sulfentrazone (F6285) 4F and Sulfentrazone (F6285) 75DF. These formulated products are applied via groundboom application equipment only. For risk assessment purposes, this evaluation includes daily exposure and the average annual daily exposure assessments. Dermal and inhalation unit exposures are combined to calculate a total exposure value.

The toxicology endpoint of concern arises from a developmental toxicity NOEL of 100 mg/kg/day. Sulfentrazone is a Tox Category III compound for acute oral, acute dermal, acute inhalation toxicity, and primary eye irritation. It is a Tox Category IV compound for primary skin irritation and is not a dermal sensitizer. Dermal absorption is estimated to be approximately 10%.

HED/OREB conducted an exposure assessment for the use of sulfentrazone on soybeans to control weeds based on surrogate exposure data from Pesticide Handlers Exposure Database (PHED). Mixer/loader and applicator exposure to Sulfentrazone (F6285). 4F and Sulfentrazone (F6285) 75DF are evaluated for daily and average annual daily exposure.

DETAILED CONSIDERATIONS:

Since this is a new ai, OREB did not have chemical specific exposure data on which to perform a worker exposure assessment and therefore relied on PHED (version 1.1) to estimate

occupational exposures to sulfentrazone. The assumptions used to calculate worker exposure are as follows:

LE 2: Assumptions Used to Calculate Sulfentrazone Worker Exposure Estimates	
Applicator Weight	60 kg
Mixer/loader Weight	60 kg
Applicator unit exposure (GB open cab)*	13.3 ug/lb ai applied
Mixer/loader unit exposure (liquid open pour)*	38.4 ug/lb ai handled
Mixer/loader unit exposure (dry flowable open)*	83.6 ug/lb ai handled
LBS. A.I. handled/day	40.5 lbs.ai/day
Application rate:liquid	0.375 lb ai/A
Application rate:DF	0.375 lb ai/A
Average farm size(2)	148 acres
Acres treated/day	108
Adjustment for Dermal Absorption	None

* From PHED, version 1.1 (see calculations below); clothing scenario: long pants, long sleeves, gloves.

HED/OREB concludes that the following worker exposures result from the handling and application of sulfentrazone to soybeans. These exposures were calculated using the pesticide handlers exposure database (PHED), version 1.1.

APPLICATOR EXPOSURE GROUNDBOOM/OPEN CAB
Based on a Long Sleeve Shirt, Long Pants, Glove Clothing Scenario

Dermal Exposure = 12.5886 μg/lb ai + Inhalation Exposure = 0.6795 μg/lb ai
Total Unit Exposure = 13.2681 μg/lb ai

MIXER/LOADER EXPOSURE LIQUID/OPEN POUR
Based on a Long Sleeve Shirt, Long Pants, Glove Clothing Scenario
(*Exposure to the feet has been omitted)

Dermal Exposure = 37.4164 μg/lb ai + Inhalation Exposure = 1.0416 μg/lb ai
Total Unit Exposure = 38.458 μg/lb ai

MIXER/LOADER EXPOSURE DRY FLOWABLE/OPEN POUR
Based on a Long Sleeve Shirt, Long Pants, Glove Clothing Scenario

Dermal Exposure = 82.8995 μg/lb ai + Inhalation Exposure = 0.6668 μg/lb ai
Total Unit Exposure = 83.5663 μg/lb ai

HED/OREB also concludes that the appropriate personal protective equipment (PPE) as specified by the Worker Protection Standards (WPS) is:

- o long sleeved shirt
- o long pants
- o shoes & socks.

Using the assumptions above and the total exposures, the daily and average annual daily exposures were calculated as followed:

CALCULATIONS FOR DAILY EXPOSURE

Amount handled per day for all Workers

108 acres/day x 0.375 lbs ai/acre = 40.5 lbs ai/day

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Daily Exposure Applicator - groundboom open cab

13.3 µg/lb ai x 40.5 lb ai/day x 1 mg/1000 µg ÷ 60 kg = 0.009 mg/kg/day

Average Annual Daily Dose Applicator - ground boom open cab

0.009 mg/kg/day x 1 day/year ÷ 365 days/year = 0.00002 mg/kg/day

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Daily Mixer/loader Exposure - liquid open pour

38.4 µg/lb ai x 40.5 lb ai/day x 1 mg/1000 µg/ 60 kg = 0.03 mg/kg/day

Average Annual Daily Dose Mixer/loader-liquid open pour

0.03 mg/kg/day x 1 day/year ÷ 365 days/year = 0.00008 mg/kg/day

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Daily Mixer/loader Exposure - dry flowable open pour

83.6 ug/lb ai x 40.5 lb ai/day x 1 mg/1000 mg ÷ 60 kg = 0.06 mg/kg/day

Average Annual Daily Dose Mixer/loader-dry flowable open pour

0.06 mg/kg/day x 1 day/year ÷ 365 days/year = 0.0002 mg/kg/day

It should be noted that while the reproduction study/NOEL was used to establish the RfD, the dermal developmental study/NOEL is used for the occupational risk assessment. The NOEL in this dermal developmental study is 100 mg/kg/day following dermal administration of Sulfentrazone to the dams. The Developmental LOEL is 250 mg/kg/day, based on decreased fetal weight, and delays/alterations in skeletal development The use of this NOEL is supported by the NOEL of 14 mg/kg/day established in a 2-generation reproduction study when the 10% dermal absorption rate is used; i.e., the comparable dermal dose is approximately 140 mg/kg/day (oral NOEL of 14 mg/kg/day ÷ 0.1 dermal absorption = 140 mg/kg/day). For the RfD, the reproduction study was selected since the route of exposure was dietary which is appropriate for RfD. For this occupational risk assessment, the dermal developmental toxicity study is used since the expected route of exposure is dermal.

TABLE 3: Worker Exposure (Short, Intermediate, and Chronic Term) Estimates for the Use of Sulfentrazone on Soybeans (mg/kg/day)			
Job Function	Daily Exposure	Average Annual Daily Exposure	MOE
Applicator GB	0.009	0.00002	10,000
Mixer/loader open pour liquid	0.03	0.00008	3,000
Mixer/loader open pour-dry flowable	0.06	0.0002	1,700

*The chronic MOEs are not shown since they would be extremely high and therefore of no concern.

The Margin of Exposure (MOE) is a measure of how close the high end exposure comes to the NOEL (the highest dose at which no effects were observed in the laboratory test), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). Since an additional modifying factor (10X) was warranted due to developmental/reproduction effects; HED's level of concern will be 1000 for sulfentrazone. The lowest MOE is 1,700 for a mixer/loader using the open pour method of a dry flowable end-use product (MOE = 100 mg/kg/day ÷ 0.06 mg/kg/day) demonstrates no concern for females of child-bearing age considering the proposed use practices. All of the MOEs are above the level of concern for short- and intermediate-term, and chronic occupational use and do not trigger a risk concern for sulfentrazone on soybeans

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