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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 10, 1998

MEMORANDUM

SUBJECT: PP# 3F04225. TRIASULFURON. Human Health Risk Assessment for Use on Grasses. Submission of Data on Magnitude of Residues in or on Grasses.

Submission # S537234	DP Barcode: D244111
Case #: 284773	40 CFR: 180.459
EPA Reg#: 100-701	Tox. Chem. (Caswell) #: 861C
PC Code: 128969	Trade Name: Amber, Logran
Class: Herbicide	MRID#: 444981-01

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I. BACKGROUND

Triasulfuron is a selective herbicide used for pre-emergence control of broadleaf and grassy weeds in wheat and post-emergence in wheat, barley, pastures, and rangeland. The formulation type is a water-dispersible granule consisting of 75% active ingredient, marketed in 1.4 oz water-soluble packets. There are no registered residential uses. Triasulfuron is applied by either ground or aerial spray equipment at a rate of 0.013-0.026 lbs ai/acre, not to exceed 0.039 lbs ai/acre in a calendar year. A maximum of 2 applications per year may be made with the second application no more than 60 days later.

Time-limited tolerances are established for triasulfuron on grass forage, grass hay and the kidney of cattle, goats, horses, and sheep pending submission of additional residue trials on grasses to capture a larger percentage of the U.S. grass acres and to have a more representative distribution among grass species tested. The tolerances are due to expire on July 20, 1998. Novartis has submitted the residue data requested.

The expiring tolerances are for residues of the herbicide [3-(6-methoxy-4-methyl-1,3,5-triazin-2-yl)-1-(2-(2-chloroethoxy)phenylsulfonyl)urea] (triasulfuron) established under 40 CFR 180.459 as follows:

Commodity	**Parts per million**
Cattle, kidney	0.5
Goats, kidney	0.5
Grass, forage	7.0
Grass, hay	2.0
Horses, kidney	0.5
Sheep, kidney	0.5

Permanent tolerances are already established on barley, wheat, and various livestock commodities (fat, meat and meat by product of cattle, hogs, sheep, goats and horses) other than the kidney, and milk.

II. EXECUTIVE SUMMARY

Triasulfuron is a sulfonylurea herbicide used for pre-emergence control of broadleaf and grassy weeds in wheat and post-emergence in wheat, barley, pastures, and rangeland. Time-limited tolerances for triasulfuron on grasses (forage and hay) and the kidney of cattle, goats, horses, and sheep are due to expire on July 20, 1998 due to a deficiency in residue data in grasses. The new residue data for triasulfuron in grasses were recently submitted by the registrant and are reviewed in this report. As part of this assessment, the toxicity data and exposure scenarios for triasulfuron

were re-evaluated, and a risk assessment was conducted, in accordance with the Food Quality Protection Act (FQPA) of 1996. The purpose of this report is to determine whether the time-limited tolerances should be made permanent based on the supplemental grass residue data, in addition to the toxicity and exposure concerns of FQPA.

Triasulfuron has a low order of acute toxicity and is classified in toxicity categories III and IV for the oral, dermal and inhalation routes of exposure. There is no evidence that triasulfuron is neurotoxic, teratogenic, carcinogenic, mutagenic, or clastogenic. In rodents, it caused developmental effects (delayed skeletal maturation) and reproductive effects only at high doses that also induced maternal and/or parental toxicity.

The toxicology data of triasulfuron were recently evaluated by the Health Effects Division's (HED) Hazard Identification Assessment Review Committee (HIARC) (June 30, 1998), and toxicological endpoints (acute and chronic dietary, occupational and residential exposure) were selected for use in risk assessment pursuant to the FQPA of 1996. No endpoints were identified for acute dietary exposure due to an absence of appropriate toxicological data. Because triasulfuron does not have any registered residential uses, and chronic occupational exposures are unlikely, no endpoints were identified for these exposure scenarios. The short- and intermediate-term dermal and inhalation endpoints are based on oral developmental and subchronic studies, respectively and route-to-route extrapolation. The short-term dermal and inhalation No Observable Effect Level (NOEL) dose of 100 mg/kg/day is based on decreased body weight and decreased body weight gain in pregnant rats, while the intermediate-term dermal and inhalation NOEL dose of 10 mg/kg/day is based on decreased body weight and food intake in rats of both sexes. Triasulfuron is a category E carcinogen, evidence of non-carcinogenicity for humans. Therefore, a carcinogenic risk assessment for triasulfuron is not required. The chronic dietary endpoint for triasulfuron was selected from the chronic carcinogenicity study in mice (2 years) and is based on a dose-related statistically significant increased incidence in centrilobular hepatocytomegaly in males. The NOEL from the chronic carcinogenicity study in mice is 1.2 mg/kg/day. Using an uncertainty factor of 100 for inter- and intra-species variation, the RfD is 0.01 mg/kg/day.

The toxicological data on triasulfuron provides no indication of enhanced sensitivity of infants and children based on the results from developmental studies conducted with rats and rabbits as well as a two-generation reproduction study conducted with rats. No effects in the offspring were observed in any of these studies, except at doses that induced maternal toxicity (HIARC 6/30/98). Because the hazard and exposure assessments for triasulfuron do not indicate a concern for potential risk to infants and children, the FQPA Safety Factor Committee determined that the 10X factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed** (FQPA Safety Factor Committee, July 1, 1998).

Triasulfuron does not have any registered residential uses, therefore, this risk assessment does not evaluate residential dermal or inhalation exposures.

The risk assessment evaluated occupational risks to workers who could contact triasulfuron through simultaneous dermal and inhalation exposure. Agricultural worker populations evaluated in this analysis include: groundmixer/loaders, ground applicators, aerial mixer/loaders, and aerial applicators. In addition, workers that could dermally contact triasulfuron during harvest or irrigation activities were evaluated. Short-term dermal and inhalation margin of exposure (MOEs) for triasulfuron handlers ranged from 70,000 for aerial mixer/loaders to 300,000 for ground applicators. Intermediate-term dermal and inhalation MOEs ranged from 7,000 for aerial mixer/loaders to 30,000 for ground applicators. Workers that could contact triasulfuron via postapplication activities had slightly higher risks. Short-term MOEs for this population ranged from 5,000 to 13,000, while intermediate-term MOEs ranged from 500 to 1,300 for harvest and irrigation activities, respectively. All of these risks are well below HED's level of concern (i.e., acceptable MOE≥100) for occupationally exposed workers, indicating that these workers are unlikely to experience adverse health effects under the conditions evaluated.

Chronic dietary (food only) exposure estimates for triasulfuron do not exceed the Health Effects Division's (HED's) level of concern. The most highly exposed population subgroup was non-nursing infants (<1 year old) at 15% of the RfD. In conducting this chronic dietary risk assessment, HED conservatively assumed that all commodities having triasulfuron tolerances will contain residues of triasulfuron at the tolerance level. This results in an overestimate of human dietary exposure.

The predicted triasulfuron surface and ground water concentrations are well below the estimated drinking water levels of concern (DWLOC). The Environmental Fate and Effects Division (EFED) generated a Tier 1 drinking water assessment for triasulfuron using conservative screening models. The Generic Estimated Environmental Concentration (GENEEC) model estimated surface water concentrations and the SCI-GROW model estimated ground water concentrations. The GENEEC model predicted that with the present use pattern, triasulfuron surface water concentrations would range from a peak of 1.8 µg/L (ppb) to a 56-day average of 1.68 µg/L (ppb). The SCI-GROW model estimated that the ground water concentration from the current uses of triasulfuron would be 0.19 µg/L (ppb). In comparison, the lowest calculated drinking water level of concern (DWLOC) is 85 µg/L (ppb) for non-nursing infants (< 1 yr old). Therefore, exposure from water is below HED's DWLOC for chronic dietary exposure for all of the populations examined. In addition, the aggregate (food and water) chronic exposure for infants, children, and adults does not exceed HED's level of concern, and these populations are unlikely to develop adverse health effects following chronic exposure.

In conclusion, HED determined that the triasulfuron residue data in grasses are adequate to support the tolerance levels of 7 ppm in forage grass, 2 ppm in hay grass and 0.5 ppm in kidneys, and that triasulfuron residues do not pose an adverse health risk to humans under the pathways evaluated. Therefore, HED recommends permanently establishing these tolerances for residues of the herbicide [3-(6-methoxy-4-methyl-1,3,5-triazin-2-yl)-1-(2-(2-chloroethoxy)phenylsulfonyl)urea](triasulfuron) in grasses and kidneys under 40 CFR 180.459.

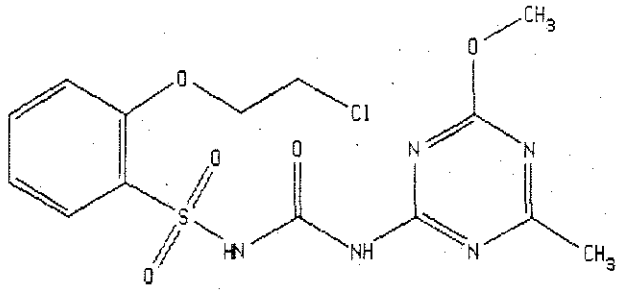
III. SCIENCE ASSESSMENT

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

1. Identification of Active Ingredient

Triasulfuron is a sulfonylurea herbicide with the chemical name 3-(6-methoxy-4-methyl-1,3,5-triazin-2-yl)-1-[2-(2-chloroethoxy)phenylsulfonyl]urea.

Its chemical structure is:



Empirical Formula: $C_{14}H_{16}ClN_5O_5S$
Molecular Weight: 401.82
CAS Registry No.: 82097-50-5
Shaughnessy No.: 128969

2. Other Product Chemistry Considerations

The product chemistry of triasulfuron has been previously reviewed and found to be adequate. [See Confidential Appendix (Attachment 12) to L. Cheng, RCB/HED review of PP#7G3551, triasulfuron/wheat & barley, 2/5/88, and Confidential Appendix (Attachments 2 and 8) to DEB/HED review of PP#8F3658, triasulfuron/wheat, barley, & animal products, transmitted by R. Schmitt (reviewed by M. Bradley), 6/22/89; MRID#s 402719-01 thru -03 and 405285-01]. No additional data are needed to support this petition.

B. HUMAN RISK ASSESSMENT

1. Hazard Assessment

a. Acute Studies

Triasulfuron has a low order of acute toxicity and is classified in toxicity categories III and IV for the oral, dermal and inhalation routes of exposure. Clinical signs of toxicity include moderate dyspnea and ruffled fur with recovery by days 9-10, mild curved body position for 7 days, and exophthalmus for 9 days in the acute oral study; sedation, piloerection, dyspnea, exophthalmus and

curved body position ("ventral and curved") which subside by day 13 in the acute dermal study and ruffled fur which subsides by day 2 in the acute inhalation study. Triasulfuron is a mild eye irritant, produced very slight skin irritation in one study and is negative for dermal sensitization. The acute toxicity studies of technical grade triasulfuron and the formulation 75WP-B are summarized in the table below:

Acute Toxicity of Triasulfuron

Study Type	Formulation	Results	Tox Category
Acute Oral (Rat) (a)	95%, 99% technical, 75WP-B formulation	LD_{50} > 5 g/kg[1]	IV
Acute Dermal (b)	95% technical grade (rat) 75WP-B formulation (rabbit)	LD_{50} > 2 g/kg	III
Acute Inhalation (Rat) (c)	95% technical grade 75WP-B formulation	LC_{50} > 5.185 mg/L/4 hrs LC_{50} > 2.32 mg/L/4 hrs	IV
Primary Eye Irritation (Rabbit)	96.5% technical (d) 75WP-B formulation	mild conjunctival irritation that subsided by day 7 mild conjunctival irritation that subsided by day 4	III
Primary Skin Irritation	96.5% technical (e) 75WP-B formulation	very slight erythema and *edema* Negative	IV
Dermal Sensitization (f)	95%, 96.5% technical; 75WP-B formulation	Negative	NA[2]
Acute Neurotoxicity	Not conducted		NA

[1]LD_{50} (LC_{50}) = the estimated dose (concentration) which is acutely lethal to 50% of the animals tested.
[2]NA = Not applicable because a Toxicity Category is not assigned for this particular type of acute study.
(a-f) MRID#s 40271930 thru -33, 40271935 thru -39; HED Document Numbers 006601, 007582.

b. Subchronic Studies

The major target organ for the subchronic oral study in mice appears to be the liver at 1,500 mg/kg/day, while the most sensitive toxicological finding in rats is decreased body weight and food consumption, observed at a dose level of 500 mg/kg/day. Clinical signs of toxicity (i.e., dyspnea, and ruffled fur) were observed in the 21-day dermal study in rabbits at doses as low as 10 mg/kg/day. This study was not considered to be appropriate for risk assessment. There is low confidence in the dermal rabbit study and the clinical observations are common findings in stressed laboratory animals. The following table summarizes the subchronic toxicity studies for triasulfuron:

Subchronic Toxicity of Triasulfuron (Technical)		
GDLN	STUDY	RESULTS
82-1(a)	Subchronic feeding in Rats (13 weeks) MRID #: 40271947 Date: 1985 Core Grade: acceptable guideline	**Triasulfuron technical (94.5% a.i.)** NOEL: 10 mg/kg/day LOEL: 500 mg/kg/day[1] Effects: decreased weight gain and food intake in both sexes.
82-1(a)	Subchronic feeding in mice (13 weeks) MRID #: 40728316 Date: 1988 Core Grade: not acceptable guideline	**Triasulfuron technical (94.5% a.i.)** NOEL: not identified (< 1,500 mg/kg/day) LOEL: 1,500 mg/kg/day (LDT) Effects: hepatocellular necrosis in females.
82-2	21-day dermal in rabbits MRID #: 41585801 Date: 1986 Core Grade: acceptable guideline	**Triasulfuron technical (94.5% a.i.)** NOEL for systemic effects: not identified NOEL for irritation: 1,000 mg/kg/day LOEL for systemic effects: 10 mg/kg/day Effects: dyspnea, and ruffled fur that were not considered appropriate endpoints for human risk assessment.

[1]LOEL = Lowest Observable Effect Level

c. **Chronic Studies**

Triasulfuron was evaluated for carcinogenic potential in both rats and mice. There was no evidence of carcinogenicity. The major target organ in mice is the liver (centrilobular hepatocytomegaly), while the most sensitive toxicological finding in rats is decreased body weight and decreased body weight gain. In dogs, prostate cystic hyperplasia was observed following chronic exposure. The following table summarizes the chronic toxicity/carcinogenicity studies for triasulfuron:

Chronic Toxicity/Carcinogenicity of Triasulfuron (Technical)		
GDLN	STUDY	RESULTS
83-1b	Chronic feeding study in dogs MRID # 40271965 and 40542401 Date: 1986 Core Grade: acceptable guideline	**Triasulfuron technical (purity not specified)** NOEL: 2.5 mg/kg/day LOEL: 25 mg/kg/day Effects: increased prostate cystic hyperplasia.

Chronic Toxicity/Carcinogenicity of Triasulfuron (Technical)		
GDLN	STUDY	RESULTS
83-2	Oncogenicity study in mice MRID # 40728316 Date: 1988 Core Grade: acceptable guideline	**Triasulfuron technical (93.7-96.5% a.i.)** NOEL = 1.2 mg/kg/day LOEL: 129 mg/kg/day Effects: centrilobular hepatocytomegaly in males. There was no evidence of oncogenicity.
83-5	Chronic feeding/ carcinogenicity study in rats MRID # 40728318 and 41585802 Date: 1987 Core Grade: acceptable guideline	**Triasulfuron technical (92.5% a.i.)** NOEL: 32.1 mg/kg/day LOEL: 220.8 mg/kg/day Effects: decreased mean body weight and decreased body weight gain. Negative for carcinogenicity.

d. **Developmental Toxicity Studies**

Triasulfuron was evaluated for developmental toxicity in rats and rabbits. In rats, developmental effects (reduced ossification of vertebrae, metatarsals and phalanges) were noted at extremely high doses of 900 mg/kg/day (HDT), that were also associated with maternal toxicity. However, no developmental effects were noted in rabbits at the highest dose tested (240 mg/kg/day). Maternal toxicity was observed in both rats and rabbits (decreased body weight, and/or decreased body weight gain in both species). The following table summarizes the developmental studies for triasulfuron:

Developmental Toxicity of Triasulfuron (Technical)		
GDLN	STUDY	RESULTS
83-3a	Developmental Study in rats MRID# 40271948 Date: 1986 Core Grade: acceptable guideline	**Triasulfuron technical (94.5% a.i.)** Maternal NOEL: 100 mg/kg/day Maternal LOEL: 300 mg/kg/day based on decreased body weight and decreased body weight gain during gestation. Developmental NOEL: 300 mg/kg/day Developmental LOEL: 900 mg/kg/day (HDT) based on reduced ossification of vertebrae, metatarsals and phalanges.
83-3b	Developmental Study in rabbits MRID# 40271949 Date: 1986 Core Grade: acceptable guideline	**Triasulfuron technical (94.5% a.i.)** Maternal NOEL: 120 mg/kg/day Maternal LOEL: 240 mg/kg/day based on reduced maternal weight gain during gestation. Developmental NOEL: >240 mg/kg/day (HDT)

e. Reproduction Studies

Triasulfuron induced reproductive toxicity in rats, but only at dose levels that induced parental toxicity. Reproductive effects included reduced F1a pup weights at birth and during lactation, while parental effects included significant decreases in premating and total body weight gain. The following table summarizes the reproduction study for triasulfuron:

Reproductive Toxicity of Triasulfuron (Technical)

GDLN	STUDY	RESULTS
83-4	2-Generation Reproduction Toxicity in Rats MRID 40728317 Date: 1987 Core Grade: acceptable guideline	Parental NOEL: 50 mg/kg/day Parental LOEL: 250 mg/kg/day based on significant decreases in premating and total body weight gain for F0 and F1 parental animals. Reproductive NOEL: 50 mg/kg/day Reproductive LOEL: 250 mg/kg/day (HDT) based on reduced F1a pup weights at birth and during lactation.

f. Mutagenicity Studies

Triasulfuron is not mutagenic in bacteria, yeast, or mammalian cells. Triasulfuron was negative in the Ames assay at cytotoxic concentrations, was negative in the recombinant/conversion assay in S. Cerevisiae D7, failed to induce micronuclei and/or nuclear anomalies at concentrations up to 5,000 mg/kg, and did not cause DNA damage/repair in rat hepatocytes at concentrations up to the solubility limit. Furthermore, triasulfuron did not induce forward mutations in mouse lymphoma cells with and without metabolic activation.

Mutagenicity Studies with Triasulfuron

GDLN	STUDY	RESULTS
84-2	Reverse gene mutation - Salmonella typhimurium MRID: 40271951 Date: 5/31/83 Core Grade: Acceptable Guideline	Strains TA 98, 100, 1535, 1537, 1538 tested at 0, 4, 16, 64, 256 μg/0.1 ml in absence and presence of metabolic activation. Negative up to cytotoxic concentrations, 64 and 256 μg/0.1 ml.

Mutagenicity Studies with Triasulfuron		
GDLN	STUDY	RESULTS
84-2	Reverse gene mutation, recombination and gene conversion in Saccharomyces cerevisiae MRID: 40271952 Date: 6/29/84 Core Grade: Provisionally Acceptable	Strain D7 exposed to test article at 0, 46.9, 187.5, 750, 3000 μg/ml in absence and presence of metabolic activation. Negative up to 3000 μg/ml. Deficiency: not tested up to limit concentration for negative study: 5000 μg/ml. Provisionally acceptable pending toxicity test and new study at 5000 μg/ml.
84-4	Forward gene mutation in mammalian cells: L5178Y/TK MRID: 40271953 Date: 7/31/86 Core Grade: Acceptable	Cells tested with and without metabolic activation at 0, 260, 520, 1040, 1560, 2080, 2340, 2600 μg/ml and 0, 300, 600, 1200, 1800, 2400, 2700, 3000 μg/ml, respectively. Negative up to levels of moderate cytotoxicity.
84-2	In vivo cytogenicity study (micronucleus/Chinese hamsters) MRID: 40271954 Date: 9/6/84 Core Grade: Acceptable	Administered orally to Chinese hamsters at 0, 625, 1250, 2500 mg/kg/day on each of 2 consecutive days. Negative for induction of micronuclei and/or other nuclear anomalies at doses reaching the limit dose: 5000 mg/kg (2500 mg/kg/day X 2).
84-2	UDS study: DNA damage and repair in vitro in rat hepatocytes MRID: 40271955 Date: 9/6/84; 12/9/86 (supplement) Core Grade: Acceptable	Rat hepatocytes exposed to test substance at 0, 2, 10, 50, 250 μg/ml. Negative up to limit of solubility (250 μg/ml) for inducing UDS.
84-2	UDS study: DNA damage and repair in vitro in human fibroblasts MRID: 40271956 Date: Date: 9/6/84; 12/9/86 (supplement) Core Grade: Unacceptable	Fibroblasts exposed to test substance at 0, 10, 50, 250 μg/ml. Negative, however, no metabolic activation series, no attempt to minimize background of S-phase cells, no background grain counts included in analysis.

g. **Metabolism Studies**

In the rat, triasulfuron is excreted primarily in the urine (70-99%) with lesser amounts excreted in the feces. The majority of excretion occurs in the first 24 hours following exposure. Residue levels in the tissues are <0.1% of the administered dose. The major excretion product is unchanged triasulfuron in both urine and feces. The following table summarizes the metabolism studies for triasulfuron:

Metabolism Studies on Triasulfuron		
GDLN	STUDY	RESULTS
85-1	MRID: 40728319 Date: 3/4/88 Core Grade: Acceptable Guideline	Metabolism of [(U-^{14}C)Phenyl]triasulfuron was studied in 5/sex Wistar rats. Material administered orally as a single low dose (0.5 mg/kg) & high dose (300 mg/kg), single low dose after daily doses of unlabeled material for 14 days (0.5 mg/kg/day) or single i.v. dose of 0.5 mg/kg. 92-109% of dose recovered within 96 hours: 74-99% in urine & 2-14% in feces. Elimination rates after repeated oral dosing faster than after single dose. Residue levels in tissue < 0.1%. Levels in tissues higher after single high dose than after single low dose. Even after repeated administration at low dose, no radioactivity retained by animals. Metabolite patterns in urine, fecal and liver extracts show mainly parent compound. Variety of minor metabolites: 12 urinary (6.6-8.1%), 10 fecal (1.2-2.9%) of the administered radioactivity, respectively. No significant differences in metabolite patterns between sexes.
85-1	Distribution, degradation and excretion in the rat after oral application MRID: 40271966 Date: 4/10/85 Core Grade: Unacceptable for a total metabolism study.	When uniformly labeled in the phenyl ring, triasulfuron is excreted mainly in the urine (>87%) and to a lesser extent in the feces. Most of the radiolabel is excreted within the first 24 hours. The major metabolite is tentatively identified as unchanged triasulfuron in both urine and feces. Three minor metabolites have also been separated by TLC but not structurally identified. Only 2 rats/sex/dose (2 dose levels).
85-1	Metabolism in the rat after oral application MRID: 40271966 Date: 11/26/86 Core Grade: Unacceptable for a total metabolism study	Six metabolites and the parent compound were identified in the pooled 24 hour urine of 10 male rats. Major radio labeled component of urine was the parent (68.3%). Cleavage of the bridge between the phenyl and triazine rings occurred to a slight extent. Other metabolic pathways consisted of hydroxylation, sulfate formation, demethylation and cleavage of the choroethyl side chain. Only male rats were used and no attempt was made to identify fecal metabolites.
85-1	Distribution, degradation and excretion of triasulfuron in the rat after oral administration MRID: 40271966 Date: 4/10/85 Core Grade: Unacceptable for total metabolism study.	When labeled in the 2 and 6 position of the triazine ring, triasulfuron is mainly excreted in the urine (>70%) and to a lesser extent in the feces. Most of the radiolabel is excreted within the first 24 hours. The major metabolite is tentatively identified as unchanged triasulfuron in both urine and feces. Three minor metabolites have also been separated by TLC but not structurally identified. Only 2 rats/sex/dose (2 dose levels).

2. Dose/Response Assessment

a. Sensitivity of Infants and Children

(1) **Developmental Toxicity**

Triasulfuron was evaluated in a developmental study in Tif: RAIF (SPF) rats (MRID# 40271948). The following dose levels were administered by gavage on days 6-15 of gestation: 0, 100, 300 or 900 mg/kg/day. The maternal NOEL was 100 mg/kg/day and the maternal LOEL was 300 mg/kg/day based on decreased body weight and decreased body weight gain during gestation. The developmental NOEL and LOEL were 300 and 900 mg/kg/day (HDT), respectively based on reduced ossification of vertebrae, metatarsals and phalanges.

Triasulfuron was administered to pregnant female chinchilla rabbits by gavage at dose levels of 0, 40, 120, or 240 mg/kg from days 6 through 18 of gestation (MRID# 40271949). Triasulfuron did not elicit evidence of developmental toxicity at doses up to and including the high dose of 240 mg/kg/day. The developmental toxicity NOEL is >240 mg/kg/day. Maternal toxicity was observed at 240 mg/kg/day manifested as decreased body weight gain during gestation. The maternal toxicity LOEL is 240 mg/kg/day and the NOEL is 120 mg/kg/day.

(2) **Reproductive Toxicity**

Triasulfuron was evaluated in a 2-generation reproduction study in the Sprague-Dawley rat (MRID# 40728317). Dosage levels employed were 0, 0.5, 50, or 250 mg/kg/day. The parental LOEL is 250 mg/kg/day based on significant decreases in premating and total body weight gain for the F0 and F1 parental animals. The parental NOEL is 50 mg/kg/day. The reproductive NOEL and LOELs are 50 and 250 mg/kg/day, respectively based on reduced F1a pup weights at birth and during lactation.

(3) **Neurotoxicity**

Neurotoxicity has not been observed in any of the acute, subchronic, chronic, developmental or reproductive studies performed with triasulfuron. There is no indication that triasulfuron is a neurotoxic herbicide. Neurotoxicity studies in accordance with 81-8 and 82-7 guidelines have not been requested for triasulfuron.

(4) **Determination of Susceptibility to Infants and Children**

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to triasulfuron. In the two-generation reproduction study in rats, the parental NOEL of 50 mg/kg/day is identical to the pup NOEL of 50 mg/kg/day. These data demonstrate that there are no extra sensitivities with respect to pre--and post-natal toxicity between adult and infant animals. In addition, there is no indication that triasulfuron is a neurotoxic herbicide.

(5) **Recommendation for a Developmental Neurotoxicity Study**

Based upon a review of the currently available data base for triasulfuron, a developmental neurotoxicity study in rats is **not required**. None of the toxicology studies indicated that the nervous system was specifically affected by treatment with triasulfuron. The studies evaluated include: subchronic rat and mice studies, chronic rat, mice and dog studies, and developmental toxicity studies in rats and rabbits. Thus, there is no indication that triasulfuron is a neurotoxic herbicide.

b. **Uncertainty/Safety Factor**

The FQPA Committee determined that for triasulfuron the additional **10 x factor** for enhanced sensitivity to infants and children (as required by FQPA) **should be removed** since the hazard and exposure assessments for triasulfuron do not indicate a concern for potential risk to infants and children (FQPA Committee, 7/1/98). The FQPA factor is removed based on the following information:

(1) The HIARC determined that the data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to triasulfuron.

(2) Any detectable residues in food and drinking water would be expected to be at low levels since application rates are very low (i.e., not to exceed 0.039 lb ai/acre/year).

(3) There are currently no registered residential uses for triasulfuron.

c. **Reference Dose (RfD)**

The HIARC (6/30/98) concurred with the NOEL of 1.2 mg/kg/day established by the RfD committee in 1991 based on a chronic feeding/carcinogenicity study in mice. The LOEL was 129 mg/kg/day based on a statistically significant increased incidence in centrilobular hepatocytomegaly in male mice. A 100-fold uncertainty factor (UF) was applied to the NOEL of 1.2 mg/kg/day to account for inter- and intra- species variation. The resulting RfD was calculated to be 0.01 mg/kg/day (MRID No. 40728316).

For chronic dietary risk assessment, the FQPA Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed. Thus, an uncertainty factor (UF) of 100 is adequate.**

d. **Cancer Classification and Risk Quantification**

(1) **Combined Chronic Toxicity/Carcinogenicity Study- Rats** §83-5

MRID Nos: 40728318 and 41585802

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID #40728318), male and female Sprague Dawley rats [70/sex/dose] were fed diets containing triasulfuron (92.5%) at 0, 10, 1000 or 6000 ppm (Males: 0, 0.3, 32.1, or 220.8 mg/kg/day, respectively; Females: 0, 0.4, 42.9 or 274.4 mg/kg/day, respectively) for up to 24 months. In addition, 10/sex/dose were sacrificed at 12 months. Parameters evaluated were: survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, and gross and histological changes.

Significant reductions in mean body weight (25.4% for males and 39.4% for females at 103 weeks) and body weight gains (18-28.7% at week 13 and 25.4-39.4% at week 103) were noted in both sexes in the highest dose groups. There were no treatment-related effects on mortality, clinical signs, ophthalmic changes, organ weights, or gross or microscopic pathology. No toxicologically significant effects were observed in the hematological, clinical chemistry or urinalysis results. Marginal statistically significant increases in relative organ weights in male and female rats were not considered toxicologically significant primarily because of decreased mean body weights, and because absolute organ weights were not elevated. High dose males exhibited a significant decrease in the mean absolute heart weight, which was not considered to be toxicologically significant due to an absence of a dose-response in histopathologic findings. A significant increase in mean testes weight was noted in the high dose males, which is not considered to be an adverse effect because it is associated with decreased testicular atrophy. Furthermore, a dose-related increased incidence in gross lesions (tissue masses) did not correlate with any histological lesion. There were no treatment-related effects on food consumption in males or females throughout the study, with the exception of females in the 6000 ppm group at 103 weeks (11.8% reduction observed). **The chronic toxicity LOEL is 6000 ppm (220.8 mg/kg/day) based upon a significant decrease in mean body weight in both sexes throughout the study and a significant decrease in body weight gain in both sexes at weeks 13 and 103. The NOEL is 1000 ppm (32.1 mg/kg/day).**

This chronic toxicity/carcinogenicity study in rats (MRID# 40728318) coupled with supplementary information summarizing the survival incidence and compound purity (MRID # 41585802) fulfill the guidelines 83-5 for rats.

Discussion of Tumor Data: **There was no evidence of carcinogenicity.**

Adequacy of the Dose Levels Tested: The dose levels were adequate based on significant decreases in mean body weight throughout the study and in body weight gain in both sexes at weeks 13 and

103 in the highest dose group of 220.8 and 274.4 mg/kg/day for males and females, respectively.

(2) **Carcinogenicity Study - Mice** §83-2b

MRID No: 40728316

Executive Summary: In a carcinogenicity study (MRID #40728316), male and female CD-1 albino mice [50/sex/dose] were fed diets containing triasulfuron (93.7-96.5%) at 0, 10, 1000, 5000 or 10,000 ppm (Males: 0, 1.2, 129, 619.6 or 1301.3 mg/kg/day, respectively; Females: 0, 1.5, 157.5, 792.5, or 1473.5 mg/kg/day, respectively) for up to 24 months. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, organ weights, and gross and histological changes. In addition, mice were palpated weekly for tissue masses.

There were no treatment-related effects on mortality, clinical observations, organ weights, water consumption, hematology parameters, ophthalmic findings, or clinical chemistry parameters. In males and females receiving 5,000 or 10,000 ppm, mean body weight and/or body weight gain were marginally depressed below control values (not statistically significant except for females at 2 and 5 weeks in the 10,000 ppm group and at 81 weeks in the 5,000 ppm group); this was accompanied by a decreased food consumption in females. There was a noticeable decrease in food consumption in females at dietary levels of 5,000 and 10,000 ppm during the early phase of the study. These findings were not considered to be of toxicologic importance. Centrilobular hepatocytomegaly was observed in male mice receiving 1,000, 5,000, or 10,000 ppm (significant, $p<0.01$) and in females receiving 10,000 ppm (significant, $p<0.05$). Increased centrilobular degeneration, focal accumulation of inflammatory cells, microgranulomas, and pigment depositions were also observed in the liver of 10,000 ppm males.

The incidence of alveolar/bronchiolar adenoma in the lung was statistically increased ($p<0.05$) in male mice fed 10,000 ppm (28%) when compared to the controls (12%), but the combined incidence of alveolar/bronchiolar adenoma and carcinoma was not significantly different. Female mice exhibited a negative trend for lung adenomas. The histologic importance of the increased incidence of lung adenomas in males is equivocal because of variability of tumors (12, 22, 22, 12 and 28% in the 0, 10, 1,000, 5,000, 10,000 ppm groups, respectively) and the lack of a dose-response. Furthermore, the reported laboratory control incidence (38%) and that found in other laboratories is considerably higher than the concurrent control incidence (12%). No other neoplastic lesions were considered to be of biological importance. **The chronic LOEL is 1000 ppm (129 mg/kg/day) based upon centrilobular hepatocytomegaly in males. The NOEL is 10 ppm (1.2 mg/kg/day).**

Discussion of Tumor Data: **There was no evidence of carcinogenicity.**

Adequacy of the Dose Levels Tested: The dose levels are adequate based on the observation of

dose-related liver toxicity in males and females.

(3) **Classification of Carcinogenic Potential**

The chemical was classified as a "Group E - Evidence of non-Carcinogenicity for humans."

A carcinogenic risk assessment for triasulfuron is not required because triasulfuron is classified as a "Group E - Evidence of non-Carcinogenicity for humans".

d. **Dermal Absorption**

No dermal absorption studies are available. The only studies that could be compared are the 21-day dermal toxicity and the oral developmental studies in rabbits. However, similar toxicological endpoints were not observed in these studies. Following oral administration to pregnant rabbits, triasulfuron decreased maternal body weight gains and following repeated dermal application the test material caused ruffled fur and dyspnea. Since a common endpoint was not observed in the same species via the two different routes, a dermal absorption factor could not be estimated. Therefore, the HIARC (6/11/98) recommended a dermal absorption factor of 100% (default) value.

e. **Other Toxicological Endpoints for Use in Human Risk Assessment**

(1) **Acute Dietary**

The HIARC (6/30/98) did not select a dose and endpoint for an acute dietary risk assessment due to the lack of toxicological effects attributable to a single exposure (dose) in studies available in the data base including the developmental toxicity studies in rats and rabbits. Therefore, a dose and endpoint were not selected for this risk assessment. Additionally, there were no data requirements for acute or subchronic rat neurotoxicity studies since there was no evidence of neurotoxicity in any of the toxicology studies at very high doses. **This risk assessment is not required.**

(2) **Occupational/Residential Exposure Endpoints**

There are no residential uses of triasulfuron, therefore, the short-and intermediate-term exposure endpoints described below are applicable to occupational exposures, exclusively.

(a) *Short- (1 day to 7 days), and Intermediate- (1 week to several months), Term Occupational Dermal and Inhalation Exposure*

(i) Short-term - The HIARC selected an oral NOEL of 100 mg/kg/day based on maternal toxicity as evidenced by

statistically significant decreased body weight (3%) and decreased body weight gain (16%) in pregnant females at 300 mg/kg/day (LOEL). Therefore, the HIARC concluded that a **short-term** occupational risk assessment **is required**.

(ii) Intermediate-term - The HIARC selected an oral NOEL of 10 mg/kg/day based on significantly decreased body weight and food intake in male and females rats at 500 mg/kg/day (LOEL). Therefore, the HIARC concluded that an **intermediate-term** occupational risk assessment **is required**.

(iii) Except for some acute inhalation toxicity studies, for which triasulfuron is placed in Toxicity Category IV ($LC_{50} \geq$ 2 mg/L), no other studies are available via this route. Therefore, HIARC selected the oral NOELs of 100 mg/kg/day for short-term and 10 mg/kg/day for intermediate-term inhalation occupational risk assessment, respectively.

(b) *Chronic Occupational and Residential Dermal and Inhalation Exposure*

There are no residential uses of triasulfuron, and there is no chronic exposure scenario. Therefore, the HIARC Committee (6/30/98) did not identify a chronic occupational or residential dose or endpoint for the triasulfuron risk assessment. **This risk assessment is not required.**

Summary of Toxicological Endpoints for Triasulfuron

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	No endpoint was identified.
Short-, Intermediate and Long-Term Residential	Dermal/Inhalation	There are no residential uses of triasulfuron.
Short-Term (1-7 days) Occupational	Dermal	Oral to Dermal Extrapolation NOEL: 100 mg/kg/day LOEL: 300 mg/kg/day (reduced maternal body weight and reduced body weight gain in pregnant rats during gestation in oral study). Acceptable MOE ≥ 100 Dermal absorption factor = 100%

Summary of Toxicological Endpoints for Triasulfuron		
Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Intermediate-Term (one week to several months) Occupational	Dermal	Oral to Dermal Extrapolation NOEL: 10 mg/kg/day LOEL: 500 mg/kg/day (decreased body weight and food consumption in oral study). Acceptable MOE ≥ 100 Dermal absorption factor = 100%
Long-Term (several months-lifetime) Occupational	Dermal	Use pattern does not indicate potential for long-term dermal exposure; risk assessment not required.
All time periods	Inhalation	Short-term See short-term dermal (except oral to inhalation extrapolation) Intermediate-term See intermediate-term dermal (except oral to inhalation extrapolation)
Cancer	Dietary/Dermal/Inhalation	Classified as category E: not likely to be a human carcinogen.
Chronic (non-cancer)	Dietary	RfD: 0.01 mg/kg/day. NOEL: 1.2 mg/kg/day. LOEL: 129 mg/kg/day (liver effects) UF = 100

3. Exposure and Risk Assessment/Characterization

a. Summary of Use Patterns and Formulations

Triasulfuron is a herbicide used for pre-emergence control of broadleaf and grassy weeds in wheat and post-emergence in wheat, barley, pastures, and rangeland. The formulation type is a water-dispersible granule consisting of 75% active ingredient, marketed in 1.4 oz water-soluble packets. There are no registered residential uses. Triasulfuron is applied by either ground or aerial spray equipment at a rate of 0.013-0.026 lbs ai/acre, not to exceed 0.039 lbs ai/acre in a calendar year. A maximum of 2 applications per year may be made with the second application no more than 60 days later.

TABLE 1
Summary of Use Patterns/Formulations Information Relevant to Occupational Exposure/Risk Assessment

Formulation type, % ai range	Equipment used for mixing/loading and application	Use Sites	Application rate range	Timing and frequency of applications	Comments
Water Dispersible granules in water soluble packets, 75% ai	ground and aerial spray equipment	pastures, grasses, wheat, barley, rangelands	0.013 - 0.026 lb ai/acre; not to exceed 0.039 lbs ai/acre/yr	2 X season; (second application no more than 60 days later)	may be applied at a standard rate of 0.013 lb ai/acre or enhanced rate of 0.026 lb/ai/acre. Not to exceed 0.039 lb/acre/year.

b. Occupational and Residential Exposure and Risk Assessment/Characterization

(1) Occupational Exposure and Risks

(a) Handler Exposure and Risks

(i) Handler scenarios, data, and assumptions

The proposed label (Amber, EPA Reg. No 100-701) requires the following personal protection equipment (PPE) for applicators and mixer/loaders:

- long-sleeved shirt and long pants;
- waterproof gloves; and
- shoes plus socks

Personal Protective Equipment (PPE). Per the Worker Protection Standard (WPS), the minimum level of PPE is based on the acute toxicity of the end-use product. Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with WPS.

(ii) Handler exposure and risk estimates

Occupational exposure assumptions are summarized in **Table 2**. Worker exposure estimates are based on surrogate data from the Pesticide Handlers Exposure Database (PHED), as presented in PHED Surrogate Exposure Guide (5/97) with workers wearing a single layer of clothing plus gloves. It was assumed that workers would apply the maximum application rate of 0.026 lb ai/acre one time.

The MOEs or risk estimates were calculated by comparing the toxicity criteria established by the HIARC (6/30/98) to the total estimate of exposure (or the total average daily dose, ADD). As discussed previously, the HIARC selected the maternal oral NOEL from a rat developmental toxicity study for a route-to-route extrapolation to assess short-term dermal and inhalation exposures. HIARC also selected an oral NOEL from a rat subchronic study for route-to-route extrapolation to assess intermediate-term dermal and inhalation exposures.

Table 2. Occupational Exposure Assumptions

PARAMETER	ASSUMPTION
Pesticide Handlers Exposure Database (PHED), Version 1.1, PHED Surrogate Exposure Guide, (PSEG, 5/97)	Ground and Aerial Mixer/Loader (**Water-soluble packets - WDG** Open Mixing, single layer clothing and gloves): Dermal =**9.8** μg/lb ai handled **(low confidence run);** Inhalation = **0.106** μg/lb ai handled **(low confidence run**).
	Ground Applicator - (groundboom, open cab, single layer clothing and gloves): Dermal = **14** μg/lb ai applied **(medium confidence run);** Inhalation = **0.74** μg/lb ai handled **(high confidence run).**
	Aerial Applicator - (liquid formulation; aerial-fixed wing, closed cockpit, single layer clothing, no gloves): Dermal = **5.01** μg/lb ai applied **(medium confidence run;** Inhalation = **0.07** μg/lb ai handled **(medium confidence run**).
Percent Absorption	Dermal: **100%** (Default) Inhalation: **100%** (Default)
Application Type	Ground and air
Minimum Finish Spray	Ground: **20** gal/A; air **5** gal/A
Maximum Application Rate	**0.026** lb ai/A per application
Applications Per Year	**1** application at the highest allowable rate (2 applications are allowed per year)

Table 2 . Occupational Exposure Assumptions	
PARAMETER	**ASSUMPTION**
Acres Treated/Day (Y, NG, BEAD)	Ground: 80 ; Air 350
Worker Weight	60 kg

The dermal, inhalation and total ADDs, and resulting short- and intermediate-term MOEs are presented on **Table 3**. The total ADD is the sum of the dermal and inhalation exposure. The short-term total MOEs ranged from 70,000 for aerial mixer/loaders to 300,000 for ground applicators. Intermediate-term total MOEs ranged from 7,000 for aerial mixer/loaders to 30,000 for ground applicators. These risks do not exceed HED's level of concern (i.e., acceptable MOE ≥ 100) for occupationally exposed workers, indicating that the pesticide handlers are unlikely to experience adverse health effects following exposure to triasulfuron under the conditions evaluated.

Table 3. Occupational Exposure and Risk Assessment

Worker	ADD (a) Dermal (mg/kg/day)	ADD (b) Inhalation (mg/kg/day)	Total ADD (c) (mg/kg/day)	Short Term MOE (d)	Intermediate Term MOE(f)
Ground Mixer/loader	0.00034	0.0000037	0.00034	300,000	30,000
Ground Applicator	0.0005	0.000025	0.00053	200,000	20,000
Aerial Mixer/loader	0.0015	0.000016	0.0015	70,000	7,000
Aerial Applicator (e)	0.00076	0.00001	0.00077	130,000	13,000

(a) Average Daily Dose (ADD) = [PHED unit exposure(ug/lb) x % dermal absorption x application rate (lb/ac)x acres treated/day * 1E-3 mg/ug] / body weight (kg). Assumes one application of 0.026 lb ai/acre.

(b) Average Daily Dose (ADD) = [PHED unit exposure (ug/lb) x % inhalation absorption x application rate (lb/ac) x acres treated/day * 1E-3 mg/ug] / body weight (kg). Assumes one application of 0.026 lb ai/acre.

(c) Total ADD = Dermal ADD + Inhalation ADD

(d) Short-Term Occupational Exposure MOE = NOEL/ Total ADD (where NOEL =100 mg/kg/day).

(e) gloves, and coveralls are not expected to be worn by aerial applicators

(f) Intermediate-Term Occupational Exposure MOE = NOEL/ Total ADD (where NOEL =10 mg/kg/day).

(b) Post-Application Exposure and Risks

(i) Default transfer coefficients (Tc) of 2,500 cm^2/hr for harvest and a Tc of 1,000 cm^2/hr for irrigation activities were used to estimate dermal exposure during post application activities. These defaults were established by the HED Exposure SAC (5/7/98, policy #3). The registered label has a restricted re-entry interval (REI) of 4 hours because triasulfuron is a "Low Risk Pesticide", and is classified in toxicity categories III/IV (PR notice 95-3, Reduction Intervals for Certain Low Risk Pesticides, 5/3/95). Typically, the Worker Protection Standards (WPS) require an REI of 12 hours for technical material designated as toxicological categories III and IV.

The proposed label (Amber, EPA Reg. No 100-701) requires the following early entry PPE :

- coveralls over long-sleeved shirt and long pants;
- waterproof gloves; and
- shoes plus socks

A summary of the Postapplication Exposure and Risk Assessment is included as **Table 4.**

Table 4. Postapplication Occupational Exposure and Risk Assessment

Transfer Coefficient (Tc) (cm^2/hr)	DFR_t (c) (ug/cm^2)	ADD_t (d) (mg/kg/day)	Short-term MOE (e)	Intermediate Term MOE (f)
2,500 (a)	0.058	0.02	5,000	500
1,000 (b)	0.058	0.0077	13,000	1,300

(a) Tc = 2,500 cm^2/hr for harvest activities

(b) Tc = 1,000 cm^2/hr for irrigation activities.

(c) DFR_t =AR * F * (1-D)^t *4.54E+8 ug/lb*24.7E-9 acre/cm^2

where:

DFR	=	dislodgeable foliar residue on day "t" (ug/cm^2),
AR	=	application rate (0.026 lb ai/acre),
F	=	fraction of ai retained on foliage (0.2, unitless),
D	=	fraction of residue that dissipates daily (0.1, unitless), and
t	=	postapplication day on which exposure is being assessed (day 0).

(d) ADD_t = (DFR_t * 1E-3 mg/ug * Tc * ET * DA) / BW

where:

ADD_t = Average Daily Dose on day "t" (mg/kg/day),
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2),
Tc = transfer coefficient (cm^2/hr),
ET = exposure time (8 hr/day),
DA = dermal absorption factor [1, (default factor), unitless], and
BW = body weight (60 kg).

(e) Short-Term Occupational Exposure MOE = NOEL/ Total ADD (where NOEL =100 mg/kg/day).
(f) Intermediate-Term Occupational Exposure MOE = NOEL/ Total ADD (where NOEL =10 mg/kg/day).

(ii) Summary of postapplication risks: short-term MOEs ranged from 5,000 to 13,000, while intermediate-term MOEs ranged from 500 to 1,300 for harvest and irrigation activities, respectively. Risks did not exceed HED's level of concern (i.e., acceptable MOE ≥ 100) for post-application exposure and consequently, these workers are unlikely to experience adverse health effects under the conditions evaluated.

(c) Occupational Risk Characterization

HED's worker exposure estimates are based on surrogate data from the Pesticide Handlers Exposure Database (PHED) as presented in the Best Available Surrogate Exposure Table (5/97). The unit exposure values from PHED are considered to be central tendency. The application rates, and number of acres treated used in this assessment are upper percentile values. In addition, it was conservatively assumed that 100% of triasulfuron would be absorbed through dermal and inhalation exposure, which is likely to over-estimate exposure. Therefore, the potential doses and risks are characterized as central to high-end.

(2) Residential and Other Non-Occupational Exposures and Risks

Triasulfuron is not registered for any residential uses.

c. Dietary Exposure and Risk Assessment/Characterization

The residue chemistry of triasulfuron (aka CGA-131036; Amber) for this petition on grasses (PP#3F4225) has been previously reviewed by CBTS/HED; see memos of:

G. Kramer, 2/18/94 (D193754 & D193756; MRID#s 427716-01, 428519-01 & -02);
G. Kramer, 1/18/95 (D210064 & D210065; MRID#s 434512-00 & -01); and,
G. Kramer, 4/7/95 (D213652 & D213650; MRID#s none).

Additional magnitude of the residue field trial studies on grasses were requested (see G. Kramer memos) to support *permanent* tolerances. Those additional field trial studies have now been submitted (MRID# 444981-01) and are included in the discussion of Crop Field Trials, below. Based on a review of this data, HED recommends establishing permanent tolerances (40 CFR

180.459) for grass forage (7 ppm); grass hay (2 ppm); and, the kidneys of cattle, goats, horses, and sheep (0.5 ppm); which expire on 7/20/98.

(1) Dietary Exposure (Food Sources)

(a) Directions for Use

Amber Herbicide [EPA Reg. No. 100-701; triasulfuron, active ingredient (ai)] is a 75% ai water-dispersible granular formulation marketed in 1.4 oz water-soluble packets. It is to be applied post-emergence as a broadcast spray by ground (≥3 gpa) or aerial (≥2 gpa) equipment to pastures, rangeland, and Conservation Reserve Program (CRP) acres for control of various actively growing susceptible weed species.

Mechanism of Action: Triasulfuron inhibits acetolactate synthase (ALS), a key enzyme in the biosynthesis of the branched-chain amino acids isoleucine, leucine, and valine. Plant death results from chlorosis and necrosis occurring in response to ALS inhibition.

When using Amber, a suitable (80%) non-ionic surfactant should always be added to the spray mix at 1-2 quarts/100 gallons of spray volume (0.25-0.5% v/v). For control of ALS-resistant weed biotypes, Amber should be applied in a tank mixture with a registered herbicide having a different mode of action on grasses (see label for list), observing all label directions, restrictions, and precautions. Do not use Amber alone in any field where ALS-resistant biotypes of any weed species have been identified. Do not apply Amber through irrigation systems.

When applying Amber to pastures, rangeland, or CRP acres, do not apply more than a total of 0.039 lbs ai (0.63 oz ai)/acre per year, as follows: one application of 0.013 lbs ai (0.21 oz ai)/acre postemergence, followed by a second application not more than 60 days later at up to 0.026 lbs ai (0.42 oz ai)/acre, depending on the weed species to be controlled.

Preharvest Intervals (PHIs): Grazing may occur immediately following application. Do not cut for hay for 30 days following application.

Use of Amber is limited to the states of: CO, ID, KS, MN, MT, ND, NE, NM, NV, OK, OR, SD, TX, UT, WA, and WY. To reduce the possibility of selecting sulfonylurea-resistant biotypes, do not apply Amber or any other herbicide with the same mode of action in pastures, rangeland, or CRP acres more frequently than in one year out of three.

There are extensive, very specific rotational crop restrictions on the Amber label for the crops: barley, rye, oats, bermudagrass, proso millet, field corn, grain sorghum, soybeans, sugar beets, sunflowers, and onions. There are no rotational or reseeding restrictions for the planting of wheat.

RAB2 considers these directions for use to be adequately delineated. No additional information are needed to support this petition. [Information excerpted from 2/18/94 memo, G. Kramer and revised Section B of 2/13/95, no MRID#.]

(b) Nature of the Residue - Plants

No new metabolism studies were submitted with this petition. The nature of the residue in wheat is considered to be adequately understood (6/22/89 review, R. Schmitt, DEB/HED, PP#8F3658, MRID# 402719-06). Residues of triasulfuron are systemic. Metabolism proceeds by hydroxylation of the phenyl ring and hydrolytic cleavage of the urea bridge. The residue of regulatory concern is parent compound only. CBTS/ HED has previously concluded that the metabolism study in wheat can be translated to grasses, and that the residue of regulatory concern for grasses is also parent compound only (2/18/94 review, G. Kramer, CBTS/HED, PP#3F4225). No additional data are needed to support this petition.

(c) Nature of the Residue - Animals

No new metabolism studies were submitted with this petition. The nature of the residue in ruminants and poultry is considered to be adequately understood with the residue of regulatory concern being parent compound only (6/22/89 review, R. Schmitt, DEB/HED, PP#8F3658, MRID# 402719-07 and -08, 407283-02). The levels of secondary residues transferred to animal products are extremely low; metabolism proceeds mainly by cleavage of the urea bridge. No additional data are needed to support this petition.

(d) Residue Analytical Method - Plants

Suitable analytical methodology exists to enforce the extension of the tolerances on grasses. Method AG-500 (column switching HPLC with UV detection; MRID# 402719-09 and 410479-01) has undergone successful petition method validations on wheat grain and straw (memos of H. Tai, ACB/BEAD, 2/14/89 and 7/14/89; L. Cheng, DEB/HED, PP#7G3551, 3/23/89; and, M. Bradley, PP#8F3658, 8/17/89) and has been accepted by the Agency (in its AG-500B revised form; MRID# 413075-02) as the enforcement analytical method for wheat and barley (memo, M. Bradley, PP#8F3658, 8/24/90). The registrant has validated this method in grass forage and hay at the limit of quantitation (LOQ), 0.05 ppm. CBTS/HED has previously concluded that Method AG-500B is acceptable to enforce tolerances on grass hay and forage (2/18/94 review, G. Kramer, CBTS/HED, PP#3F4225). No additional data are needed to support this petition.

(e) Residue Analytical Method - Animals

Suitable analytical methodology exists to enforce the tolerances on animal commodities, including the extension of the tolerances on kidneys. Method AG-508 (column switching HPLC with UV detection; MRID# 402719-10) has undergone successful petition method validation on milk, beef muscle and kidney (memos of H. Tai, ACB/BEAD, 2/14/89 and L. Cheng, DEB/HED, 3/23/89) in re PP#7G3551 and has been accepted by the Agency (in its AG-508B revised form; MRID# 413075-03) as the enforcement analytical method for animal commodities (memo, M. Bradley, PP#8F3658, 8/24/90). The validated LOQ (MRID# 402719-10) is 0.01 ppm for milk; 0.05 ppm for beef muscle, fat, liver, and kidney; 0.05 ppm for eggs; and 0.05 ppm for poultry meat, fat, and liver. No

additional data are needed to support this petition.

(f) Multiresidue Methods

Triasulfuron and four of its metabolites were tested through the FDA multiresidue protocols. The submission was forwarded to FDA for evaluation (3/1/89 letter, M. Bradley, DEB/HED, PP# 8F3658, MRID# 407283-04). Triasulfuron was not determinable by any of the protocols (per Sec. G, PP#3F4225, 4/16/93, no MRID#).

(g) Storage Stability Data - Plants

No new storage stability studies were submitted with this petition. Triasulfuron has been shown to be stable (-15° C) in wheat forage, grain, and straw samples for up to 2 years (6/22/89 review, R. Schmitt, DEB/HED, PP#8F3658, MRID# 402830-06, 402719-16 & 407283-06). Samples in the grasses residue field trial studies were stored for ≤2 years prior to analysis. CBTS/HED has previously concluded that the storage stability data for wheat can be translated to grasses (2/18/94 review, G. Kramer, CBTS/HED, PP#3F4225). No additional data are needed to support this petition.

(h) Storage Stability Data - Animals

Triasulfuron has been shown to be stable (-15° C) in beef liver, poultry breast, eggs, and milk for up to 6 months (6/22/89 review, R. Schmitt, DEB/HED, PP#8F3658, MRID# 407601-01). The longest interval in the feeding studies (PP#7G3551) between animal sacrifice and analysis was 6 months (2/18/94 review, G. Kramer, CBTS/HED, PP#3F4225, MRID#427716-01). Stability data for 2 years of freezer storage have also been submitted (MRID#428519-02; 2/18/94, G. Kramer review, PP#3F4225). No additional data are needed to support this petition.

(i) Crop Field Trials

The data base for use of triasulfuron on grasses consists of 16 crop field trials. Geographic representation (approximately 70% of the U.S. pasture and rangeland grasses acreage) is adequate. Eleven of these trials (representing 33% geographic representation) have been reviewed previously (2/18/94 review, G. Kramer, CBTS/HED, PP#3F4225, MRID#428519-01). To summarize briefly, those 11 trials were conducted in 11 states, using the representative commodities for the grass forage, fodder and hay group (bermudagrass, bluegrass, and bromegrass or fescue), as specified in 40 CFR 180.41 (Crop Group 17). Amber was applied postemergence broadcast, by ground or aerial application. Two applications (0.29 oz ai/acre followed by 0.57 oz ai/acre) were made in each trial for a total yearly application rate of 0.86 oz ai/acre (1.4X yearly max/acre). These rates slightly exceed the application rates recommended on the product label. Forage was harvested at 0 days and hay approximately 30 days after each application. Residues of triasulfuron were measured using Method AG-500B. The method was validated using control grass forage and hay samples from each field trial fortified with triasulfuron at 0.05-20 ppm; average recovery was 89% (n=103). The maximum residue in grass forage was 6.4 ppm (CO) and in grass hay was 1.7 ppm (ND). These data were deemed adequate to establish time-limited tolerances on grass forage (7 ppm) and grass hay

(2 ppm). [Also see Meat, Milk, Poultry, Eggs.] Additional field trial studies were required (to capture a larger percentage of the U.S. grass acreage and to provide a more representative distribution among grass species tested) as a condition of registration and to support permanent tolerances.

By letter dated 2/25/98, the registrant (Novartis, formerly Ciba-Geigy) submitted the results of 5 additional field trials (representing an additional 37% geographic representation, for a grand total of approximately 70%) on grasses (MRID# 444981-01). These 5 trials (bermudagrass, NM, CA; bluegrass, NV, MT; bromegrass, WY) were conducted in 1996 using Amber (75WG) and a spray additive (either X-77 or R-11, 0.50% v/v). Data are available for untreated controls and treated samples receiving one (12 g ai/A; ⅔X yearly max g ai/A) or two applications (12 g ai/A + 12 g ai/A; 1⅓X yearly max g ai/A; between-application-interval, 30-62 days) per trial made as postemergence broadcast sprays (10-30 gpa) using ground application equipment. Forage samples were harvested with 0-day PHI; hay samples were harvested with 28-35 day PHIs. Harvested samples were held in frozen storage (ca -20°C) for 8-17 months prior to analysis (2 samples/treatment level/test site) for triasulfuron residues by enforcement Method AG-500B (LOQ, 0.05 ppm). Procedural recoveries from controls fortified with triasulfuron at 0.05 ppm or 25 ppm prior to extraction ranged 78-102% (avg 94%, n=10) for grass forage and 80-101% (avg 88%, n=10) for grass hay. Representative chromatograms of controls, fortified controls, and field-treated samples of grass forage and hay are provided. Residues of triasulfuron in control samples of grass forage and hay were all <0.05 ppm. Residues of triasulfuron in field-treated grasses are summarized in **Table 5**, below. The maximum residues of triasulfuron following one application were 4.7 ppm (avg 3.1 ppm, n=6) in forage and 1.6 ppm (avg 0.32 ppm, n=10) in hay. The maximum residues of triasulfuron following two applications (totaling 1⅓X yearly max g ai/A) were 7.4 ppm (avg 2.5 ppm, n=10) in forage and 0.30 ppm (avg 0.09 ppm, n=10; for averaging, a value of 0.025 ppm was used for samples with residues of <0.05 ppm) in hay. **These field trial data, and the data from the previous 11 field trials (discussed above), support tolerance levels of 7 ppm in forage grass and 2 ppm in hay grass for residues of triasulfuron in conjunction with the proposed use pattern.** [Also see Meat, Milk, Poultry, and Eggs.] No additional field trial data are required for this petition.

TABLE 5.
Triasulfuron on Grasses: Field Residue and Storage Interval Data for 1996 Field Trials With Amber (75WG) Plus Spray Additive, Using Ground Application Equipment

Trial Site 1996	Use Rate (g ai/A)	Spray Volume (gpa)	Days Between Applications	PHI (days)	Maximum Months Frozen	Triasulfuron Residue (ppm)	
						Forage	Hay
NM	12	11	--	0 32	14.1 13.2	1.8, 1.8 --	-- <0.05, <0.05
	12 + 12	11	62	0 28	12.1 11.3	2.4, 1.7 --	-- 0.06, 0.10

TABLE 5.
Triasulfuron on Grasses: Field Residue and Storage Interval Data for 1996 Field Trials With Amber (75WG) Plus Spray Additive, Using Ground Application Equipment

Trial Site 1996	Use Rate (g ai/A)	Spray Volume (gpa)	Days Between Applications	PHI (days)	Maximum Months Frozen	Triasulfuron Residue (ppm)	
						Forage	Hay
MT	12	10	--	-- 32	-- 16.0	-- --	-- <0.05, <0.05
	12 + 12	10	39	0 30	15.6 14.8	2.0, 1.4 --	-- <0.05, <0.05
NV	12	17	--	0 30	**17.3** 16.5	3.2, 2.7 --	-- <0.05, <0.05
	12 + 12	18	30	0 31	16.3 15.5	2.3, 1.9 --	-- <0.05, <0.05
CA	12	30	--	0 28	11.1 10.4	4.1, 4.7 --	-- **1.6**, 1.1
	12 + 12	30	60	0 35	9.2 8.2	3.2, **7.4** --	-- 0.30, 0.25
WY	12	17	--	-- 30	-- 16.8	-- --	-- 0.21, 0.16
	12 + 12	16	61	0 30	15.5 14.8	1.6, 1.6 --	-- <0.05, <0.05

(j) Processed Food/Feed

Not applicable; there are no processed commodities associated with grasses.

(k) Meat, Milk, Poultry, and Eggs

No new feeding studies were submitted with this petition. Grasses are feedstuffs for beef and dairy cattle. An acceptable feeding study in dairy cattle (conducted at 15, 75, and 150 ppm) has previously been reviewed (2/5/88 memo, L. Cheng, RCB/ HED, PP#7G3551, MRID# 402719-14) and various animal commodity tolerances were subsequently established (milk, 0.02 ppm; meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep at 0.1 ppm). The G. Kramer memo of 2/18/94, this current petition (PP#3F4225) on grasses, contains a summary of the study and a calculation of the maximum theoretical daily dietary burden (20 ppm) in cattle. [Recalculating based upon information in Table 1, OPPTS 860.1000, issued 8/96, the maximum theoretical daily dietary burden is 18 ppm.] It was concluded that all existing tolerances for triasulfuron in animal commodities were adequate to cover the use of triasulfuron on grasses (even taking the existing tolerances on wheat and

barley commodities into consideration) with the exception of the tolerances (0.1 ppm) on kidneys. Accordingly, *higher* triasulfuron tolerances of 0.5 ppm (the level deemed to be adequate) for the kidneys of cattle, goats, horses, and sheep were established as time-limited tolerances in conjunction with the establishment of the time-limited tolerances on grasses. These time-limited tolerances expire 7/20/98. The additional field trial studies on grasses, which have now been submitted and reviewed, herein support these previous conclusions about the adequacy of the animal commodity tolerances. Thus, the time-limited tolerance of 0.5 ppm on kidneys should be made permanent, concurrently with the time-limited tolerances on grasses.

There are no poultry or swine feed items associated with grasses, so tolerances in these animal commodities are not germane to *this* petition. [Note: The poultry feeding study, MRID# 4022719-15, is reviewed in the 2/5/88 review of L. Cheng, PP#7G3551.]

No additional data are needed to support this petition.

(l) Water, Fish, and Irrigated Crops

Not applicable; there are no uses of triasulfuron that should result in residues in potable water or fish. Based on very conservative assumptions, EFED modeling results indicated that low concentrations (< 2 ppb) could occur in surface water or groundwater. However, these concentrations are not expected to pose a health risk to humans. The label prohibits applying Amber through irrigation systems.

(m) Food Handling

Not applicable; there are no food handling uses for triasulfuron.

(n) Confined/Field Accumulation in Rotational Crops

Confined crop rotation studies were submitted in conjunction with PP#8F3658 and were reviewed by EFGWB/EFED (S. Termes, memos of 2/27/90 and 6/10/91). Soil was treated with phenyl- and triazine-labeled triasulfuron at a rate of 0.864 oz ai/A (1.4X yearly max/A). Lettuce, sugar beets, soybeans, barley, and corn were planted 109 days later. The total radioactive residue was <0.01 ppm in all mature plant parts at harvest. Since the trials representing an emergency plantback (i.e., 30 days) were not performed, the label directions for Amber must specify that the plantback interval for crops on which triasulfuron is not registered should be at least 4 months. [Excerpted from 2/18/94 memo, G. Kramer.] Such a restriction is on the Amber draft label. No additional data are needed to support this petition.

(o) International Harmonization

Not applicable; there are no CODEX, Canadian, or Mexican maximum residue limits for residues of triasulfuron.

(2) Dietary Exposure (Drinking Water Source)

No monitoring data are available to perform a quantitative drinking water risk assessment for triasulfuron at this time. However, the Environmental Fate and Effects Division (EFED) provided a Tier I drinking water assessment (EFED memo from James Lin May 11-1998, see Attachment 1). This assessment utilized the GENEEC and SCI-GROW screening models to provide estimates of ground and surface water contamination from triasulfuron, but did not consider the behavior of degradates. Limitations and assumptions for these screening models are documented in EFED memoranda.

(i) **Ground Water**

Using available fate parameters and assuming an annual application rate of 0.039 lb ai/acre, the estimated groundwater concentration from triasulfuron using SCI-GROW was 0.187 µg/L. The current label application rate allows for a total of 0.039 lb ai/acre per year, as follows: one application of 0.013 lbs ai/acre postemergence, followed by a second application not more than 60 days later at up to 0.026 lbs ai/acre, depending on the weed species to be controlled.

The SCI-GROW model (Screening Concentrations in Ground Water) is a screening model used to estimate concentrations of a pesticide in ground water under "worst case" conditions. The SCI-GROW model is based on scaled groundwater concentration from ground water monitoring studies, environmental fate properties (aerobic soil metabolism half-lives and sorption coefficients) and application rates. The current version of SCI-GROW appears to provide realistic estimates of pesticide concentrations in shallow, highly vulnerable groundwater (i.e., sites with sandy soils and depth to groundwater of 10 to 20 feet).

(ii) **Surface Water**

GENEEC (Generic Estimated Environmental Concentration) is a screening model used in Tier I (generic high runoff site) to estimate pesticide concentrations found in surface water up to 56 days. GENEEC is a single runoff event model, but accounts for spray drift from multiple applications. GENEEC represents a 10-hectare field immediately adjacent to a 1-hectare pond that is 2-meter deep with no outlet. The pond receives a pesticide load from spray drift for each application plus what runs off in one rainfall event, usually two days after the last application. The runoff event transports a maximum of 10% of the pesticide remaining in the top 2.5 cm of soil. This amount can be reduced through soil adsorption. The amount of pesticide remaining on the field in the top 2.5 cm of soil depends on the application rate, number of applications, interval between applications, incorporation depth, and degradation rate in soil. Spray drift is determined by method of applications (5% drift for aerial spray and airblast, 1% for ground spray, no drift for soil incorporation). The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to triasulfuron use. Thus, the GENEEC model predicts that triasulfuron surface water concentrations range from a peak of 1.75 µg/L to a 56 day average of 1.68 µg/L (EFED memo from James Lin of May 11, 1998).

(3) Risk from Food Sources

(a) Acute Dietary Risk

An acute dietary risk assessment is not required because no acute toxicological endpoints were identified for triasulfuron.

(b) Chronic, Non-Carcinogenic Dietary (Food) Risk

HED's Dietary Risk Exposure System (DRES) was used for conducting a chronic dietary (food only) exposure analysis (risk assessment). The analysis (appended as Attachment 2) evaluates individual food consumption, as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey, and accumulates exposure to the chemical for each commodity.

In conducting this chronic dietary (food) risk assessment, HED has made very conservative assumptions: that all commodities having triasulfuron tolerances will contain residues of triasulfuron and those residues will be at the level of the tolerance. This results in an overestimate of human dietary exposure.

Using the assumptions and data parameters described above, the DRES exposure analysis results in an anticipated residue contribution (exposure) that is equivalent to the following percentages of the RfD:

Population Subgroup	$TMRC_{food}$ (mg/kg/day)	%RfD
U.S. Population (48 states)	0.00046	4.6%
Nursing Infants (<1 year old)	0.00040	4.0%
Non-Nursing Infants (<1 year old)	0.0015	15%
Children (1-6 years old)	0.0011	11%
Children (7-12 years old)	0.00073	7.3%
Females (13-19 years old, not preg. or nursing)	0.00040	4.0%
Hispanics	0.00056	5.6%
Non-Hispanic others	0.00050	5.0%
Males (13-19 years old)	0.00052	5.2%

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; (3) the female subgroup; (4) hispanics; (5) non-hispanic others; and (6) males with the highest percentage of the RfD occupied. If the percent RfD for the U.S. population is rounded to 5%, there are no remaining subgroups beyond those listed above with a percentage of the RfD occupied that is greater than that occupied by the subgroup U.S. population (48 states).

(c) Chronic Carcinogenic Risk

In 1991, the HED RfD Peer Review Committee classified triasulfuron forms as a "Group E - Evidence of non-carcinogenicity for humans." Therefore, a carcinogenic risk assessment is not required.

(4) Combined Dietary Risk from Food and Water Sources

(a) Acute Risk

Because no acute dietary endpoint was determined (HIARC, 6/30/98), an acute water and dietary exposure risk assessment is not required.

(b) Chronic Risk

Based on the chronic dietary (food) exposure and using default body weights and water consumption figures, chronic drinking water levels of concern (DWLOC) for drinking water were calculated. To calculate the DWLOC, the chronic dietary food exposure was subtracted from the RfD.

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [RfD - (chronic food + residential exposure) (mg/kg/day)]

The Agency's default body weights and water consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male), 60 kg/2L (adult female), and 10 kg/1L (child). The results are summarized the Table below:

Population Subgroup[1]	Chronic Scenario					
	RfD mg/kg/day	Food Exposure mg/kg/day	Maximum Water Exposure mg/kg/day[2]	SCI-GROW (μg/L)[3]	GENEEC (ppb)	DWLOC (μg/L)
U.S. Population	0.01	0.00046	0.0095	0.187	1.68	334
Females (13-19 years, not pregnant or nursing)	0.01	0.00090	0.0091	0.187	1.68	273
Hispanic	0.01	0.00056	0.0094	0.187	1.68	329
Non-Nursing Infants (< 1yr old)	0.01	0.0015	0.0085	0.187	1.68	85

[1]Population subgroups chosen were U.S. population (70 kg. body weight assumed), the female subgroup with the highest food exposure (60 kg. body weight assumed), the hispanic subgroup (70 kg body weight assumed) which has higher dietary exposure than the U.S. population, and the infant/child subgroup with the highest food exposure (10 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = RfD (mg/kg/day) - TMRC from DRES (mg/kg/day)
[3]The crop producing the highest level was used.

For the most highly exposed populations subgroup, non-nursing infants (< 1 year old), chronic dietary (food only) exposure occupies 15% of the RfD. This is a conservative risk estimate for reasons described above. The chronic DWLOC for the non-nursing infants (< 1 year old) subgroup is 85 ppb. The predicted 56-day average surface water concentration by the GENEEC model is 1.68 μg/L (ppb) and the estimated ground water concentration by the SCI-GROW model is 0.19 μg/L (ppb). Therefore, exposure from water is below HED's DWLOC for chronic dietary exposure for ~~any~~ all of the populations examined.

d. Data Requirements

(1) Occupational/Residential Data

None

(2) Residue Chemistry Data

There are no data gaps to be resolved for this petition in the areas of product or residue chemistry.

(3) Toxicology Data

None

e. Food Quality Protection Act Considerations

(1) Cumulative Risk

Triasulfuron is a sulfonylurea herbicide. Other herbicides in this class include halosulfuron, ethametsulfuron, rimsulfuron and chlorsulfuron.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve

the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether triasulfuron has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of these tolerance actions, therefore, EPA has not assumed that triasulfuron has a common mechanism of toxicity with other substances.

(2) Aggregate Exposure and Risk Assessment/Characterization

(a) Acute Aggregate Risk

Because no acute dietary endpoint was determined (HIARC, 6/30/98), an acute aggregate risk assessment is not required.

(b) Short and Intermediate Term Aggregate Risk

There are no residential uses. An aggregate risk assessment for short and intermediate term endpoints is not required for residential use.

(c) Chronic Aggregate Risk

HED concludes that chronic exposure to triasulfuron from food will utilize ≤5% of the RfD for the U.S. population and <6% for all other groups except for non-nursing infants <1 year old (15%), children 1-6 years old (11%), and children 7-12 years old (7.3%). The DWLOC's are 334 μg/L for the U.S. population, 273 μg/L for females 13-19 years old (not pregnant or nursing) and 85 μg/L for non-nursing infants <1 year old. Under the current HED criteria, the registered uses of triasulfuron do not constitute a chronic residential exposure. Therefore, HED concludes that there is reasonable certainty that no harm will result to either adults or children from chronic aggregate exposure to triasulfuron residues.

(d) Aggregate Risk for Cancer

In 1991, the HED RfD Review Committee classified triasulfuron as a "Group E - Evidence of non-carcinogenicity for humans." Therefore, a carcinogenic risk assessment is not required.

(3) Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

(4) Special Sensitivity of Infants and Children

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to triasulfuron. In the prenatal developmental toxicity study in rats, developmental toxicity was seen only in the presence of maternal toxicity. In the developmental toxicity study in rabbits, no evidence of developmental toxicity was seen, even in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels that resulted in evidence of parental toxicity. In addition, there is no indication that triasulfuron is a neurotoxic herbicide.

IV. RISK MANAGEMENT AND REREGISTRATION DECISION

Not applicable

V. ACTIONS REQUIRED BY REGISTRANTS

None.

Attachment I: EFED memo from James Lin, 5/11/98
Attachment II: Chronic DRES Run: William Cutchin, 6/11/98
Attachment III: Report of the Hazard Identification Assessment Review Committee, June 30, 1998.
Attachment IV: Report of the FQPA Safety Factor Committee. (July 1, 1998)

cc: (with All Attachments): RAB2 Reading file, Debbie Smegal, Pamela Hurley, Maxie Jo Nelson, Margarita Collantes
RDI: RAB2: //98

MAY 11 1998

PC Code 128969

MEMORANDUM

SUBJECT: Tier 1 Drinking Water Assessment for Triasulfuron with GENEEC and SCI-GROW. PC Code: 128969; DP BARCODE: D245874

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Daniel Rieder 5/11/98
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DATE: May 11, 1998

The Environmental Fate and Effects Division (EFED) has been requested to generate a Tier 1 Drinking Water Assessment for triasulfuron. This memo provides a Tier 1 drinking water assessment for this chemical. The degradates were not considered in this Tier 1 assessment. Currently, Tier 1 drinking water assessments use the EFED Screening Models - GENEEC for surface water estimations and SCI-GROW for ground water estimations.

GENEEC (Generic Estimated Environmental Concentration) is a screening model used in Tier 1 (generic high runoff site) to estimate pesticide concentrations found in surface water up to 56 days. It provides an upper-bound concentration value. GENEEC is a single runoff event model,

but accounts for spray drift from multiple applications. GENEEC represents a 10-hectare field immediately adjacent to a 1-hectare pond that is 2-meter deep with no outlet. The pond receives a pesticide load from spray drift for each application plus what runs off in one rainfall event, usually two days after the last application. The runoff event transports a maximum of 10% of the pesticide remaining in the top 2.5-cm of soil. This amount can be reduced through soil adsorption. The amount of pesticide remaining on the field in the top 2.5-cm of soil depends on the application rate, number of applications, interval between applications, incorporation depth, and degradation rate in soil. Spray drift is determined by method of application (5% drift for aerial spray and airblast, 1% for ground spray, no drift for soil incorporation).

The SCI-GROW model (Screening Concentrations in Ground Water) is a screening model used to estimate concentrations of pesticides in ground water under "worst case" conditions. The SCI-GROW model is based on scaled ground water concentration from ground water monitoring studies, environmental fate properties (aerobic soil metabolism half-lives and sorption coefficients) and application rates. The current version of SCI-GROW appears provide realistic estimates of pesticide concentrations in shallow, highly vulnerable groundwater (i.e., sites with sandy soils and depth to groundwater of 10 to 20 feet).

Environmental Fate

The environmental fate data for triasulfuron used in GENEEC and SCI-GROW are summarized below:

Parameter	Input	Rationale for Selection	Source
Aerobic Soil Metabolism $t_{1/2}$	181.46 days	15 weeks and 9.5 weeks (upper 90% bound half-life is 181.46 days)	MRID 40493901
K_{oc}	69.3 ml/g	median value (51.61, 65.18, 73.37 and 190.60)	MRID 41656207
Solubility in H2O	1500 ppm	@ pH 7	
Aqueous Photolysis $t_{1/2}$	145.7 days	@ pH 9 (87 days vs. dark control of 216 days)	
Hydrolysis (pH 7) $t_{1/2}$	3.1 years	@ pH 7	MRID 40271921
Aerobic Aquatic Metabolism $t_{1/2}$	not considered	no data	

Proposed Use Label

The formulation Amber® contains 75% of active ingredient - triasulfuron. The proposed use is to control various weeds on pasture grasses. Either ground or aerial spray equipment can be used. Triasulfuron can be applied postemergence at the standard rate of 5.95 g ai/ac or enhanced rate of 11.9 ai/ac. The maximum amount of triasulfuron which can be applied in a calendar year is 17.86 g ai/ac.

Drinking Water Assessment

Using the fate properties and the use rate discussed previously, GENEEC was used to estimate the drinking water concentrations from surface water and SCI-GROW was used to estimate the drinking water concentration from ground water. Concentration estimated were based on the maximum application rate.

GENEEC Results

Based on (1) an aerobic soil metabolism half-life input of 181.46 days, (2) a median soil organic carbon sorption coefficient of 69.28 ml/g, (3) a water solubility of 1500 mg/L, (4) no aerobic aquatic metabolism half-life, (5) a water photolysis half-life at pH 9 of 145.7 days, (6) a hydrolysis half-life at pH 7 of 1131.5 days, and (7) aerial application with the total rate of 0.0394 lb ai/ac, the estimated surface water concentrations are 1.75, 1.75, 1.72, and 1.68 ug/L, respectively for peak, 4-day average, 21-day average, and 56-day average. The GENEEC outputs are listed in Table 1.

SCI-GROW Results

Based on (1) an aerobic soil metabolism half-life input of 181.46 days, (2) a median soil organic carbon sorption coefficient of 69.275 ml/g, and (3) an annual application rate of 0.0394 lb/ac, the estimated ground water concentration is 0.187 ug/L. The SCI-GROW outputs are listed in Table 2.

Table 1. GENEEC Output for Triasulfuron Use on Pasture Grasses

RUN No. 1 FOR Triasulfuron INPUT VALUES

RATE (#/AC) ONE(MULT)		APPLICATIONS NO.-INTERVAL		SOIL KOC	SOLUBILITY (PPM)	% SPRAY DRIFT	INCORP DEPTH(IN)
.039	(.039)	1	1	69.3	1500.0	5.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
181.46	2	1131.50	145.70-17877.39	.00	1064.15

GENERIC EECs (IN PPB)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
1.75	1.75	1.72	1.68

Table 2. SCI-GROW Output for Triasulfuron Use on Pasture Grasses

RUN No. 1 FOR triasulfuron on grass INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL AEROBIC METABOLISM (DAYS)
.039	1	.039	69.3	181.5

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

.187244

A= 176.460 B= 74.275 C= 2.247 D= 1.871 RILP= 4.783
F= .677 G= 4.752 URATE= .039 GWSC= .187244

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Triasulfuron (Amber) Caswell #861C CAS No. 82097-50-5 A.I. CODE: 128969 CFR No. 180.459	2yr feeding- mouse NOEL= 1.2000 mg/kg 10.00 ppm LEL= 12.9000 mg/kg 1000.00 ppm ONCO: E (HED)	Centrilobular hepatocyto-megaly in males. No evidence of carcinog-enicity in rats or mice.	PADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.010000	Chronic feed/carcino- rat (Current study maybe up-graded).	HED reviewed 04/11/90 EPA verified 08/22/90 RfD/PR reviewed 02/12/91 On IRIS.

POPULATION SUBGROUP	TOTAL TMRC (MG/KG BODY WEIGHT/DAY) CURRENT TMRC*	NEW TMRC**	NEW TMRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC	%RFD
U.S. POPULATION - 48 STATES	0.000463	0.000463	4.634160	0.000000		
U.S. POPULATION - SPRING SEASON	0.000446	0.000446	4.464090	0.000000		
U.S. POPULATION - SUMMER SEASON	0.000464	0.000464	4.637020	0.000000		
U.S. POPULATION - FALL SEASON	0.000477	0.000477	4.771280	0.000000		
U.S. POPULATION - WINTER SEASON	0.000466	0.000466	4.664930	0.000000		
NORTHEAST REGION	0.000475	0.000475	4.747400	0.000000		
NORTH CENTRAL REGION	0.000484	0.000484	4.841970	0.000000		
SOUTHREN REGION	0.000425	0.000425	4.250980	0.000000		
WESTERN REGION	0.000484	0.000484	4.842150	0.000000		
HISPANICS	0.000564	0.000564	5.636580	0.000000		
NON-HISPANIC WHITES	0.000461	0.000461	4.606560	0.000000		
NON-HISPANIC BLACKS	0.000429	0.000429	4.293060	0.000000		
NON-HISPANIC OTHERS	0.000504	0.000504	5.040920	0.000000		
NURSING INFANTS (< 1 YEAR OLD)	0.000398	0.000398	3.978770	0.000000		
NON-NURSING INFANTS (< 1 YEAR OLD)	0.001543	0.001543	15.434480	0.000000		
FEMALES (13+ YEARS, PREGNANT)	0.000332	0.000332	3.317490	0.000000		
FEMALES 13+ YEARS, NURSING	0.000383	0.000383	3.828220	0.000000		
CHILDREN (1-6 YEARS OLD)	0.001091	0.001091	10.910720	0.000000		
CHILDREN (7-12 YEARS OLD)	0.000734	0.000734	7.341720	0.000000		
MALES (13-19 YEARS OLD)	0.000516	0.000516	5.158230	0.000000		
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000397	0.000397	3.974900	0.000000		
MALES (20 YEARS AND OLDER)	0.000346	0.000346	3.462570	0.000000		
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000283	0.000283	2.834370	0.000000		

*Current TMRC does not include new or pending tolerances.
**New TMRC includes new, pending, and published tolerances.

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Triasulfuron (Amber) Caswell #861C CAS No. 82097-50-5 A.I. CODE: 128969 CFR No. 180.459	2yr feeding- mouse NOEL= 1.2000 mg/kg 10.00 ppm LEL= 12.9000 mg/kg 1000.00 ppm ONCO: E (HED)	Centrilobular hepatocyto-megaly in males. No evidence of carcinog-enicity in rats or mice.	PADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.010000	Chronic feed/carcino- rat (Current study maybe up-graded).	HED reviewed 04/11/90 EPA verified 08/22/90 RfD/PR reviewed 02/12/91 On IRIS.

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
24001AA	BARLEY	8F3658			0.020000
24007AA	WHEAT-ROUGH	8F3658			0.020000
24007GA	WHEAT-GERM	8F3658			0.020000
24007HA	WHEAT-BRAN	8F3658			0.020000
24007WA	WHEAT-FLOUR	8F3658			0.020000
50000DB	MILK-NON-FAT SOLIDS	8F3658			0.020000
50000FA	MILK-FAT SOLIDS	8F3658			0.020000
50000SA	MILK SUGAR (LACTOSE)	8F3658			0.020000
53001BA	BEEF-MEAT BYPRODUCTS	8F3658			0.100000
53001BB	BEEF(ORGAN MEATS)-OTHER	8F3658			0.100000
53001DA	BEEF-DRIED	8F3658			0.100000
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	8F3658			0.100000
53001KA	BEEF(ORGAN MEATS)-KIDNEY	3F4225			0.500000
53001LA	BEEF(ORGAN MEATS)-LIVER	8F3658			0.100000
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658			0.100000
53002BA	GOAT-MEAT BYPRODUCTS	8F3658			0.100000
53002BB	GOAT(ORGAN MEATS)-OTHER	8F3658			0.100000
53002FA	GOAT(BONELESS)-FAT	8F3658			0.100000
53002KA	GOAT(ORGAN MEATS)-KIDNEY	3F4225			0.500000
53002LA	GOAT(ORGAN MEATS)-LIVER	8F3658			0.100000
53002MA	GOAT(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658			0.100000
53003AA	HORSE	3F4225			0.500000
53005BA	SHEEP-MEAT BYPRODUCTS	8F3658			0.100000
53005BB	SHEEP(ORGAN MEATS)-OTHER	8F3658			0.100000
53005FA	SHEEP(BONELESS)-FAT	8F3658			0.100000
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	3F4225			0.500000
53005LA	SHEEP(ORGAN MEATS)-LIVER	8F3658			0.100000
53005MA	SHEEP(BONELESS)-LEAN (W/O REMOVEABLE FAT	8F3658			0.100000
53006BA	PORK-MEAT BYPRODUCTS	8F3658			0.100000
53006BB	PORK(ORGAN MEATS)-OTHER	8F3658			0.100000
53006FA	PORK(BONELESS)-FAT (INCLUDING LARD)	8F3658			0.100000
53006KA	PORK(ORGAN MEATS)-KIDNEY	3F4225			0.500000
53006LA	PORK(ORGAN MEATS)-LIVER	8F3658			0.100000
53006MA	PORK(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658			0.100000

012651

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

DATE: **June 30, 1998**

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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

FROM: Deborah Smegal, Toxicologist Deborah Smegal 6/30/98
Toxicology Branch II
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary Jess Rowland 6/30/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, Jess Rowland for KCS 6/30/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Pam Hurley, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128969

On June 11, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Triasulfuron,** re-assessed the Reference Dose (RfD) established in 1991 and selected or attempted to select the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to **Triasulfuron** as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Clark Swentzel, Bill Burnam, Karl Baetcke, Sue Makris, Bob Fricke, and Melba Morrow. Member(s) in absentia: Mike Metzger, Karen Hamernik and John Redden. Data were presented by Debbie Smegal of Toxicology Branch II.

Also in attendance were Steven Dapson, Margarita Collantes, and Maxie Jo Nelson.

Data Presentation:
and
Report Presentation

Deborah Smegal.
Toxicologist

Report Concurrence:

Jess Rowland
Executive Secretary

I. INTRODUCTION

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: None §

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: No appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies including the developmental toxicity studies.

This Risk Assessment is NOT required.

B. Chronic RfD The RfD established in 1991 and available on IRIS was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Study Selected: Two-Year Mouse Feeding Carcinogenicity Study § 83-2

MRID No.: 40728316

Executive Summary:

In a carcinogenicity study, male and female CD-1 albino mice [50/sex/dose] were fed diets containing triasulfuron (93.7-96.5%) at 0, 10, 1000, 5000 or 10,000 ppm (Males: 0, 1.2, 129, 619.6 or 1301.3 mg/kg/day, respectively; Females: 0, 1.5, 157.5, 792.5, or 1473.5 mg/kg/day, respectively) for up to 24 months. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, organ weights, and gross and histological changes. In addition, mice were palpated weekly for tissue masses.

There were no treatment-related effects on mortality, clinical observations, organ weights, water consumption, hematology parameters, ophthalmic findings, or clinical chemistry parameters. In males and females receiving 5,000 or 10,000 ppm, mean body weight and/or body weight gain were marginally depressed below control values (not statistically significant except for females at 2 and 5 weeks in the 10,000 ppm group and at 81 weeks in the 5,000 ppm group); this was accompanied by a decreased food consumption in females. There was a noticeable decrease in food consumption in females at dietary levels of 5,000 and 10,000 ppm during the early phase of the study. These findings were not considered to be of toxicologic importance. Centrilobular hepatocytomegaly was observed in male mice receiving 1,000, 5,000, or 10,000 ppm (significant,

$p<0.01$) and in females receiving 10,000 ppm (significant, $p<0.05$). Increased centrilobular degeneration, focal accumulation of inflammatory cells, microgranulomas, and pigment depositions were also observed in the liver of 10,000 ppm males.

The incidence of alveolar/bronchiolar adenoma in the lung was statistically increased ($p<0.05$) in male mice fed 10,000 ppm (28%) when compared to the controls (12%), but the combined incidence of alveolar/bronchiolar adenoma and carcinoma was not significantly different. Female mice exhibited a negative trend for lung adenomas. The histologic importance of the increased incidence of lung adenomas in males is equivocal because of variability of tumors (12, 22, 22, 12 and 28% in the 0, 10, 1,000, 5,000, 10,000 ppm groups, respectively) and the lack of a dose-response. Furthermore, the reported laboratory control incidence (38%) and that found in other laboratories is considerably higher than the concurrent control incidence (12%). No other neoplastic lesions were considered to be of biological importance. **The chronic LOEL is 1000 ppm (129 mg/kg/day) based upon centrilobular hepatocytomegaly in males. The NOEL is 10 ppm (1.2 mg/kg/day).**

Dose and Endpoint for Establishing RfD: NOEL of 1.2 mg/kg/day based on a statistically significant increased incidence in centrilobular hepatocytomegaly in males at 129 mg/kg/day (LOEL) which was dose-related.

Uncertainty Factor(s): 100 (10 x for inter-species extrapolation and 10 x for intra-species variation).

$$\textbf{Chronic RfD} = \frac{1.2 \text{ mg/kg/day}}{(100)} = \textbf{0.01 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: HIARC concurred with the dose, endpoint and the Uncertainty Factor selected by the RfD Committee in deriving the RfD. The database is essentially complete. The chronic mouse study has the most sensitive endpoint (liver effects). The most sensitive toxicological finding in dogs is prostate cystic hyperplasia (25 mg/kg/day) and in rats is decreased body weight and body weight gain (220.8 mg/kg/day). Developmental and reproductive effects were not observed until higher doses (250-900 mg/kg/day), which were maternally toxic.

This risk assessment is required.

C. Occupational/Residential Exposure

There are no registered residential uses at the present time. Therefore, the following risk assessments are applicable only for occupational exposures.

1. Dermal Absorption

No dermal absorption studies are available. The only studies that could be compared are the 21 day dermal toxicity and the oral developmental toxicity studies in rabbits. However, similar toxicological endpoints were not observed in these studies. Following oral administration to pregnant rabbits, Trisulfuron decreased maternal body weight gains and following repeated dermal application the test material caused ruffled fur and dyspnea. Since a common endpoint was not observed in the same species via the two different routes, a dermal absorption factor could not be estimated. Therefore, HIARC recommended a dermal absorption factor of 100% (default) value.

Dermal Absorption Factor: 100% (default)

2. Short-Term Dermal - (1-7 days)

Study Selected: Developmental Rat Study § 83-3

MRID No.: 40271948

Executive Summary: In a developmental toxicity study Triasulfuron 94.5% a.i. was administered to 24 Tif: RAIF (SPF) pregnant female rats/dose by gavage at dose levels of 0, 100, 300 or 900 mg/kg from days 6 through 15 of gestation, inclusive.

Mean body weight and, body weight gain and food consumption were significantly reduced in the 300 and 900 mg/kg dose groups during the treatment period. At 900 mg/kg, two dams had deciduomata that was seen only at the high dose and could, therefore be treatment-related. There were no treatment-related effects in mortality, or clinical signs. In addition, there were no statistically significant differences or trends in the pregnancy rate, the number of pregnant dams that aborted, number of implantation sites, live fetuses/dam, resorptions/dam, dead fetuses/dam, dead implants/dam, or in post-implantation loss, total live fetuses, litter size, fetal viability or sex ratio. **The maternal LOEL is 300 mg/kg, based on decreased body weight (↓ 3%) and body weight gain(↓ 16% on days 6-16) during gestation. The maternal NOEL is 100 mg/kg.**

Male and female fetal body weights were significantly reduced at the 900 mg/kg dose level compared to controls. There were no treatment-related gross or visceral abnormalities in the fetuses. The number of fetuses with unossified vertebrae, metatarsals, and phalanges was significantly increased in the 900 mg/kg dose group relative to historical controls. **The developmental LOEL is 900 mg/kg based on reduced ossification of vertebrae, metatarsals and phalanges. The developmental NOEL is 300 mg/kg.**

Dose and Endpoint for Risk Assessment: Maternal NOEL of 100 mg/kg/day based on maternal toxicity as evidenced by statistically decreased body weight (↓ 3%) and body weight gain (↓ 16%) in pregnant female rats at 300 mg/kg/day (LOEL).

Comments about Study/Endpoint: The oral (maternal) NOEL of 100 mg/kg/day selected is supported by a similar NOEL (100 mg/kg/day) that can be established for the 1-7 day exposure period in the 21-day dermal toxicity study in New Zealand white rabbits. In that study, repeated dermal application of Trisulfuron (94.5%) in 0.5% carboxymethylcellulose and 0.1% polysorbate 80 at doses of 0, 10, 100 or 1000 mg/kg/day, 6 hours/day for 21 days did not result in any treatment-related effects on survival, dermal irritation, body weight, food consumption, clinical pathology, organ weight, gross pathology or histopathology. However, rabbits at all dose levels exhibited clinical signs characterized as ruffled fur and/or dyspnea at various time intervals during the study. At 10 mg/kg/day, 1 of 5 females exhibited dyspnea on days 11, 12 and 13 and ruffled fur on days 11 through 15.; these effects were not observed in males. At 100 mg/kg/day, 1/5 males exhibited dyspnea on days 5 through 21; no effects were seen in females until day 9. Rabbits at 1000 mg/kg/day exhibited increased incidences as well as earlier onset of these symptoms. Thus, due to the minimal and transient effect seen only in one sex (males), the 100 mg/kg/day dose can be established as the NOEL for these effects for the exposure period of concern (i.e., 1-7 days).

The Committee decided not to use the 21-day dermal toxicity study for this risk assessment because: 1) of the low confidence in the clinical signs (ruffled fur and dyspnea) observed in this study in conjunction with the low toxicity profile via the dermal route for the sulfonylurea compounds; 2) these types of clinical signs are not relevant for human risk assessment since they can occur in stressed laboratory conditions (i.e., may have been due to the impermeable dressing that were fastened tighter in treated groups to prevent loss of test material); and 3) of the questionable biological significance of these effects in the absence of other signs at the same dose levels. Therefore, the dose and endpoints observed in this study was not considered to be appropriate for use in regulatory decision making or risk assessments.

Since an oral NOEL was selected for this risk assessment, a dermal absorption factor of 100% (default) should be used in risk assessments.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 13-Week Rat Dietary Study § 82-1

MRID No.:40271947

Executive Summary: In a 90-day subchronic toxicity study, triasulfuron (94.5%) was administered to male and female Sprague-Dawley Crl:COB CD(SD)BR strain rats [10/sex/dose] in the diet at dose levels of 0, 200, 10,000, or 20,000 ppm (0, 10, 500, or 1,000 mg/kg/day, respectively). In addition, 5/sex in the control and high-dose groups were sacrificed

after a 4 week recovery period. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, hematology, clinical chemistry parameters, urinalysis, indirect ophthalmoscopy, organ weights, and gross and histological changes.

Rats of both sexes in the mid and high dose groups weighed significantly less (17-25% for males and 19-22% for females) and ate significantly less (10-16% for males and 14-18% for females) than controls. Hematuria, which appeared to be treatment-related, was noted in both sexes (3/5 high dose males, and 1/10 and 10/15 mid- and high-dose females, respectively). Dose-related histopathologic changes were noted in the kidney of females (atrophy and epithelial hyperplasia), but not males, which were statistically significant in the 20,000 ppm dose group. In addition, basophilia (5/10) and chronic lymphocytic inflammation (6/10) were also statistically increased in high-dose females. Renal and urinary bladder calculi were observed in 3/10 and 8/10 females in the mid- and high-dose groups, respectively (significance not reported). Significant hematological and clinical chemistry findings in females include: increased neutrophils, creatinine, and phosphorus in the 10,000 ppm group, increased neutrophils, white blood cells, platelets, BUN, creatinine, and phosphorus, and decreased red blood cells, hematocrit, protein, albumin, urinary pH and bilirubin in the 20,000 ppm group. In males, significant findings include: decreased protein, bilirubin, potassium, calcium, urinary protein and ketones in the 10,000 ppm group, decreased neutrophils, monocytes, protein, bilirubin, potassium, calcium, BUN, LDH, SGOT, urinary pH, protein and ketone levels, and increased lymphocytes, creatinine, phosphorus and A/G ratio in the 20,000 ppm group. Significant findings in the 20,000 ppm recovery group include: decreased protein, cholesterol, BUN, chloride, glucose, and A/G ratio (females) and increased phosphorus (males). While many of these changes are statistically elevated and consistent with kidney damage, most of these parameters are within control ranges for rats.

A number of statistically significant changes in absolute and relative organ weights were observed. However, increases in relative organ weight may be a direct consequence of decreases in body weight. Significant changes in absolute organ weights in the 10,000 ppm group include: decreased heart weight (female), and decreased spleen and brain weights (male). Significant changes in the 20,000 ppm include: increased kidney weight (females), decreased heart weight (males and females), and decreased liver, spleen, heart and brain weights (males). The only significant absolute organ weight change in the 20,000 ppm recovery group was reduced kidney weight in males. **The subchronic LOEL is 10,000 ppm (500 mg/kg) based upon decreased body weight and decreased food intake in males and females and increased kidney atrophy and epithelial hyperplasia in females (not statistically significant until 20,000 ppm). The NOEL is 200 ppm (10 mg/kg/day).**

Dose/Endpoint for Risk Assessment: A NOEL of 10 mg/kg/day was selected based on significantly decreased body weight and food intake in both sexes at 500 mg/kg/day (LOEL).

Comments about Study/Endpoint: The oral NOEL of 10 mg/kg/day selected is supported by a similar NOEL (10 mg/kg/day) that can be established in the 21-day dermal toxicity study in rabbits. As discussed under Short-Term, no systemic toxicity was seen at the Limit-Dose (1000 mg/kg/day) but rabbits at all dose levels exhibited clinical signs characterized as ruffled fur and/or dyspnea at various time intervals during the study. At 10 mg/kg/day, 1 of 5 females exhibited dyspnea on days 11, 12 and 13 and ruffled fur on days 11 through 15; these effects were not observed in males. Since these effects were observed in only one sex, at a low frequency and were transient in nature, this dose (10 mg/kg/day) can be considered to be the NOEL for this exposure period of concern (i.e., 7 -days to several months).

The Committee selected the oral NOEL because this study (90-day) is appropriate for this exposure period of concern. In addition, the Committee determined that the 21-day dermal toxicity study is not appropriate for use because of the reasons discussed under Section II. Short-Term dermal risk assessment.

Since an oral NOEL was selected for this risk assessment, a dermal absorption factor of 100% (default) should be used in risk assessments.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None. §

MRID No.: None.

Executive Summary: None.

Dose and Endpoint for Risk Assessment: None.

Comments about Study/Endpoint:. Based on the current use pattern (i.e., 2 applications/year, and applied once every 3 year), there is minimal concern for potential Long-Term dermal exposure/risk.

This risk assessment is NOT required.

5. Inhalation Exposure

Short-and Intermediate-Term.

Except for an acute inhalation toxicity study, for which triasulfuron is placed in Toxicity Category IV (LC_{50} = >2.0 mg/L), no other studies are available via this route. Therefore, the HIARC selected the oral NOELs of 100 mg/kg/day for Short-Term and 10 mg/kg/day for intermediate-Term inhalation risk assessments. These doses were used in respective dermal risk assessments. Since the doses identified for inhalation risk assessments are from oral studies route-to-route extrapolation should be as follows

Step I. The inhalation exposure component (i.e., µg a.i/day) using a 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 100% dermal absorption factor and application rate should be converted to an **equivalent oral dose.** This dose should then be combined with the converted oral dose in Step I.

Step III To calculate the MOE's, the combined dose from Step II should then be compared to the oral NOEL of 100 mg/kg/day for Short-Term exposure and to the oral NOEL of 10 mg/kg/day for Intermediate-Term exposures.

Based on the use pattern, Long-Term inhalation exposure risk assessment is not required.

This risk assessment is required.

D. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

Since there are no registered residential uses at the present time, aggregate exposure risk assessement will be limited to Food + Water only.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational (dermal and inhalation) exposure risks. There are no registered residential uses at the present time, therefore, a MOE is not required for residential exposures.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 40728318 and 41585802 (supplemental information)

Discussion of Tumor Data. No significant increased in tumors were observed. A dose-related increased incidence in gross lesions (tissue masses) did not correlate with any histological lesion.

Adequacy of the Dose Levels Tested. The dose levels were adequate based on significant decreases in mean body weight throughout the study and in body weight gain in both sexes at weeks 13 and 103 in the highest dose group.

2. Carcinogenicity Study in Mice

MRID No. 40728316

Discussion of Tumor Data. The incidence of alveolar/bronchiolar adenoma in the lung was statistically increased ($p<0.05$) in male mice fed 10,000 ppm (28%) when compared to the controls (12%), but the combined incidence of alveolar/bronchiolar adenoma and carcinoma was not significantly different. Female mice exhibited a negative trend for lung adenomas. The histologic importance of the increased incidence of lung adenomas in males is equivocal because of variability of tumors (12, 22, 22, 12 and 28% in the 0, 10, 1,000, 5,000, 10,000 ppm groups, respectively) and the lack of a dose-response. Furthermore, the reported laboratory control incidence (38%) and that found in other laboratories is considerably higher than the concurrent control incidence (12%). No other neoplastic lesions were considered to be of biological importance.

Adequacy of the Dose Levels Tested The dose levels are adequate based on the observation of dose-related liver toxicity in males and females.

3. Classification of Carcinogenic Potential

In 1991, the HED RfD/Peer Review Committee classified Trisulfuron as a **Group E** Chemical (no evidence of carcinogenicity for humans) based on lack of evidence of carcinogenicity in mice and rats. The HIARC concurred with this classification.

IV. MUTAGENICITY

Triasulfuron is not mutagenic in bacteria, yeast, or mammalian cells. Triasulfuron was negative in the Ames assay at cytotoxic concentrations, was negative in the recombinant/conversion assay in *S. Cerevisiae* D7, failed to induce micronuclei and/or nuclear anomalies at concentrations up to 5000 mg/kg, and did not cause DNA damage/repair in rat cells at concentrations up to solubility limit. Furthermore, triasulfuron did not induce forward mutations in mouse lymphoma cells with and without metabolic activation.

V. FQPA CONSIDERATIONS

1. Neurotoxicity:

No neurotoxicity studies are available.

There is no evidence of neurotoxicity resulting from triasulfuron exposure except for significantly decreased mean absolute brain weights in Sprague Dawley male rats exposed to very high doses of 10,000 and 20,000 ppm (500 and 1,000 mg/kg/day, respectively) for 90 days. Mean decreases in brain weights were 2.1 ±.02 g for the mid- and high-dose groups versus 2.2 ±.02 g for the controls ($p=0.01$). At these dose levels, body weights were significantly decreased and the relative brain weights were significantly increased. There were no adverse histopathologic changes, and these effects were not noted in females. In addition, no adverse neurologic effects were noted in male Sprague Dawley rats chronically exposed to 6,000 ppm (220.8 mg/kg/day) triasulfuron for up to 2 years.

2. Developmental Toxicity

(I) Rat

In a developmental toxicity study Triasulfuron 94.5% a.i. was administered to 24 Tif: RAIF (SPF) pregnant female rats/dose by gavage at dose levels of 0, 100, 300 or 900 mg/kg from days 6 through 15 of gestation, inclusive.

Mean body weight, body weight gain and food consumption were significantly reduced in the 300 and 900 mg/kg dose groups during the treatment period. At 900 mg/kg, two dams had deciduomata that was seen only at the high dose and could, therefore be treatment-related. There were no treatment-related effects in mortality, or clinical signs. In addition, there were no statistically significant differences or trends in the pregnancy rate, the number of pregnant dams that aborted, number of implantation sites, live fetuses/dam, resorptions/dam, dead fetuses/dam, dead implants/dam, or in post-implantation loss, total live fetuses, litter size, fetal viability or sex ratio. **The maternal LOEL is 300 mg/kg, based on decreased body weight and body weight gain during gestation. The maternal NOEL is 100 mg/kg.**

Male and female fetal body weights were significantly reduced at the 900 mg/kg dose level compared to controls. There were no treatment-related gross or visceral abnormalities in the fetuses. The number of fetuses with unossified vertebrae, metatarsals, and phalanges was significantly increased in the 900 mg/kg dose group relative to historical controls. **The developmental LOEL is 900 mg/kg based on reduced ossification of vertebrae, metatarsals and phalanges. The developmental NOEL is 300 mg/kg.**

The developmental toxicity study in the rat is classified as acceptable Guideline and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; § 83-3 (a)) in rats when considered with the historical control data for rats.

(ii) Rabbit

In a developmental toxicity study Triasulfuron 94.5% a.i. was administered to 20 chinchilla pregnant female rabbits/dose by gavage at dose levels of 0, 40, 120, or 240 mg/kg from days 6 through 18 of gestation, inclusive.

There were no treatment-related effects on mean body weight, food consumption, mortality, or clinical signs. Body weight gain was significantly reduced in the does of the 240 mg/kg dose group from day 6 through 10 of gestation, and was statistically elevated in the does of the 120 mg/kg dose group over the entire study duration. There were no statistically significant differences or trends in the pregnancy rate, the number of pregnant dams that aborted, mean number of implantation sites/dam, live fetuses/dam, resorptions/dam, dead fetuses/dam, pre- or post-implantation loss, mean number of corpora lutea, implantation efficiency, litter size, fetal viability, sex ratio or mean body weights of pups by litter. **The maternal LOEL is 240 mg/kg, based on decreased body weight gain during gestation. The maternal NOEL is 120 mg/kg.**

In the fetuses, there were no treatment-related gross, visceral, or skeletal abnormalities. **The developmental NOEL is >240 mg/kg.**

The developmental toxicity study in the rabbit is classified as acceptable and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; § 83-3 (b)) in rabbits.

3. Reproductive Toxicity:

In the two generation reproduction study, effects in the offspring (decreased F1a pup weights at birth and during lactation) were observed only at or above treatment levels which resulted in evidence of parental toxicity (decreased premating and total body weight gain).

In a two-generation reproduction study, 30 Sprague-Dawley Rats per sex per dose received either 0, 10, 1000 or 5000 ppm (0, 0.5, 50, or 250 mg/kg/day, respectively) of technical Triasulfuron (purity not specified) in the diet. The F0 animals were mated on a one-to-one ratio and were

given test diets for 12 and 14 weeks before mating. Two matings were conducted for the first generation producing the F1a and F1b weanlings. The F1 parental animals were paired only once to produce an F2a generation.

Significant reductions in mean body weight and body weight gain were noted in parental animals. The mean body weights of the high-dose F1 males were significantly reduced at weeks 12 and 25, while total body weight gain was significantly reduced in high-dose F0 females and F1 males. In addition, premating weight gain was significantly reduced in F0 males exposed to 5000 ppm. There were no treatment-related effects on mortality, clinical signs, food consumption or gross or microscopic pathology. **The parental LOEL is 5000 ppm (250 mg/kg/day) based upon significant decreases in premating and total body weight gain for high-dose F0 and F1 parental animals. The parental NOEL is 1000 ppm (50 mg/kg/day).**

A significant decreasing trend in mean body weight of pups was noted for the F1a generation. Pup weights were significantly reduced in the high-dose F1a at birth, and in the mid- and high-dose pups on day 7 of lactation. There were no treatment-related effects on fertility, gestation length, number of pups born/litter, or offspring viability. **The reproductive toxicity LOEL is 5000 ppm (250 mg/kg/day) based on reduced F1a pup weights at birth and during lactation. The reproductive toxicity NOEL is 1000 (50 mg/kg/day).**

This reproductive study in the rat is classified as acceptable and does satisfy the guideline requirement for a reproductive toxicity study (§ 83-4) in rats.

4. Additional information from the literature (IF AVAILABLE)

No literature search was conducted for this chemical.

5. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits *in utero* and/or post natal exposure to triasulfuron. In the prenatal developmental toxicity study in rats, developmental toxicity was seen in the presence of maternal toxicity. In the developmental toxicity study in rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

In conclusion, there is no increased susceptibility for infants and children based on an adequate data base, no evidence of neurotoxicity, and the results from the developmental/reproductive toxicity studies

6. Recommendation for a Developmental Neurotoxicity Study

Based on the available data, the HIARC concluded that a developmental neurotoxicity study **is not required.**

i. Evidence that suggest requiring a developmental neurotoxicity study:

None.

ii. Evidence that **do not** support a need for a developmental neurotoxicity study:

There is no evidence from the developmental studies, or reproduction study that there would be potential for developmental neurotoxicity. Although, decreased absolute brain weight was noted in male rats exposed to high doses of triasulfuron (500 and 1000 mg/kg/day) for 90 days, the mean decreases were small, 2.1 ±.02 g for the mid- and high-dose groups, versus 2.2 ±.02 g for the controls. At these dose levels, body weights were significantly decreased and the relative brain weights were significantly increased. In addition, these findings were not supported by clinical signs or microscopic evidence of neurotoxicity, and were not observed in females. Furthermore, there was no evidence of neurotoxicity in rats or mice fed triasulfuron (up to 274 and 1,473 mg/kg/day, respectively) for 2 years or dogs fed triasulfuron (up to 125 mg/kg/day) for one year.

7. Determination of the FQPA Safety Factor:

The HIARC, based on hazard assessment alone, recommends to the FQPA Safety Committee, that the additional 10 x factor should be removed because:

(a) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(b) A two generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults.

© There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies. Neither brain weight nor histopathology (perfused or nonperfused) of the nervous system was affected in the subchronic or chronic toxicity studies.

(d) The toxicology database is complete and there are no data gaps. There is no evidence to require a developmental neurotoxicity study.

The final recommendation on the FQPA Safety Factor, however will be made during the risk characterization by the FQPA Safety Committee.

VI. HAZARD CHARACTERIZATION

The database is essentially complete and all of the toxicology studies are acceptable and satisfy the Subdivision F Hazard Evaluation Guidelines. An acute RfD was not derived because no appropriate endpoint attributable to a single dose was identified from oral toxicity studies including the developmental toxicity studies.

There is high confidence in the chronic RfD, which received agency-wide consensus and is available on IRIS. In the critical study, the dose spread is very large, i.e., NOEL of 10 ppm (1.2 mg/kg/day) and LOEL of 1,000 ppm (129 mg/kg/day) for liver effects (centrilobular hepatocytomegaly) in male mice, which is the most sensitive endpoint following chronic exposure. The most sensitive toxicological finding in dogs is prostate cystic hyperplasia (25 mg/kg/day) and in rats is decreased body weight and body weight gain (220.8 mg/kg/day) following chronic exposure.

The database is adequate and consists of developmental studies in the rat and rabbit, and a two generation rat reproduction study. There is no evidence that triasulfuron is neurotoxic, and no additional studies are required, including a developmental neurotoxicity study.

There is no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure in developmental studies. In the rat study, maternal toxicity (characterized by decreased body weight and body weight gain) was noted at 300 mg/kg/day, while developmental effects (reduced ossification of vertebrae, metatarsals, and phalanges) were not observed until 900 mg/kg/day (highest dose tested). In the rabbit study, no developmental toxicity was noted at 240 mg/kg/day (highest dose tested), which induced maternal toxicity (decreased body weight gain).

In the two generation reproduction study, effects in the offspring (decreased F1a pup weights at birth and during lactation) were observed only at or above treatment levels (250 mg/kg/day) which resulted in evidence of parental toxicity (decreased premating and total body weight gain). In conclusion, there is no increased susceptibility for infants and children based on an adequate data base, no evidence of neurotoxicity, and the results from the developmental/reproductive toxicity studies.

VII. DATA GAPS

The toxicology data base is complete for Triasulfuron; there are no data gaps.

VIII. ACUTE TOXICITY

Acute Toxicity of Triasulfuron				
Guideline No.	**Study Type**	**MRID**	**Results**	**Tox Category**
81-1	Acute Oral (Rat)	40271931 (95% tech); 40271930 (99% tech); 40271940 (75WP-B)	LD_{50} > 5 g/kg	IV
81-2	Acute Dermal (Rat)	40271932 (95% tech)	LD_{50} > 2 g/kg	III
81-2	Acute Dermal (Rabbit)	40271941 (75WP-B)	LD_{50} > 2 g/kg	III
81-3	Acute Inhalation (Rat)	40271933 (95% tech); 40271942 (75WP-B)	LC_{50} > 5.185 mg/L/4 hrs LC_{50} > 2.32 mg/L/4 hrs	IV
81-4	Primary Eye Irritation (Rabbit)	40271937 (96.5% tech); 40271943 (75WP-B)	mild conjunctival irritation that subsided by day 7 mild conjunctival irritation that subsided by day 4	III
81-5	Primary Skin Irritation	40271935 (96.5% tech); 40271944 (75WP-B)	very slight erythema and edema Negative	IV
81-6	Dermal Sensitization	40271938 (95% tech); 40271939 (96.5% tech); 40271945 (75WP-B)	Negative	
81-8	Acute Neurotoxicity	Not available		

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IX SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	None	An appropriate endpoint attributable to a single exposure (dose) was not identified from oral toxicity studies including the developmental toxicity studies in rats and rabbits	None
	This risk assessment is not required.		
Chronic Dietary	NOEL = 1.2	Centrilobular hepatomegaly in male mice	Carcinogenicity-Mice
	UF = 100	**Chronic RfD = 0.01 mg/kg/day**	
Short-Term [a] (Dermal)	Oral NOEL=100	Decreased body weight and body weight gains in maternal animals.	Developmental toxicity-Rat
Intermediate-Term (Dermal)	Oral NOEL=10	Decreased body weight and food intake in both sexes of rats.	Subchronic toxicity-Rat
Long-Term (Dermal)	None	Based on the current use pattern (2 applications/year, applied once every 3 years), there is minimal concern for potential Long-Term dermal exposure. Therefore, this risk assessment is not required	
Short Term [b] (Inhalation)	Oral NOEL=100	Decreased body weight and body weight gains in maternal animals.	Developmental toxicity-Rat
Intermediate Term (Inhalation)	Oral NOEL=10	Decreased body weight and food intake in both sexes of rats.	Subchronic toxicity-Rat
Long Term (Inhalation)	None	Based on the current use pattern (2 applications/year, applied once every 3 years), there is minimal concern for potential Long-Term inhalation exposure. Therefore, this risk assessment is not required	

a = Since an oral NOEL was selected, a dermal absorption factor of 100% (default value) should be used in route-to-route extrapolation.

b = Since an oral NOEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

HED DOC. NO. 012663

01-JULY-1998

MEMORANDUM

SUBJECT: ***TRIASULFURON*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Rick Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128969

The Health Effects Division (HED) FQPA Safety Factor Committee met on June 22, 1998 to evaluate the hazard and exposure data for Triasulfuron and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to this pesticide. The Committee recommended that the 10x Safety Factor for increased susceptibility of infants and children should be removed for this pesticide.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available studies **indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Triasulfuron.** In the prenatal developmental toxicity studies, developmental toxicity was seen at a dose higher than that which caused maternal toxicity in rats and no developmental toxicity was seen at the highest dose tested in rabbits. In the two-generation reproduction study in rats, effects in the offspring were observed atthe same dose that caused parental systemic toxicity (*Preliminary Report of the HIARC* provided by J. Rowland).

2. Adequacy of Toxicity Database

There are **no data gaps** for the assessment of the effects of Triasulfuron following *in utero* and/or postnatal exposure. Based on the toxicity profile, a developmental neurotoxicity study in rats was not required by the HIARC.

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations

Permanent tolerances are established for residues of Triasulfuron, per se, in/on wheat, barley, and animal commodities (except poultry) at levels of 0.02 - 5.0 ppm [40 CFR 180.459(a)]. Time-limited tolerances are also established on grasses and livestock kidney (except poultry) at levels of 0.5 - 7 ppm [40 CFR 180.377(b)]. There are no CODEX MRLs.

Triasulfuron is a sulfonylurea herbicide. The maximum annual application rate for Triasulfuron is very low (18 gm. a.i./acre) and may be used in only one year out of three. Additionally, the use of Triasulfuron is limited to the following states: CO, ID, KS, MN, MT, ND, NE, NM, NV, OK, OR, SD, TX, UT, WA, and WY. No percent crop treated (%CT) or monitoring data are currently available.

The HED DRES system is used to assess the risk from chronic dietary exposure to Triasulfuron in food (an acute assessment is not required). The chronic dietary risk assessment is unrefined, so the very conservative assumption is made that all commodities contain residues of Triasulfuron at the level of the tolerance. This results in an overestimate of dietary exposure.

2. Drinking Water Exposure Considerations

The required environmental fate data for Triasulfuron have been submitted to EFED and are currently under review. Preliminary reviews indicate a high potential for leaching and surface runoff, however, low application rates attenuate the concentrations in surface and ground waters.

Since Triasulfuron is a new pesticide, monitoring data are not available for drinking water exposure assessment. Preliminary Estimated Environmental Concentrations (EECs) have been calculated for ground and surface water based on the current EFED first level screening models, SCI-GROW and GENEEC respectively.

3. Residential Exposure Considerations

There are currently no registered residential uses for Triasulfuron.

III. RISK CHARACTERIZATION

1. Determination of the Factor

The Committee recommended that the **10x factor** for increased susceptibility of infants and children (as required by FQPA) should be **removed.**

2. Rationale for Selection of the FQPA Factor

The Committee recommended that the10x Safety Factor should be removed. since: 1) the developmental and reproductive toxicity data did not indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 2) any detectable residues in food and drinking water would be expected at low levels since application rates are very low; and 3) there are currently no registered residential uses for Triasulfuron.

Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300
www.cp.us.novartis.com

Tel 336 632 6000

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NOVARTIS

Via Federal Express

February 25, 1998

Document Processing Desk (AMEND)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attn: Mr. Jim Tompkins, PM 25

Dear Mr. Tompkins:

SUBJECT: PESTICIDE PETITION 3F4225 - TRIASULFURON ON GRASSES
SUBMISSION OF NOTICE OF FILING TO EXTEND EXPIRING TOLERANCES
SUBMISSION OF DATA REQUIRED AS PART OF CONDITIONAL REGISTRATION

As discussed with you last week, tolerances for triasulfuron on grass forage, grass hay and kidney are due to expire on July 20, 1998. As part of the July, 1995 conditional registration of triasulfuron on pastures, rangeland and Conservation Reserve Program acres, Novartis was asked to conduct additional residue trials to capture a larger percentage of the U.S. grass acres and to have a more representative distribution among grass species tested. That data has now been finalized and is provided in the three copies of two volumes accompanying this letter. Results of these additional trials indicate no residues exceeding the current time-limited tolerances in the aforementioned grass commodities.

Because it is unlikely the Agency will review these data before the grass tolerances are set to expire in July, Novartis is providing a Notice of Filing under PP3F4225 in accordance with the Food Quality Protection Act of 1996, requesting that tolerances in grass forage (7.0 ppm), grass hay (2.0 ppm) and kidney of cattle, goats, horses, hogs, and sheep (0.5 ppm) be extended for an appropriate length of

time to allow for Agency review of the data, hopefully leading to an unconditional registration for this use. Two paper copies of the Notice of Filing are provided as well as an electronic version on disk in WordPerfect 5.X for Windows.

Please contact me if you have any questions regarding this submission or if you see any problem with extending these tolerances before the expiration date of July 20, 1998.

Thank you for your consideration of these matters.

Sincerely,

Karen S. Stumpf
Senior Regulatory Manager
Regulatory Affairs

Enclosures

VOLUME 1 OF 2 OF SUBMISSION
(TRANSMITTAL DOCUMENT)

1. **Name and Address of Submitter**

Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

2. **Regulatory Action in Support of which this Package is Submitted**

CGA-131036 Technical, EPA Reg. No. 100-692
Amber Herbicide, EPA Reg. No. 100-701
CustomPak Amber, EPA Reg. No. 100-768
PP3F4225/Grasses
Submission of Additional Agency Requested Residue Data

3. **Transmittal Date**

2/25/98

4. **List of Submitted Studies**

MRID NUMBER	VOLUME NUMBER	STUDY TITLE	EPA GUIDELINE NUMBER
	1 of 2	TRANSMITTAL DOCUMENT	NOT APPLICABLE
44198101	2 of 2	TRIASULFURON - MAGNITUDE OF THE RESIDUES IN OR ON GRASSES (STUDY NO. 32-96)(372/32-96)	860-1500

Company Official: Stumpf, Karen S Karen S Stumpf
(Name) **(Signature)**

Company Name: NOVARTIS CROP PROTECTION, INC.

Company Contact: Stumpf, Karen S 336-632-2169
(Name) **(Phone)**

1. Novartis Crop Protection, Inc.

PP 3F4225

EPA has received a pesticide petition PP 3F4225 from Novartis Crop Protection, Inc. P.O. Box 18300, Greensboro, NC. 27419, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40CFR Part 180 by extending the time-limited tolerances for residues of triasulfuron in or on the agricultural commodities grass, forage at 7.0 ppm, grass, hay at 2.0 ppm and kidney of cattle, goats, hogs, horses, and sheep at 0.5 ppm. Tolerances are set to expire on July 20, 1998. The proposed analytical method involves extraction with methanol and phosphoric acid, dilution with water, partitioning into dichloromethane and cleanup on a BondElut CN solid phase extraction column. Residues are determined by column-switching HPLC utilizing a Lichrosorb CN column followed by a Zorbax ODS column, with UV detection at 232 nm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. Plant Metabolism. The nature of the residue in plants is understood. The metabolism of triasulfuron in wheat proceeds by hydroxylation of the phenyl ring and hydrolytic cleavage of the urea bridge. The residue of regulatory concern is parent triasulfuron. Because the metabolism work in wheat can be translated to grasses, parent compound is the residue of regulatory concern for grasses.

2. Analytical method. Triasulfuron in grass was analyzed by Analytical Method AG-500B which is the validated tolerance enforcement method. According to Method AG-500B, triasulfuron is extracted with a mixture of methanol and phosphoric acid. The extract is diluted with water. Triasulfuron residues are partitioned into dichloromethane and cleaned up on a BondElut CN solid phase extraction column. Residues are determined by column-switching HPLC utilizing a Lichrosorb CN column followed by a Zorbax ODS column, with UV detection at 232 nm.

3. Magnitude of residues. A total of 16 field trials have been conducted in 16 states. Seven sites tested bromegrass or fescue, 5 used bluegrass, and 4 used bermudagrass. A total of 69.6% of U.S. pastureland was represented by these trials. Two post broadcast spray applications were made 60 days apart at a rate of

12 grams active ingredient/A/application. Time-limited tolerances were previously established at 7 ppm in grass, forage and 2 ppm in grass, hay pending the submission of additional residue trials. These additional field trials which are included in the numbers above did not show residues exceeding the current tolerances in either grass, forage (0-day PHI) or grass, hay (30 day PHI). The feeding of either substrate to beef or dairy cattle will not result in existing tolerances in animal commodities being exceeded.

B. Toxicological Profile

1. Acute Toxicity. Triasulfuron has a low order of acute toxicity. The rat oral LD50 is > 5000 mg/kg, the acute rabbit dermal LD50 is > 2000 mg/kg and the rat inhalation LC50 is > 5.2 mg/L. Triasulfuron is slightly irritating to the eye but not irritating to skin. It is not a skin sensitizer in guinea pigs. The commercial formulation of triasulfuron (75WP) has a similar acute toxicity profile. Both the technical material and the 75WP formulation require a Category III CAUTION Signal Word on the label.

2. Genotoxicity. Assays for genotoxicity were comprised of tests evaluating the potential of triasulfuron to induce point mutations (Salmonella typhimurium, Saccharomyces cerevisiae and mouse lymphoma L5178Y/TK/+/- cells), chromosome aberrations (micronucleus test in Chinese hamsters) and the ability to induce either unscheduled DNA synthesis in rat hepatocytes and human fibroblasts. The results indicate that triasulfuron is not mutagenic or clastogenic and does not induce unscheduled DNA synthesis.

3. Reproductive and developmental toxicity. The developmental and teratogenic potential of triasulfuron was investigated in rats and rabbits. The results indicate that triasulfuron was maternally toxic in the rat at doses of $\geq$ 300 mg/kg/day. Developmental toxicity in the form of delayed skeletal maturation was observed only at the highest dose tested of 900 mg/kg/day. The corresponding maternal and developmental no observed effect levels were established at doses of 100 and 300 mg/kg/day, respectively in the rat. In the rabbit, maternal toxicity was observed at the highest dose tested of 240 mg/kg/day; no evidence of developmental toxicity was present at 240 mg/kg/day. The maternal developmental no observed effect levels were 120 and 240 mg/kg/day, respectively. No evidence of teratogenicity was observed at the highest dose tested in either the rat or rabbit. There was no effect of triasulfuron on reproductive performance in a 2 generation rat reproduction study conducted at doses of 1, 50 and 250 mg/kg/day. Maternal and fetal toxicity as indicated by decreased body weight gain was noted at the high dose tested of 250 mg/kg/day. The maternal and developmental no observed effect level was 50 mg/kg/day.

4. Subchronic toxicity. The subchronic toxicity of triasulfuron was evaluated in the rat and dog at high doses. Triasulfuron was poorly tolerated in the rat at doses of ≥ 516 mg/kg/day as indicated by increased mortality, decreased body weight gain and kidney damage due to the presence of triasulfuron-containing calculi present in the urogenital tract. The no observable effect level in the rat was 10 mg/kg/day. Triasulfuron was not well tolerated by the dog at doses of 10000 ppm (~250 mg/kg/day) as indicated by body weight reduction, anemia, and effects on the spleen, liver and kidney. The no observed effect level was 1000 ppm (33 mg/kg/day).

5. Chronic toxicity. The chronic toxicity of triasulfuron was investigated in long term studies in the rat, mouse and dog. Target organs included the liver, kidney and blood. No observed effect levels were established at dose levels of 32.1, 1.2, and 129 mg/kg/day, respectively. The mouse is the most sensitive species with a NOEL = 1.2 mg/kg/day). The carcinogenicity studies on triasulfuron showed no evidence of an oncogenic response in either mouse or rat. The chemical is classified in category E.

6. Animal metabolism. The metabolism of triasulfuron has been well characterized in standard FIFRA rat, goat and poultry metabolism studies. Parent triasulfuron accounts for the majority of the excreted dose in these species. Cleavage of the sulfonylurea bridge occurs at a low rate but it is more prevalent in goats and hens than in rats. Hydroxylation of the phenyl ring, which constitutes the major metabolic pathway elucidated in wheat, also was found in the rat. None of the metabolites identified in these studies are considered to be toxicologically different than parent.

7. Metabolite toxicology. The metabolism of triasulfuron has been well characterized in rat, goat and poultry metabolism studies. None of the metabolites identified in these studies are considered to be toxicologically different than parent.

8. Endocrine effects. Triasulfuron does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. There was no effect of triasulfuron on reproductive performance in a 2 generation rat reproduction study conducted at doses of 1, 50 and 250 mg/kg/day. Although residues of triasulfuron have been found in raw agricultural commodities, there is no evidence that triasulfuron bioaccumulates in the environment.

C. Aggregate Exposure

1. Dietary exposure.

a. Food. Novartis has estimated the aggregate exposure to triasulfuron based on the established and time-limited tolerances for triasulfuron (40CFR180.459). The theoretical maximum residue contribution to diet is obtained by multiplying the tolerance level residue for all these raw agricultural commodities by the consumption data which estimates the amount of these products consumed by various population subgroups. Because some of these raw agricultural commodities (e.g. wheat and barley forage and fodder, grass forage and hay) are fed to animals, the transfer of residues to animal commodities has been calculated based on a conservatively constructed cattle diet. In addition, Novartis has conservatively assumed that 100% of the raw agricultural commodities contain residues of triasulfuron at tolerance levels.

b. Drinking Water. Another potential source of exposure of the general population to residues of pesticides are residues in drinking water. The potential for triasulfuron to enter surface or ground water sources of drinking water is limited because of the low use rate. The Maximum Contaminant Level Guideline (MCLG) calculated for triasulfuron according to EPA's procedures is 84 ppb, a value that is substantially greater than levels that are likely to be found in the environment under proposed conditions of use.

2. Non-dietary exposure. Novartis has evaluated the estimated non-occupational exposure to triasulfuron and concludes that the potential for non-occupational exposure to the general population is unlikely since triasulfuron is not planned to be used in or around the home, including home lawns.

D. Cumulative Effects

Novartis also has considered the potential for cumulative effects of triasulfuron and other chemicals belonging to this class that may have a common mechanism of toxicity. Novartis concluded that consideration of a common mechanism of toxicity is not appropriate at this time since there is no data to establish whether a common mechanism exists.

E. Safety Determinations

1. U.S. population. Using the conservative exposure assumptions described above, based on the completeness and reliability of the toxicity data, Novartis has concluded that aggregate exposure to triasulfuron will utilize a maximum of 4.63

percent of the RfD for the U.S. population based on chronic toxicity endpoints. EPA generally has no concern for exposures below 100 percent of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Therefore, Novartis concludes that there is a reasonable certainty that no harm will result from aggregate exposure to triasulfuron or residues of triasulfuron that may appear in raw agricultural commodities.

2. Infants and children. In assessing the potential for additional sensitivity of infants and children to residues of triasulfuron, Novartis has considered data from developmental toxicity studies in the rat and rabbit and a 2-generation reproduction study in the rat on triasulfuron. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from chemical exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to a chemical on the reproductive capability of mating animals and data on systemic toxicity.

Developmental toxicity in the form of delayed skeletal maturation was observed in the rat only at the highest dose tested of 900 mg/kg/day. The corresponding maternal and developmental no observed effect levels were established at doses of 100 and 300 mg/kg/day, respectively in the rat. In the rabbit, maternal toxicity was observed at the highest dose tested of 240 mg/kg/day; no evidence of developmental toxicity was present at 240 mg/kg/day.

There was no effect of triasulfuron on reproductive performance in a 2 generation rat reproduction study conducted at doses of 1, 50 and 250 mg/kg/day. Maternal and fetal toxicity as indicated by decreased body weight gain was noted at the highest dose tested of 250 mg/kg/day. The maternal and developmental no observed effect levels were 50 mg/kg/day.

FFDCA section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on the current toxicological data requirements, the database relative to pre- and post-natal effects for children is complete. Further, for triasulfuron, the NOEL of 1.2 mg/kg/day from the mouse oncogenicity study, which was used to calculate the RfD of 0.01 mg/kg/day, was approximately 50 times lower than the developmental no observed effect level from the rat multigeneration reproduction study. There is no evidence to suggest that developing organisms are more sensitive to the effects of triasulfuron than are adults.

Using the conservative exposure assumptions described above and the chronic toxicity no observed effect level of 1.2 mg/kg/day (RfD of 0.01 mg/kg/day), Novartis has determined that the percent of the RfD that will be utilized by aggregate exposure to residues of triasulfuron is 3.98 percent for nursing infants less than 1 year old, 15.43 percent for non-nursing infants, 10.91 percent for children 1 to six years old and 7.34 percent for children 7 to 12 years old. Therefore, based on the completeness and reliability of the toxicity data and the conservative exposure assessment, Novartis concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to triasulfuron residues.

F. International Tolerances

There are no Codex Alimentarius Commission (CODEX) maximum residue levels (MRL's) established for residues of triasulfuron in or on raw agricultural commodities.

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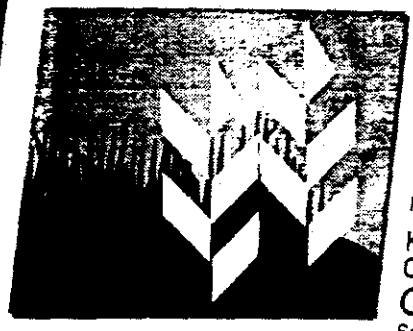

HERBICIDE

For control of various weeds in wheat, barley, pastures, rangeland, and Conservation Reserve Program acres

Made in Switzerland

KEEP OUT OF REACH OF CHILDREN.

CAUTION

See additional precautionary statements and directions for use inside booklet.

Active Ingredient:	
Triasulfuron: 3-(6-methoxy-4-methyl-1,3,5-triazin-2-yl)-1-[2-(2-chloro-ethoxy)-phenylsulfonyl]-urea	*75.0%*
Inert Ingredients:	*25.0%*
Total:	*100.0%*

Amber is water-dispersible granules.

This outer protective bag contains Amber in 8 small water-soluble packets. These packets and their contents dissolve in water. After opening outer bag, immediately dump the required number of unopened packets into the partially filled sprayer or mix tank. Do not handle the soluble packets or expose them to moisture, as this may cause rupturing.

EPA Reg. No. 100-701
EPA Est. 100-SW-0C1©,
EPA Est. 100-SW-2©
(Superscript is first letter of lot number on bag)

NCP 89L7L 0397

40327 USA/5A (USA)

8 x 1.4 OUNCE
Water-Soluble Packets

11.2 OUNCES
TOTAL NET WEIGHT

NOVARTIS

DIRECTIONS FOR USE AND CONDITIONS OF SALE AND WARRANTY

IMPORTANT: Read the entire **Directions for Use** and the **Conditions of Sale and Warranty** before using this product. If terms are not acceptable, return the unopened product container at once.

CONDITIONS OF SALE AND WARRANTY

The **Directions for Use** of this product reflect the opinion of experts based on field use and tests. The directions are believed to be reliable and should be followed carefully. However, it is impossible to eliminate all risks inherently associated with use of this product. Crop injury, ineffectiveness, or other unintended consequences may result because of such factors as weather conditions, presence of other materials, or the manner of use or application all of which are beyond the control of Novartis Crop Protection, Inc. or the Seller. All such risks shall be assumed by the Buyer.

Novartis warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes referred to in the **Directions for Use** subject to the inherent risks referred to above. **Novartis makes no other express or implied warranty of Fitness or Merchantability or any other express or implied warranty. In no case shall Novartis or the Seller be liable for consequential, special, or indirect damages resulting from the use or handling of this product.** Novartis and the Seller offer this product, and the Buyer and user accept it, subject to the foregoing **Conditions of Sale and Warranty**, which may be varied only by agreement in writing signed by a duly authorized representative of Novartis.

NOT REVIEWED
In Accordance with PR Notice 82-2
Based On Draft Labeling Dated
[illegible]

NCP 130-00749K

RECD EPA/OPP/OPD1
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DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

AGRICULTURAL USE REQUIREMENTS

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), and restricted-entry interval. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 4 hours.

PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is:

- Coveralls
- Waterproof gloves
- Shoes plus socks

FAILURE TO FOLLOW THE DIRECTIONS FOR USE AND PRECAUTIONS ON THIS LABEL MAY RESULT IN CROP INJURY, POOR WEED CONTROL, AND/OR ILLEGAL RESIDUES.

GENERAL INFORMATION

Amber is a selective herbicide for the control of many weeds in wheat (including durum wheat), barley, fallow cropland, pastures, rangeland, and Conservation Reserve Program acres. Refer to Table 1 for a listing of weeds controlled. Amber is a 75% water-dispersible granule which must be thoroughly mixed in water and applied as a spray.

This herbicide controls weeds by inhibiting a biochemical process which produces certain essential amino acids necessary for plant growth. The inhibited enzyme system is acetolactate synthase (ALS). Growth of susceptible weeds is inhibited soon after Amber application. Leaves of susceptible plants turn yellow and/or red followed by death of the growing point. These visible effects of control may not be observed until 1-3 weeks after application depending upon weed species, growing conditions, and Amber rate.

Thorough coverage is necessary to provide good weed control.

Use Amber in the following states only: CO, ID, KS, MN, MT, ND, NE, NM, NV, OK, OR, SD, TX, UT, WA, and WY.

Do not use Amber in the San Luis Valley of CO or in sections of WA and OR, west of the Cascade Mountains. In WA, abide by all sulfonylurea aerial application rulings in effect by the Washington Department of Agriculture.

SPRAY EQUIPMENT

Use either ground or aerial spray equipment. Calibrate spray equipment before use.

Use equipment which is capable of continuous and vigorous tank agitation. When the tank is full, the agitation system should be capable of creating a rippling or rolling action on the liquid surface.

Use a 16-mesh strainer at the tank outlet. For the nozzles, use the screen recommended by the nozzle supplier. For ground application of 3-20 gals./A, use only conventional or low pressure flat fan nozzles to assure adequate coverage. For ground application of more than 20 gals./A, rain-drop or floodjet nozzles may be used. In dense stands of wheat or barley, use an adequate spray volume to provide uniform coverage of the weeds.

For aerial application to wheat, barley, and fallow cropland, use a spray volume of 2-5 gals./A. For aerial application to pastures, rangeland, and Conservation Reserve Program acres, apply in a minimum of 2 gals. of spray volume per acre. Apply at a maximum height of 10 ft. above the crop with low-drift nozzles at a maximum pressure of 40 psi and wind speed not exceeding 10 mph to assure accurate application within the target area.

Avoid application under conditions where uniform coverage cannot be obtained or where excessive spray drift may occur.

Avoid application to humans or animals. Flagmen and loaders should avoid inhalation of spray mist and prolonged contact with skin.

Do not apply Amber through irrigation systems.

MIXING PROCEDURES

Water as Carrier

1. Be sure the sprayer is clean.
2. Always use clean water. Fill the tank with 25% of the total water volume needed, and begin agitation.
3. Be certain that the agitation system is working properly and that it creates a rippling or rolling action on the liquid surface.
4. Add the appropriate number of Amber soluble packets to the tank all at once (Refer to Table 2).
5. Complete filling of the tank, maintaining sufficient agitation at all times to ensure surface action. This applies to both spray and nurse tanks.
6. Disperse Amber completely (agitate for 3-5 minutes) before adding surfactant or another chemical to the tank.
7. A nonionic surfactant with a minimum of 80% of the constituents effective as a spray adjuvant (e.g., X-77®) must be added at 1-2 qts./100 gals. of spray volume (0.25-0.5% volume per volume) for all applications to emerged weeds. Use 0.5% surfactant when applying Amber to dense weed populations or when applying Amber in a spray volume of 10 gals./A or less.
8. Maintain continuous agitation while the spray suspension is in the tank.
9. Mix only sufficient spray suspension to be used the same day; however, Amber will remain active in the spray mixture for at least 36 hours.

Liquid Fertilizer as Carrier

The mixing steps are the same as listed above except the Amber must first be dispersed in water as described in the following steps prior to adding it to the spray tank (step number 4 above).

1. Fill a 2.5 gal. container with 2 gals. of water.
2. Place the appropriate number of Amber soluble packets (Refer to Table 2) in the container and wait 30 seconds.
3. Close the container and shake it vigorously until the packets are dissolved and the product is completely dispersed.
4. When the water-soluble packets and the Amber are completely dispersed, add the mixture to the spray tank. When using a surfactant with liquid fertilizer solutions, add the surfactant to this water mixture *before* adding the mixture to the spray tank.
5. Rinse the 2.5 gal. container with water, and add the rinsate to the spray tank.
6. Continue with steps 5-9 in the **Water as Carrier** instructions.

OR

Amber may be mixed in an inductor cone before adding it to the liquid fertilizer on sprayers so equipped as described in the following steps.

1. Shut off inductor cone valve and fill the cone with 2-3 gals. of water.
2. Add the appropriate number of Amber soluble packets (Refer to Table 2) to the water in the cone all at once.
3. Wait one minute to allow the packets and Amber to completely disperse.
4. When the water-soluble packets and the Amber are completely dispersed, open the inductor cone valve in order to add the Amber mixture to the spray tank. When using a surfactant with liquid fertilizer solutions, add the surfactant to the water mixture in the cone *before* opening the inductor cone valve.
5. Rinse the inductor cone thoroughly and keep the valve open so the rinsate is added to the spray tank.
6. Continue with steps 5-9 in the **Water as Carrier** instructions.

Note: The addition of surfactant to spray mixtures more than 50% fertilizer can cause increased temporary leaf burn. The surfactant may be omitted from the spray solution if the carrier contains more than 50% fertilizer. If the surfactant is omitted, control of some of the more difficult to control weeds (bottom of Table 1) may be reduced under unfavorable conditions (i.e., larger weeds, dry soil, etc.). For optimum control of those species, a 50% fertilizer solution as a carrier should be used with an appropriate surfactant.

Recommendations to Avoid Spray Drift

Do not allow spray from ground or aerial equipment to drift onto adjacent land or crops. When drift may be a problem, do everything possible to reduce spray drift, including:

- Do not spray if wind speeds are or become excessive. Do not spray if wind speed is 10 mph or greater. If sensitive crops or plants are downwind, extreme caution must be used under all conditions. Do not spray if winds are gusty.
- Use extreme caution when conditions are favorable for drift (high temperatures, drought, low relative humidity), especially when sensitive plants are located nearby.
- Drift from aerial applications of the herbicide is likely to result in damage to sensitive plants adjacent to the treatment site. This damage can occur at levels below the concentrations that can be detected with chemical analysis.
- Do not apply when a temperature inversion exists. If inversion conditions are suspected, consult with local weather services before making an application.

- Further reductions in drift can be obtained by:
  1. Using large droplet size sprays. Do not use nozzles that produce small droplets. Orient nozzles downward and slightly backward as needed to reduce drift for ground applications.
  2. Orienting nozzles straight back with the windstream, using straight stream orifices for aerial applications. Use the lowest number of nozzles practical with the largest possible orifice size to obtain the minimum one GPA volume. Application height and boom length should be set according to manufacturer's instructions to minimize drift.
  3. Increasing the volume of spray mixture (for example, a minimum of 20 gals./A for ground applications) by using higher flow rate nozzles. Using lower pressure with the appropriate nozzles to obtain larger droplets will also reduce drift.
  4. Applying as close to target plants as practical, while maintaining a good spray pattern for adequate coverage.

Cleaning the Equipment after Amber Application

Many crops are extremely sensitive to very low rates of Amber. Special attention must be given to cleaning spray equipment before spraying a crop other than wheat or barley, pastures, rangeland, or Conservation Reserve Program acres.

Mix only as much spray suspension as needed. Immediately after spraying, remove all traces of Amber from spraying equipment using this procedure:

1. Flush tank and hoses with clean water for 10 minutes.
2. Refill spray tank with water, and add 1 gal. household ammonia (containing 3% active) per 100 gals. of water*. Flush solution through hoses, boom, and nozzles; and let stand in tank for 15 minutes with agitation before disposing, according to state and local regulations.
3. Repeat step 2.
4. Repeat step 1.
5. Clean nozzles and screens separately. To remove traces of cleaning solution, flush the nozzles and screens with clean water.
6. Flush boom and hoses with clean water for 5 minutes, just before using the sprayer for the first time after the Amber application.

*Note: A commercial tank cleaner may be used in place of the ammonia solution if it has been proven effective for use with Amber. Contact your Novartis Crop Protection representative or dealer for information about the suitability of specific tank cleaning products before using them according to the manufacturer's directions.

WEED RESISTANCE TO SULFONYLUREA HERBICIDES

In some fields, there are naturally-occurring biotypes of kochia, Russian thistle, chickweed, prickly lettuce, and annual ryegrass that will not be controlled by sulfonylurea herbicides.

Control of these weeds may be excellent with the use of Amber in many fields; but, where there is the known occurrence of ALS-resistant biotypes, Amber must be tank-mixed or applied sequentially with an appropriate registered herbicide having a different mode of action* (such as 2,4-D; MCPA; Banvel®; or Buctril®) to insure control of these ALS-resistant biotypes.

*Mode of action is the biochemical mechanism for interfering with plant growth.

The occurrence of ALS-resistant weed biotypes can be prevented or delayed by using Amber in tank mixtures and/or in sequential applications with a registered herbicide having a different mode of action, and by not allowing weed escapes to flower. Post-harvest tillage or application of a herbicide with a different mode of action must be made to control any weed escapes before they flower or set seed. If weeds will flower before harvest, make a sequential application of an appropriate herbicide with a different mode of action from Amber. A list of herbicides with the same mode of action as Amber can be obtained from your local Novartis Crop Protection representative. Amber applied to fallow cropland must be applied as a tank mixture, or be followed by a herbicide with a different mode of action within 12 months.

Do not use Amber alone in any field where ALS-resistant biotypes of any weed species have been identified.

Because of the prevalence of resistant kochia and Russian thistle biotypes in ID, WA, MT, SD, and ND, in these states Amber must be applied postemergence only in combination with a herbicide having a mode of action different from Amber, or preemergence followed by a postemergence application of a herbicide having a mode of action different from Amber. Amber may also be applied in the fall, preemergence to winter wheat or to fallow cropland, but must be followed with an application of a herbicide with a different mode of action in the spring.

In CO and the Panhandle of NE, use Amber postemergence in combination with a herbicide having a different mode of action if kochia or Russian thistle are prevalent. See Novartis literature or contact the local representative for suggested tank-mix partners.

An application of a herbicide with a different mode of action from Amber, or a tillage operation, must be made to control any weeds before they flower that may be present in fallow cropland treated with Amber.

Do not apply Amber or other herbicides with the same mode of action within a 12-month period after an Amber application, except for split applications as described below. If additional weed control is needed, use a herbicide with a different mode of action from Amber.

POSTEMERGENCE AMBER APPLICATION TO WINTER OR SPRING WHEAT, WINTER OR SPRING BARLEY, OR POSTEMERGENCE TO WEEDS IN FALLOW CROPLAND

Apply Amber at a standard or enhanced rate when the target weeds shown in Table 1 are ACTIVELY GROWING AND ARE WITHIN THE HEIGHT AND DIAMETER RANGE SPECIFIED, and the wheat is at ANY STAGE UP TO PRE-BOOT or barley is in the 2-LEAF TO PRE-BOOT STAGE. Optimal control can be obtained for most weed species when the weeds are 2 inches or less in height or diameter. Very large weeds may only be suppressed. Do not apply the enhanced rate in areas with a soil pH greater than 7.5, except in the Blacklands of TX and OK. Use the low range (0.28 oz./A) of the standard rate unless additional length of control is needed. If additional length of control is needed, or, if weeds are at or above the maximum height, use the 0.35 or 0.47 oz./A rate of Amber. These rates of Amber can also be used for the more difficult to control weeds (such as wild buckwheat) at the bottom of the standard rate section of Table 1. Include a nonionic surfactant in the spray mixture as described in the **Mixing Procedures** section.

Amber will also provide preemergence control of the weeds listed in Table 1 that may germinate after application, provided rainfall, enough to wet the soil 2-3 inches deep, moves Amber into the soil before they emerge. Application of Amber at the enhanced rate will increase the duration of weed control.

For optimum control, fall applications of Amber to weeds in winter wheat, winter barley, or fallow cropland must be made before the emerged weeds are exposed to extended freezing temperatures.

Precautions: To avoid possible crop injury, do not apply Amber to wheat or barley that is stressed due to (1) extremes in temperature or rainfall; (2) disease or insect pressure; or (3) when extremes in temperature or rainfall are expected within one week of application.

Amber **must be tank-mixed** with other appropriate herbicide(s) to obtain broad spectrum weed control in fallow cropland. Refer to the **Amber Tank Mixtures with Other Herbicides** section.

Do not plant durum wheat less than 8 months after an Amber application to fallow cropland.

PREPLANT, PREPLANT SHALLOW-INCORPORATED, OR PREEMERGENCE AMBER APPLICATION TO WINTER OR SPRING WHEAT (EXCEPT DURUM WHEAT)

Preplant, preplant shallow-incorporated (top 1 inch of soil), or preemergence Amber application at a standard or enhanced rate will provide control of the weeds listed in Table 1, provided rainfall, enough to wet the soil 2-3 inches deep, is received before weed emergence. Preplant or preplant shallow-incorporated applications should be used only if a disk drill is to be used for planting; not hoe/sweep drills.

Apply Amber preplant, preplant shallow-incorporated, or preemergence to wheat at the enhanced rate for the suppression of annual ryegrass and for suppression of light to moderate Japanese brome, downy brome, and cheat populations that have not emerged. Sufficient and timely rainfall, enough to wet the soil 2-3 inches deep, is required for preplant, preplant shallow-incorporated, or preemergence activity. It may be necessary to apply a sequential application of Sencor® or Lexone® if suppression of Japanese brome, downy brome, or cheat is not adequate after Amber application. Refer to the Sencor or Lexone label for directions for use and wheat variety restrictions. Amber will not adequately suppress heavy or dense populations of downy brome or cheat.

Precaution: Do not apply Amber preemergence to late fall-seeded winter wheat if environmental conditions that stress wheat are expected within 2 weeks after application.

SPLIT AMBER APPLICATIONS TO WINTER WHEAT (SOIL pH LESS THAN 7.5)

Amber may be applied as a split application to winter wheat to control susceptible weeds that may be expected to emerge later in the growing season. Make the initial application of Amber either preplant, preplant shallow-incorporated, preemergence or postemergence at the low standard rate (0.28 oz./A), and follow with an additional postemergence application at the low standard rate no sooner than 60 days after the first application. The second application **must be tank-mixed** with a herbicide registered for use in wheat having a different mode of action (such as 2,4-D; MCPA; Banvel; and Buctril) to avoid selection of resistant weed biotypes. The second application must be applied no later than pre-boot, or earlier if required by the directions for use of the tank-mix partner. Include a nonionic surfactant in the spray mixture as described in the **Mixing Procedures** section.

Precaution: Weed control is dependent upon weed species, size at application, growing conditions, and the level of competition from the crop. Weed control may be reduced if weeds are stressed due to drought, excess cold or warm temperatures, or other factors which reduce growth. Competition of the crop with the weeds helps in providing control.

Note: To avoid possible illegal residues, do not apply more than a total of 0.56 oz. of Amber per acre when making split applications.

Table 1: Weeds Controlled or Suppressed with Amber at the Standard and Enhanced Rates

STANDARD RATES (0.28 oz./acre = 1 soluble packet/5 acres, 0.35 oz./acre = 1 soluble packet/4 acres, or 0.47 oz./acre = 1 soluble packet/3 acres)	
Weeds Controlled	**Maximum Height/Diameter for Optimum Control (Inches)**
Blue mustard (purple mustard), field pennycress (fanweed), flixweed, shepherdspurse, tall hedge mustard, tansymustard, tumble mustard (Jim Hill mustard), wild mustard	No size limit, but control is recommended prior to weed competition with the crop resulting in yield reductions
Bur buttercup, common ragweed, common sunflower, creeping buttercup, horseweed (marestail), Indian mustard, kochia*, lanceleaf ragweed, prickly lettuce (China lettuce*), puncturevine, tall buttercup, Virginia pepperweed, wild radish	Less than 6
Annual fleabane, bushy wallflower, coast fiddleneck (tarweed), common cocklebur, common purslane, common broomweed, common yarrow, corn gromwell, cutleaf eveningprimrose, giant ragweed, hairy vetch, jagged chickweed (umbrella spurry), London rocket, marshelder, minerslettuce, Plains coreopsis, prostrate pigweed, redroot pigweed, rough fleabane, smooth pigweed, spring whitlowgrass, yellow starthistle, woolly croton	Less than 4
Annual polemonium (Jacobs-ladder), common chickweed*, common mallow, forget-me-not, Russian thistle*, wild buckwheat (treat after true leaves have emerged; not cotyledon stage)	Less than 2
Henbit	Preplant, preplant shallow-incorporated, or preemergence
Weeds Suppressed*** Wild garlic, wild onion	No limit
Western ragweed, annual morninglories	Less than 5 inches
Henbit	Less than 2 inches
ENHANCED RATE (0.56 oz./acre = 1 soluble packet/2½ acres)	
Additional Weeds Suppressed** **Canada thistle, curly dock, goldenrod, greenflower pepperweed, houndstongue, musk thistle**	**Less than 6 inches**
Annual ryegrass, cheat, downy brome, Japanese brome	Preplant, preplant shallow-incorporated, or preemergence

*See **Weed Resistance to Sulfonylurea Herbicides** section of this label.

**In addition to those controlled or suppressed by standard rates.

***Indicates "Partial Control" which means significant activity but not always at a level generally considered acceptable for commercial weed control.

Table 2: Number of Amber Soluble Packets to Use to Treat Various Acreages at the Standard or Enhanced Rates

	Number of Soluble Packets to Use			
	Standard Rates			Enhanced Rate
Acres to Treat	0.28 oz./A	0.35 oz./A	0.47 oz./A	0.56 oz./A
3	—	—	1	—
4	—	1	—	—
5	1	—	—	2
10	2	—	—	4
15	3	—	5	6
20	4	5	—	8
25	5	—	—	10
30	6	—	10	12
40	8	10	—	16
50	10	—	—	20
60	12	15	20	24
70	14	—	—	28
80	16	20	—	32
90	18	—	30	36
100	20	25	—	40
120	24	30	40	48
140	28	35	—	56
160	32	40	—	64

Note: One packet treats 3-5 acres at the standard rates. Two packets treat 5 acres at the enhanced rate.

POSTEMERGENCE AMBER APPLICATION TO PASTURES, RANGELAND, AND CONSERVATION RESERVE PROGRAM (CRP) ACRES

Amber can be applied postemergence at the standard rate (0.28 oz./A) or enhanced rate (0.56 oz./A) for weed control in the following established grasses:

Common Name	Scientific Name
Bermudagrass	***Cynodon dactylon***
Bluestem, Big	***Andropogon gerardi***
Bluestem, Little	*Andropogon scoparius*
Brome, Smooth	*Bromus inermis*
Buffalograss	*Buchloe dactyloides*
Fescue, Sheep	*Festuca ovina*
Grama, Blue	*Bouteloua gracilis*
Grama, Side-oats	*Bouteloua curtipendula*
Redtop	*Agrostis alba*
Timothy	*Phleum pratense*
Wheatgrass, Bluebunch	*Agropyron spicatum*
Wheatgrass, Crested	*Agropyron cristatum*
Wheatgrass, Intermediate	*Agropyron intermedium*
Wheatgrass, Pubescent	*Agropyron tricophorum*

For new seedings of the above grasses, do not apply Amber until at least 60 days after emergence of the desirable grasses. Even established stands of orchardgrass, red fescue, and ryegrasses will likely be injured by Amber. If desirable broadleaves, such as clovers and alfalfa, are present, they will likely be severely injured by Amber applications.

Weed Control

For information on weeds controlled, size limitations, and rate of Amber to use, refer to Table 1. Many of the weeds in that table commonly occur in rangeland, pastures, and CRP acres. In addition to the weeds listed in Table 1, Amber at the standard or enhanced rates will provide first year control and subsequent year suppression of: hoary cress (whitetop), and poison hemlock.

For all postemergence applications, Amber should be applied to actively growing weeds and a nonionic surfactant should be included in the spray mixture as described in the **Mixing Procedures** section of this label. To obtain optimum control and to manage weed resistance, Amber should be applied in tank mixture with an appropriate registered herbicide having another mode of action (examples are 2,4-D, Banvel, Crossbow®, Grazon®, Stinger®, Weedmaster®, and Weedone® LV6). The tank-mix partner should be used at a recommended tank-mix rate and all directions, restrictions, and precautions should be followed on both labels.

Biotypes of the weeds marked with an (*) in Table 1 have been selected which are resistant to certain or all sulfonylureas. Those biotypes will likely not be controlled with Amber. Follow the precautions and instructions in the **Weed Resistance to Sulfonylurea Herbicides** section of this label. In addition, to reduce the possibility of selecting sulfonylurea-resistant biotypes, do **not** apply Amber or any other herbicide with the same mode of action in pastures, rangeland, or CRP acres more frequently than in one year out of three. If additional weed control is needed during that time, use a herbicide with another mode of action from that of Amber. For a list of herbicides with the same mode of action, or for further information, contact your local Novartis Crop Protection representative.

Partial control of downy brome and cheat can be obtained by applying Amber at 0.56 oz./A prior to emergence of those grasses. Follow directions for control of downy brome in wheat as described in the **Preemergence Amber Application to Winter or Spring Wheat** section of this label.

Amber at the standard rate (0.28 oz./A) will provide partial control of western ragweed *(Ambrosia psilostachya)* if applied to plants less than 5 inches tall. A second application of the standard or enhanced rate (0.28 or 0.56 oz./A) can be made no later than 60 days after the initial application for additional control of late germinating western ragweed and for residual control.

Refer to Table 2 for the number of water-soluble packets to use to treat various acreages. The maximum amount of Amber which can be applied in a calendar year is 0.84 oz./A.

Poisonous plants: The following weeds controlled by Amber can be poisonous to livestock in pastures and rangeland: bur buttercup, coast fiddleneck, cocklebur, creeping buttercup, goldenrod, and tall buttercup.

Note: To avoid possible illegal residues, do not cut for hay for 30 days following application. Grazing may occur immediately following application.

TANK MIXTURES

Note: Amber tank mixtures with 2 or more of the products listed in the following sections or with products not listed below must be (A) tested for physical compatibility, (B) applied to a small area of the field and observed for resultant crop safety and weed control before widespread use, and (C) always add Amber soluble packets to the mix tank and allow the packets to completely dissolve and the Amber to fully disperse before adding any other tank-mix partner.

Amber Tank Mixtures with Other Herbicides

APPLY AMBER IN TANK MIXTURE ONLY WITH HERBICIDES REGISTERED FOR USE ON THE PARTICULAR CROP.

TANK MIX A STANDARD RATE OF AMBER WITH A SUITABLE HERBICIDE FROM THE LIST BELOW TO: (1) CONTROL BROADLEAF WEEDS THAT ARE BEYOND THE OPTIMUM TREATMENT SIZE; OR (2) CONTROL BROADLEAF OR GRASSY WEEDS NOT NAMED ON THIS LABEL; OR (3) CONTROL SULFONYLUREA-RESISTANT WEEDS. DO NOT APPLY MORE THAN THE RECOMMENDED LABEL RATE OF THE HERBICIDES LISTED BELOW. AMBER MUST BE APPLIED IN TANK MIXTURE FOR USE IN FALLOW CROPLAND.

Amber plus surfactant is known to be physically compatible with the following herbicides. Refer to the label of the tank-mix herbicide used for weeds controlled, directions for use, and restrictions.

- Assert® 2.5E
- Banvel 4SC or SGF 2S
- Bronate® 4E
- Buctril 2E
- Curtail® 2.38 lb. a.i./gal.
- Curtail M 2.77 lb. a.i./gal.
- diuron (various manufacturers, formulations, and product names)
- Fallow Master™ 1.6 lb. a.i./gal.
- Gramoxone® Extra 2.5 lb. a.i./gal.
- Hoelon® 3E
- Landmaster® BW 3.1 lb. a.i./gal. or Landmaster II 2.2 lb. a.i./gal.
- Lexone 75DF
- MCPA amine or ester
- Roundup® 4E
- Sencor 75DF or Solupak or 4L
- 2,4-D amine or ester

Tank Mixes for Henbit Control

If henbit has emerged, apply Amber early postemergence at a standard use rate in combination with Banvel + 2,4-D; Buctril; MCPA; Lexone; or Sencor.

Tank Mix with Metribuzin (Lexone or Sencor) for Suppression of Downy Brome and Cheat

For suppression/partial control of downy brome and cheat in wheat, apply a standard rate of Amber plus 0.062-0.25 lb. a.i./A (2-8 oz./A of 4L or 0.083-0.33 lb./A of 75DF) of metribuzin early postemergence. Refer to the Lexone or Sencor label for rates, timings, and restrictions, such as variety limitations.

Tank Mix with Fallow Master for Conservation Tillage

For burndown plus residual control of weeds in Table 1, apply a standard rate of Amber plus labeled rates of Fallow Master in fallow cropland or at least 15 days prior to seeding winter or spring wheat in no-tillage or reduced-tillage systems. To obtain good soil activity, enough rainfall is needed to wet the soil 2-3 inches deep before weed emergence. If weeds emerge, control them with a herbicide(s) having a different mode of action than Amber; for example, 2,4-D + Banvel.

Tank Mix Application with Tilt® Fungicide

For control of foot rot in wheat in the Pacific Northwest, Tilt fungicide may be applied at 0.25 pt./A in combination with Amber at either a standard or enhanced rate. Refer to the Tilt label for specific use directions and restrictions.

AMBER APPLICATION WITH ORGANOPHOSPHATE INSECTICIDES

Amber may be tank-mixed or applied sequentially with registered organophosphate insecticides **except** malathion. These tank mixtures or sequential applications may cause temporary crop discoloration or crop injury, especially if the crop is under environmental stress at the time of treatment.

Delay Amber application for at least 60 days after an in-furrow application of an organophosphate insecticide.

GRAZING AND RE-SEEDING FOLLOWING AMBER APPLICATION TO WHEAT, BARLEY, OR FALLOW CROPLAND

There are no grazing restrictions following Amber application.

Wheat may be re-seeded immediately after application of either a standard rate or the enhanced rate.

ROTATIONAL CROP RESTRICTIONS

The following crops may be planted after Amber application without a field bioassay, provided the following conditions are met and the required time has elapsed between the last Amber application and the crop planting date.

Wheat

No rotational restrictions. Refer to **Grazing and Re-seeding following Amber Application to Wheat, Barley, or Fallow Cropland** section for re-seeding time intervals.

Barley, Rye, Oats, or Bermudagrass

1. Six months ONLY under the following conditions:
   A. In CO, KS, MT, NE, OK, SD, TX, Western ND – where soil pH is 7.9 or less – and where one application of Amber at a standard rate was made.
   B. In all states – where soil pH is 6.9 or lower – one application of either a standard or enhanced rate.
2. Eighteen months after application of either a standard or enhanced rate in areas not described above.

Proso Millet

Four months after application of either a standard or enhanced rate.

Field Corn

1. Four months ONLY if an IR corn hybrid is planted; either a standard or enhanced rate.
2. Fourteen months ONLY after application of either a standard or enhanced rate in KS and NE, where soil pH is 6.9 or lower, if a "normal" (not IR) hybrid is planted.
3. Twenty-two months after application of either a standard or enhanced rate on soil with pH 7.9 or lower, if a "normal" (not IR) hybrid is planted.
4. Thirty-six months after application in areas not described above. Corn may be planted sooner if a successful field bioassay is completed.

Grain Sorghum

1. Fourteen months ONLY under the following conditions:
   A. Soil pH 7.9 or lower and one application of a standard rate in Central TX (excluding Panhandle); Western OK (excluding Panhandle); and West Central and Western KS and NE.
   B. Soil pH 7.9 or lower and one application of either a standard or enhanced rate in Eastern TX; Central and Eastern OK; and Central and Eastern KS.
2. Twenty-four months after application of either a standard or enhanced rate in areas not described above.

Soybeans

1. Eleven months ONLY if STS™ soybeans are planted; either a standard or enhanced rate.
2. Fourteen months ONLY under the following conditions:
   A. Soil pH 7.5 or lower and a minimum of 25 inches cumulative precipitation from application to planting. One application of a standard rate in Central KS.
   B. Soil pH 7.5 or less and a minimum of 25 inches cumulative precipitation from application to planting. One application of a standard or the enhanced rate in Eastern TX; Central and Eastern OK.
3. Twenty-six months ONLY under the following conditions:
   A. Soil pH 7.5 or lower and a cumulative precipitation of 46 inches from application to planting. One application of the enhanced rate in Central KS.
   B. Soil pH 7.9 or lower and cumulative precipitation of 46 inches from application to planting. One application of a standard rate in Central KS; South Central NE.
4. Thirty-six months after application of a standard or enhanced rate in areas not described above. Soybeans may be planted sooner if a successful field bioassay is completed.

Sugar Beets, Sunflowers, or Onions

These crops are extremely sensitive to low levels of Amber in the soil and should *not* be planted less than 24 months after any application of Amber *and* only after a successful field bioassay is completed.

Other Crops

All crops other than wheat, barley, rye, oats, proso millet, bermudagrass, field corn, grain sorghum, and soybeans under the specific conditions described above, may be seeded only after the completion of a successful field bioassay and no sooner than 4 months after application. Refer to **Field Bioassay Instructions** section.

Additional Rotational Precaution

If both Amber and another sulfonylurea herbicide or Assert have been applied during a single growing season, a field bioassay must be performed before planting any crop except wheat in the next growing season. If visible injury, stand reduction, or yield reduction occurs in the bioassay, the crop must not be seeded.

FIELD BIOASSAY INSTRUCTIONS

Using typical tillage, seeding practices, and timings for the particular crop, plant several strips of the desired crop variety across the field which has been previously treated with Amber. Plant the strips perpendicular to the direction Amber was applied. The strips should be located so that all the different field conditions are encountered, including differences in soil texture, pH, and drainage. If the crop does not show visible symptoms of injury, stand reduction, or yield reduction, this field can be seeded with this crop the next growing season after the bioassay. If visible injury, stand reduction, or yield reduction occurs, this crop must not be seeded, and the bioassay must be repeated the next growing season.

ADDITIONAL PRECAUTIONS

1. Do not use Amber in fields where the combination of all three of these criteria occur:
   - Historic average annual rainfall (or the combination of historic annual rainfall plus planned irrigation of the crop) exceeds 35 inches per year, and
   - The ground water table is 30 ft. or less below the soil surface, and
   - The soil is classified as a coarse soil (sand or loamy sand soil texture in the surface layer).
2. When applying to wheat, barley, or fallow cropland, do not apply more than one application of 0.56 oz./A or 2 applications of 0.28 oz./A (separated by at least 60 days) per crop. Split applications must be made within the same cropping season.
3. When applying to pastures, rangeland, or CRP acres, do not apply more than a total of 0.84 oz./A per year as follows: one application of 0.28 oz./A may be applied postemergence, followed by a second application not more than 60 days later at up to 0.56 oz./A.
4. Do not apply Amber or other herbicides with the same mode of action within a 12-month period after an Amber application, except as directed above for split applications. If additional weed control is needed, use a herbicide with a different mode of action than Amber.
5. **Do not apply Amber within 4 hours of an expected rainfall/irrigation event. Rainfall or irrigation soon after application may reduce foliar uptake by weeds, thereby reducing weed control.**
6. Do not apply Amber to wheat or barley undersown with legumes or forage grasses, as injury to the undersown crops may occur.
7. Do not apply Amber to irrigated land if the tail water will be used on non-target land.
8. Do not allow spray to drift to non-target crops, other desirable plants, recreational areas, ornamental plants, or onto land scheduled to be planted with crops other than wheat or barley.
9. Do not apply Amber to snow-covered soil or to frozen soil surfaces, since runoff may occur.
10. Do not apply Amber where its movement through the soil or on soil particles may place it in contact with non-target plants or their roots.
11. Do not apply Amber under conditions when uniform coverage cannot be obtained.
12. Do not apply Amber to stressed or dormant weeds, or when environmental conditions which stress weeds or cause weed dormancy are expected within one week after application.
13. Do not mix with or apply sequentially with malathion. Tank mixture or sequential application with other registered organophosphate insecticides may cause temporary crop discoloration or crop injury. Delay Amber application for at least 60 days after an in-furrow application of an organophosphate insecticide.
14. Do not apply Amber through irrigation systems.

STORAGE AND DISPOSAL

Pesticide Storage and Disposal

Store in a dry place. Do not contaminate water, food, or feed by storage or disposal. Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

Container Disposal

Do not re-use outer bag. Dispose of outer bag in a sanitary landfill, or by incineration, or by open burning, if allowed by state and local authorities. If burned, keep out of smoke.

For minor spills, leaks, etc., follow all precautions indicated on this label and clean up immediately. Take special care to avoid contamination of equipment and facilities during cleanup procedures and disposal of wastes. In the event of a major spill, fire, or other emergency, call 1-800-888-8372, day or night.

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

CAUTION

Harmful if inhaled or absorbed through skin. Causes eye irritation. Avoid breathing spray mist. Avoid contact with skin, eyes, or clothing.

Statement of Practical Treatment

If in eyes: Flush with plenty of water. Get medical attention if irritation persists.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

If inhaled: Remove victim to fresh air.

Personal Protective Equipment

Applicators and other handlers must wear:

- Long-sleeved shirt and long pants
- Waterproof gloves
- Shoes plus socks

Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

Engineering Control Statements

When handlers use closed systems, enclosed cabs, or aircraft in a manner that meets the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.240(d)(4-6)], the handler PPE requirements may be reduced or modified as specified in the WPS.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.

Environmental Hazards

For terrestrial uses, do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment wash waters or rinsate.

Ground Water Advisory

Amber has been identified in ground water sampling from a field research study under vulnerable conditions. There is the possibility that Amber may leach through soil to ground water, especially where soils are coarse and ground water is near the surface. Consult with the pesticide state lead agency or local agricultural agencies for information regarding soil permeability and aquifer vulnerability in your area.

Chemigation

Do not apply Amber through irrigation systems.

Novartis Crop Protection, Inc.
Greensboro, North Carolina 27419
NCP 89L7L 0397

Accu-Pak®

Amber®

HERBICIDE

For control of various weeds in wheat, barley, pastures, rangeland, and Conservation Reserve Program acres

Active Ingredient:	
Triasulfuron: 3-(6-methoxy-4-methyl-1,3,5-triazin-2-yl)-1-[2-(2-chloroethoxy)-phenylsulfonyl]-urea	75.0%
Inert Ingredients:	25.0%
Total:	100.0%

Amber is water-dispersible granules.

EPA Reg. No. 100-701
EPA Est. 100-SW-001©
EPA Est. 100-SW-2©
(Superscript is first letter of lot number on bag)

Made in Switzerland

Accu-Pak® and Amber® trademarks of Novartis
U.S. Patent No. 4,514,212

Novartis Crop Protection, Inc.
Greensboro, NC 27419
NCP 89L7L 0397

8x1.4 OUNCE
Water-Soluble Packets

11.2 OUNCES
TOTAL NET WEIGHT

See directions for use in attached booklet.

AGRICULTURAL USE REQUIREMENTS

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. Refer to supplemental labeling under "Agricultural Use Requirements" in the Directions for Use section for information about this standard.

KEEP OUT OF REACH OF CHILDREN.

CAUTION

Precautionary Statements

Hazards to Humans and Domestic Animals
Harmful if inhaled or absorbed through skin. Causes eye irritation. Avoid breathing spray mist. Avoid contact with skin, eyes, or clothing.

Statement of Practical Treatment
If in eyes: Flush with plenty of water. Get medical attention if irritation persists.

If on skin: Wash with plenty of soap and water. Get medical attention if irritation persists.

If inhaled: Remove victim to fresh air.

Environmental Hazards
For terrestrial uses, do not apply directly to water, or to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment wash waters or rinsate.

Ground Water Advisory
Amber has been identified in ground water sampling from a field research study under vulnerable conditions. There is the possibility that Amber may leach through soil to ground water, especially where soils are coarse and ground water is near the surface. Consult with the pesticide state lead agency or local agricultural agencies for information regarding soil permeability and aquifer vulnerability in your area.

Chemigation
Do not apply Amber through irrigation systems.

NOVARTIS

July 13, 1998

MEMORANDUM

TO: **Rick Whiting**
Science Analysis Branch
Health Effects Division (7509C)

FROM: **Deborah Smegal, Toxicologist**
Toxicology Branch II
Health Effects Division (7509C)

THROUGH: **Stephen Dapson, Branch Senior Scientist**
Toxicology Branch II
Health Effects Division (7509C)

RE: Revised Executive Summaries for the Triasulfuron DERs

Triasulfuron was recently revisited due to a tolerance on grass forage, grass hay and kidney that expires on July 20, 1998. As part of this assessment, new executive summaries were written for all of the triasulfuron DERs, except the acute studies. In addition, a risk assessment was conducted to address the FQPA of 1996. Below are the revised executive summaries that should be added to the toxicity one-liner database.

Developmental Rat
EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID # 40271948) Triasulfuron 94.5% a.i. was administered to 24 Tif: RAIF (SPF) pregnant female rats/dose by gavage at dose levels of 0, 100, 300 or 900 mg/kg from days 6 through 15 of gestation, inclusive.

Mean body weight, body weight gain and food consumption were significantly reduced in the 300 and 900 mg/kg dose groups during the treatment period. At 900 mg/kg, two dams had deciduomata that was seen only at the high dose and could, therefore be treatment-related. There were no treatment-related effects in mortality, or clinical signs. In addition, there were no statistically significant differences or trends in the pregnancy rate, the number of pregnant dams that aborted, number of implantation sites, live fetuses/dam, resorptions/dam, dead fetuses/dam, dead implants/dam, or in post-implantation loss, total live fetuses, litter size, fetal viability or sex ratio. **The maternal LOEL is 300 mg/kg, based on decreased body weight and body weight**

gain during gestation. The maternal NOEL is 100 mg/kg.

Male and female fetal body weights were significantly reduced at the 900 mg/kg dose level compared to controls. There were no treatment-related gross or visceral abnormalities in the fetuses. The number of fetuses with unossified vertebrae, metatarsals, and phalanges was significantly increased in the 900 mg/kg dose group relative to historical controls. **The developmental LOEL is 900 mg/kg based on reduced ossification of vertebrae, metatarsals and phalanges. The developmental NOEL is 300 mg/kg.**

The developmental toxicity study in the rat is classified as acceptable Guideline and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; § 83-3 (a)) in rats when considered with the historical control data for rats.

Developmental Rabbit
EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID #40271949) Triasulfuron 94.5% a.i. was administered to 20 chinchilla pregnant female rabbits/dose by gavage at dose levels of 0, 40, 120, or 240 mg/kg from days 6 through 18 of gestation, inclusive.

There were no treatment-related effects on mean body weight, food consumption, mortality, or clinical signs. Body weight gain was significantly reduced in the does of the 240 mg/kg dose group from day 6 through 10 of gestation, and was statistically elevated in the does of the 120 mg/kg dose group over the entire study duration. There were no statistically significant differences or trends in the pregnancy rate, the number of pregnant dams that aborted, mean number of implantation sites/dam, live fetuses/dam, resorptions/dam, dead fetuses/dam, pre- or post-implantation loss, mean number of corpora lutea, implantation efficiency, litter size, fetal viability, sex ratio or mean body weights of pups by litter. **The maternal LOEL is 240 mg/kg, based on decreased body weight gain during gestation. The maternal NOEL is 120 mg/kg.**

In the fetuses, there were no treatment-related gross, visceral, or skeletal abnormalities. **The developmental NOEL is >240 mg/kg.**

The developmental toxicity study in the rabbit is classified as acceptable and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; § 83-3 (b)) in rabbits.

Two Generation Rat Reproduction Study
EXECUTIVE SUMMARY:

In a two-generation reproduction study (MRID #40728317), 30 Sprague-Dawley Rats per sex per dose received either 0, 10, 1000 or 5000 ppm (0, 0.5, 50, or 250 mg/kg/day, respectively) of technical Triasulfuron (purity not specified) in the diet. The F0 animals were mated on a one-to-one ratio and were given test diets for 12 and 14 weeks before mating. Two matings were

conducted for the first generation producing the F1a and F1b weanlings. The F1 parental animals were paired only once to produce an F2a generation.

Significant reductions in mean body weight and body weight gain were noted in parental animals. The mean body weights of the high-dose F1 males were significantly reduced at weeks 12 and 25, while total body weight gain was significantly reduced in high-dose F0 females and F1 males. In addition, premating weight gain was significantly reduced in F0 males exposed to 5000 ppm. There were no treatment-related effects on mortality, clinical signs, food consumption or gross or microscopic pathology. **The parental LOEL is 5000 ppm (250 mg/kg/day) based upon significant decreases in premating and total body weight gain for high-dose F0 and F1 parental animals. The parental NOEL is 1000 ppm (50 mg/kg/day).**

A significant decreasing trend in mean body weight of pups was noted for the F1a generation. Pup weights were significantly reduced in the high-dose F1a at birth, and in the mid- and high-dose pups on day 7 of lactation. There were no treatment-related effects on fertility, gestation length, number of pups born/litter, or offspring viability. **The reproductive toxicity LOEL is 5000 ppm (250 mg/kg/day) based on reduced F1a pup weights at birth and during lactation. The reproductive toxicity NOEL is 1000 (50 mg/kg/day).**

This reproductive study in the rat is classified as acceptable and does satisfy the guideline requirement for a reproductive toxicity study (§ 83-4) in rats.

Chronic toxicity/carcinogenicity study in rats
EXECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID #40728318), male and female Sprague Dawley rats [70/sex/dose] were fed diets containing triasulfuron (92.5%) at 0, 10, 1000 or 6000 ppm (Males: 0, 0.3, 32.1, or 220.8 mg/kg/day, respectively; Females: 0, 0.4, 42.9 or 274.4 mg/kg/day, respectively) for up to 24 months. In addition, 10/sex/dose were sacrificed at 12 months. Parameters evaluated were: survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, and gross and histological changes.

Significant reductions in mean body weight (25.4% for males and 39.4% for females at 103 weeks) and body weight gains (18-28.7% at week 13 and 25.4-39.4% at week 103) were noted in both sexes in the highest dose groups. There were no treatment-related effects on mortality, clinical signs, ophthalmic changes, organ weights, or gross or microscopic pathology. No toxicologically significant effects were observed in the hematological, clinical chemistry or urinalysis results. Marginal statistically significant increases in relative organ weights in male and female rats were not considered toxicologically significant primarily because of decreased mean body weights, and because absolute organ weights were not elevated. High dose males exhibited a significant decrease in the mean absolute heart weight, which was not considered to be toxicologically significant due to an absence of a dose-response in histopathologic findings. A significant increase in mean testes weight was noted in the high dose males, which is not

considered to be an adverse effect because it is associated with decreased testicular atrophy. Furthermore, a dose-related increased incidence in gross lesions (tissue masses) did not correlate with any histological lesion. There were no treatment-related effects on food consumption in males or females throughout the study, with the exception of females in the 6000 ppm group at 103 weeks (11.8% reduction observed). **The chronic toxicity LOEL is 6000 ppm (220.8 mg/kg/day) based upon a significant decrease in mean body weight in both sexes throughout the study and in body weight gain in both sexes at weeks 13 and 103. The NOEL is 1000 ppm (32.1 mg/kg/day).**

This chronic toxicity/carcinogenicity study in rats coupled with supplementary information summarizing the survival incidence and compound purity (MRID # 41585802) is classified as acceptable and does satisfy the Subdivision F guideline requirement for a combined chronic toxicity/carcinogenicity study in rats (§ 83-5).

Oncogenicity feeding study in mice
EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID #40728316), male and female CD-1 albino mice [50/sex/dose] were fed diets containing triasulfuron (93.7-96.5%) at 0, 10, 1000, 5000 or 10,000 ppm (Males: 0, 1.2, 129, 619.6 or 1301.3 mg/kg/day, respectively; Females: 0, 1.5, 157.5, 792.5, or 1473.5 mg/kg/day, respectively) for up to 24 months. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, organ weights, and gross and histological changes. In addition, mice were palpated weekly for tissue masses.

There were no treatment-related effects on mortality, clinical observations, organ weights, water consumption, hematology parameters, ophthalmic findings, or clinical chemistry parameters. In males and females receiving 5,000 or 10,000 ppm, mean body weight and/or body weight gain were marginally depressed below control values (not statistically significant except for females at 2 and 5 weeks in the 10,000 ppm group and at 81 weeks in the 5,000 ppm group); this was accompanied by a decreased food consumption in females. There was a noticeable decrease in food consumption in females at dietary levels of 5,000 and 10,000 ppm during the early phase of the study. These findings were not considered to be of toxicologic importance. Centrilobular hepatocytomegaly was observed in male mice receiving 1,000, 5,000, or 10,000 ppm (significant, $p<0.01$) and in females receiving 10,000 ppm (significant, $p<0.05$). Increased centrilobular degeneration, focal accumulation of inflammatory cells, microgranulomas, and pigment depositions were also observed in the liver of 10,000 ppm males.

The incidence of alveolar/bronchiolar adenoma in the lung was statistically increased ($p<0.05$) in male mice fed 10,000 ppm (28%) when compared to the controls (12%), but the combined incidence of alveolar/bronchiolar adenoma and carcinoma was not significantly different. Female mice exhibited a negative trend for lung adenomas. The histologic importance of the increased incidence of lung adenomas in males is equivocal because of variability of tumors (12, 22, 22, 12 and 28% in the 0, 10, 1,000, 5,000, 10,000 ppm groups, respectively) and the lack of a

dose-response. Furthermore, the reported laboratory control incidence (38%) and that found in other laboratories is considerably higher than the concurrent control incidence (12%). No other neoplastic lesions were considered to be of biological importance. **The chronic LOEL is 1000 ppm (129 mg/kg/day) based upon centrilobular hepatocytomegaly in males. The NOEL is 10 ppm (1.2 mg/kg/day).**

This chronic oncogenicity study in mice is classified as acceptable and does satisfy the Subdivision F guideline requirement (§ 83-2).

Chronic toxicity study in dogs
EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID #40271965), male and female Beagle dogs [6/sex/dose] were fed diets containing triasulfuron (purity not specified) at 0, 100, 1,000 or 5,000 ppm (0, 2.5, 25, 125 mg/kg/day, respectively) for 1 year. The high dose group received 10,000 ppm for the first 10 weeks, which was reduced to 5,000 ppm due to reduced weight, food intake, and hematological changes. In addition, 2 dogs/sex/dose were sacrificed at 13 weeks. Parameters evaluated were: survival, body weight, food consumption, clinical signs of toxicity, changes in ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, and gross and histological changes. No statistical analyses were conduced for any of the parameters evaluated, rather results were presented as the mean and standard deviation.

Both sexes of dogs in the high dose group developed signs of anemia, and had increased relative organ weights (spleen, pituitary and kidney in females, and spleen, liver in males), liver vacuolization, Kupffer cell pigment, spleen pigment, red pulp hyperplasia (females), and mandibular gland lymphoid hyperplasia. Males in the 1,000 ppm group also had increased relative liver weight, which was not dose-related (3.6± 0.714 g vs. 2.91± 0.287 g in controls), and did not appear to be statistically elevated. Males at all doses showed a dose-dependant increased incidence and severity of prostate cystic hyperplasia (1/5, 2/5, 3/6 and 5/5 for males at terminal sacrifice in the 0, 100, 1,000 or 5,000 ppm groups, respectively). Slight hyperplasia was noted in the control and low dose groups, while more severe hyperplasia was present in the mid and high dose groups. There were no treatment-related effects on mortality, clinical signs, ophthalmic changes, clinical chemistry, or urinalysis results. Mean body weight and food consumption were unaffected by treatment, except for the high dose dogs during the first 10 weeks at 10,000 ppm where there were decreases of approximately 10%. **The chronic toxicity LOEL is 1,000 ppm (25 mg/kg/day) based upon increased prostate cystic hyperplasia. The NOEL is 100 ppm (2.5 mg/kg/day).**

This chronic toxicity study in dogs coupled with supplementary historical control data for pituitary cysts and prostate cystic hyperplasia (MRID#40542401) is classified as acceptable and does satisfy the Subdivision F guideline requirement for a chronic toxicity study in dogs (§ 83-1).

21 Day Dermal Study in Rabbits
EXECUTIVE SUMMARY:

In a 21 day dermal study (MRID #41585801), triasulfuron (94.5%) in 0.5% carboxymethylcellulose and 0.1% polysorbate 80 was dermally applied to the shaved backs (10% of body surface area) of male and female New Zealand rabbits [5/sex/dose] for 6 hours at doses of 0, 10, 100 or 1,000 mg/kg/day. The animals were then observed for systemic signs of toxicity and signs of local irritation. Other parameters evaluated include: survival, body weight, food consumption, hematology, blood chemistry, urinalysis, organ weights, and gross and histological changes.

There were no treatment-related effects on survival, local irritation, body weight, food consumption, blood chemistry, urinalysis results, organ weights or gross and histological changes. Clinical observations in treated animals included dyspnea, ruffled fur, signs of sedation and abnormal body positions. At 10 mg/kg/day, 1/5 females had dyspnea and ruffled fur, while no symptoms were observed in males. Dyspnea occurred on days 11, 12 and 13, and ruffled fur occurred on days 11-15. Animals exposed to 100 mg/kg/day exhibited a greater incidence of dyspnea (3/5 males and 3/5 females), and ruffled fur (2/5 males and 5/5 females). The onset of dyspnea and ruffled fur was earlier and the duration of the symptoms was longer in the 100 and 1,000 mg/kg/day groups (i.e., appearance of symptoms on day 5 and 2, respectively). Sedation (1/5 males and 3/5 females) and abnormal body position (2/5 males and 1/5 females) were also noted in the high dose group. **The systemic LOEL is 10 mg/kg/day for females and 100 mg/kg/day for males based upon observations of dyspnea and ruffled fur. The NOEL for males is 10 mg/kg/day, and a NOEL was not determined for females. The dermal LOEL is > 1,000 mg/kg/day and the dermal NOEL is 1000 mg/kg/day.**

This 21 day dermal study in rabbits is classified as acceptable and does satisfy the Subdivision F guideline requirement (§ 82-2). Although this study does not identify a NOEL for female rabbits, the observed effects are considered borderline treatment-related effects, and did not persist throughout exposure (i.e., occurred on days 11-15). Therefore, an additional study is not required.

3-Month feeding study in mice
EXECUTIVE SUMMARY:

In a 91-day subchronic toxicity study (MRID #40728316), triasulfuron (93.7%) was administered to male and female CD-1 albino mice [10/sex/dose] in the diet at dose levels of 0, 10,000, 20,000, 30,000, 40,000/1000/40,000 or 50,000/5000/50,000 ppm (0, 1500, 3000, 4500, 6000, 7500 mg/kg/day, respectively). Due to signs of toxicity, dose levels in the 40,000 and 50,000 ppm groups were reduced to 1000 and 5000 ppm, respectively during weeks 2 through 8, and were subsequently re-established on week 9. In addition, 10/sex/dose were sacrificed at 28 days. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, hematology, clinical pathology parameters, urinalysis, organ weights, and gross and histological changes. In addition, mice were palpated weekly for tissue masses.

Adverse treatment-related toxicological effects were noted on survival, body weight, food consumption, clinical laboratory parameters, and clinical, gross, and histopathological findings. Urinalysis results were unremarkable. There were no toxicologically important or significant changes in hematology values, and all values were within the normal range for historical controls.

Mean body weight changes were decreased for the 13 weeks of the study in all dosed groups of males by 24 to 62% and were significantly less than controls ($p<0.01$) in the 30,000 and 50,000 ppm groups. Total weight gains of dosed females were not significantly lower than controls at any dose. Food consumption was significantly reduced in ≥ 30,000 ppm females and in 50,000 ppm males on week 1. Liver weights were significantly increased in males and females exposed

to ≥20,000 ppm triasulfuron, while the liver enzyme SGPT was significantly increased in males exposed to 30,000 ppm. Several of the mean liver enzyme values were above the historical control range, but were not statistically significant due to a large standard deviation. Morphological changes in the liver were characterized as dose-related increases in degenerative megalocytosis in both sexes at 20,000 and 30,000 ppm, and as dose-related hepatocellular necrosis in females at doses of ≥10,000 ppm and in males at doses of ≥20,000 ppm. **The subchronic LOEL is ≤10,000 ppm (1500 mg/kg/day) based upon hepatocellular necrosis in females. The NOEL is <10,000 ppm (1500 mg/kg/day).**

This subchronic toxicity study in mice is classified as acceptable non-guideline and does not satisfy the Subdivision F guideline requirement (§ 82-1) for a subchronic oral study because microscopic examination was limited to selected tissues and no ophthalmological examination was performed. In addition, the dose levels were varied in the 40,000 and 50,000 ppm dose groups and histopathology was performed only on the animals that died in these groups.

3-Month feeding study in rats
EXECUTIVE SUMMARY:

In a 90-day subchronic toxicity study (MRID #40271947), triasulfuron (94.5%) was administered to male and female Sprague-Dawley Crl:COB CD(SD)BR strain rats [10/sex/dose] in the diet at dose levels of 0, 200, 10,000, or 20,000 ppm (0, 10, 500, or 1,000 mg/kg/day, respectively). In addition, 5/sex in the control and high-dose groups were sacrificed after a 4 week recovery period. Parameters evaluated were: moribundity, survival, body weight, food consumption, clinical signs of toxicity, hematology, clinical chemistry parameters, urinalysis, indirect ophthalmoscopy, organ weights, and gross and histological changes.

Rats of both sexes in the mid and high dose groups weighed significantly less (17-25% for males and 19-22% for females) and ate significantly less (10-16% for males and 14-18% for females) than controls. Hematuria, which appeared to be treatment-related, was noted in both sexes (3/5 high dose males, and 1/10 and 10/15 mid- and high-dose females, respectively). Dose-related histopathologic changes were noted in the kidney of females (atrophy and epithelial hyperplasia), but not males, which were statistically significant in the 20,000 ppm dose group. In addition, basophilia (5/10) and chronic lymphocytic inflammation (6/10) were also statistically increased in high-dose females. Renal and urinary bladder calculi were observed in 3/10 and 8/10 females in the mid- and high-dose groups, respectively (significance not reported). Significant hematological and clinical chemistry findings in females include: increased neutrophils, creatinine, and phosphorus in the 10,000 ppm group, increased neutrophils, white blood cells, platelets, BUN, creatinine, and phosphorus, and decreased red blood cells, hematocrit, protein, albumin, urinary pH and bilirubin in the 20,000 ppm group. In males, significant findings include: decreased protein, bilirubin, potassium, calcium, urinary protein and ketones in the 10,000 ppm group, decreased neutrophils, monocytes, protein, bilirubin, potassium, calcium, BUN, LDH, SGOT, urinary pH, protein and ketone levels, and increased lymphocytes, creatinine, phosphorus and A/G ratio in the 20,000 ppm group. Significant findings in the 20,000 ppm recovery group include: decreased protein, cholesterol, BUN, chloride, glucose, and A/G ratio (females) and increased phosphorus (males). While many of these changes are

statistically elevated and consistent with kidney damage, most of these parameters are within control ranges for rats.

A number of statistically significant changes in absolute and relative organ weights were observed. However, increases in relative organ weight may be a direct consequence of decreases in body weight. Significant changes in absolute organ weights in the 10,000 ppm group include: decreased heart weight (female), and decreased spleen and brain weights (male). Significant changes in the 20,000 ppm include: increased kidney weight (females), decreased heart weight (males and females), and decreased liver, spleen, heart and brain weights (males). The only significant absolute organ weight change in the 20,000 ppm recovery group was reduced kidney weight in males. **The subchronic LOEL is 10,000 ppm (500 mg/kg) based upon decreased body weight and decreased food intake in males and females and increased kidney atrophy and epithelial hyperplasia in females (not statistically significant until 20,000 ppm). The NOEL is 200 ppm (10 mg/kg/day).**

This subchronic toxicity study in rats is classified as acceptable and does satisfy the Subdivision F guideline requirement (§ 82-1) for a subchronic oral study.

Reverse gene mutation - Salmonella typhimurium
MRID: 40271951
Date: 5/31/83
Core Grade: Acceptable Guideline
Strains TA 98, 100, 1535, 1537, 1538 tested at 0, 4, 16, 64, 256 μg/0.1 ml in absence and presence of metabolic activation. Negative up to cytotoxic concentrations, 64 and 256 μg/0.1 ml.

Reverse gene mutation, recombination and gene conversion in Saccharomyces cerevisiae
MRID: 40271952
Date: 6/29/84
Core Grade: Provisionally Acceptable
Strain D7 exposed to test article at 0, 46.9, 187.5, 750, 3000 μg/ml in absence and presence of metabolic activation. Negative up to 3000 μg/ml. Deficiency: not tested up to limit concentration for negative study: 5000 μg/ml. Provisionally acceptable pending toxicity test and new study at 5000 μg/ml.

Forward gene mutation in mammalian cells: L5178Y/TK
MRID: 40271953
Date: 7/31/86
Core Grade: Acceptable
Cells tested with and without metabolic activation at 0, 260, 520, 1040, 1560, 2080, 2340, 2600 μg/ml and 0, 300, 600, 1200, 1800, 2400, 2700, 3000 μg/ml, respectively. Negative up to levels of moderate cytotoxicity.

In vivo cytogenicity study (micronucleus/Chinese hamsters)
MRID: 40271954
Date: 9/6/84
Core Grade: Acceptable
Administered orally to Chinese hamsters at 0, 625, 1250, 2500 mg/kg/day on each of 2 consecutive days. Negative for induction of micronuclei and/or other nuclear anomalies at doses reaching the limit dose: 5000 mg/kg (2500 mg/kg/day X 2).

UDS study: DNA damage and repair in vitro in rat hepatocytes
MRID: 40271955
Date: 9/6/84; 12/9/86 (supplement)
Core Grade: Acceptable
Rat hepatocytes exposed to test substance at 0, 2, 10, 50, 250 μg/ml. Negative up to limit of solubility (250 μg/ml) for inducing UDS.

UDS study: DNA damage and repair in vitro in human fibroblasts
MRID: 40271956
Date: Date: 9/6/84; 12/9/86 (supplement)
Core Grade: Unacceptable
Fibroblasts exposed to test substance at 0, 10, 50, 250 μg/ml. Negative, however, no metabolic activation series, no attempt to minimize background of S-phase cells, no background grain counts included in analysis.

MRID: 40728319
Date: 3/4/88
Core Grade: Acceptable Guideline
Metabolism of [(U-^{14}C)Phenyl]triasulfuron was studied in 5/sex Wistar rats. Material administered orally as a single low dose (0.5 mg/kg) & high dose (300 mg/kg), single low dose after daily doses of unlabeled material for 14 days (0.5 mg/kg/day) or single i.v. dose of 0.5 mg/kg. 92-109% of dose recovered within 96 hours: 74-99% in urine & 2-14% in feces. Elimination rates after repeated oral dosing faster than after single dose. Residue levels in tissue < 0.1%. Levels in tissues higher after single high dose than after single low dose. Even after repeated administration at low dose, no radioactivity retained by animals. Metabolite patterns in urine, fecal and liver extracts show mainly parent compound. Variety of minor metabolites: 12 urinary (6.6-8.1%), 10 fecal (1.2-2.9%) of the administered radioactivity, respectively. No significant differences in metabolite patterns between sexes.

Distribution, degradation and excretion in the rat after oral application
MRID: 40271966
Date: 4/10/85
Core Grade: Unacceptable for a total metabolism study.
When uniformly labeled in the phenyl ring, triasulfuron is excreted mainly in the urine (>87%) and to a lesser extent in the feces. Most of the radiolabel is excreted within the first 24 hours. The major metabolite is tentatively identified as unchanged triasulfuron in both urine and feces. Three minor metabolites have also been separated by TLC but not structurally identified. Only 2

rats/sex/dose (2 dose levels).

Metabolism in the rat after oral application
MRID: 40271966
Date: 11/26/86
Core Grade: Unacceptable for a total metabolism study.
Six metabolites and the parent compound were identified in the pooled 24 hour urine of 10 male rats. Major radio labeled component of urine was the parent (68.3%). Cleavage of the bridge between the phenyl and triazine rings occurred to a slight extent. Other metabolic pathways consisted of hydroxylation, sulfate formation, demethylation and cleavage of the choroethyl side chain. Only male rats were used and no attempt was made to identify fecal metabolites.

Distribution, degradation and excretion of triasulfuron in the rat after oral administration
MRID: 40271966
Date: 4/10/85
Core Grade: Unacceptable for total metabolism study.
When labeled in the 2 and 6 position of the triazine ring, triasulfuron is mainly excreted in the urine (>70%) and to a lesser extent in the feces. Most of the radiolabel is excreted within the first 24 hours. The major metabolite is tentatively identified as unchanged triasulfuron in both urine and feces. Three minor metabolites have also been separated by TLC but not structurally identified. Only 2 rats/sex/dose (2 dose levels).

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Chemical:	**Benzenesulfonamide, 2-(2-chloroethoxy)-N**
PC Code:	**128969**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/10/98**
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