

US EPA ARCHIVE DOCUMENT



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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

AUG 03 1992

MEMORANDUM

SUBJECT: F Petition for Tolerance for Sulfosate (Touchdown®; EPA reg. 10182-276) in/on Citrus, resulting from the use of Touchdown® concentrate (EPA Reg. No. 10182-276), Touchdown® 6 (EPA Reg. No. 10182-324), and the formulation Touchdown® 4LCE (EPA reg. No. 10182-277) and Labels Review.

Tox. Chem. No. 893C
PD No. 128501
Project No. 1-1785A
ID No. OF03890
Submission No. S380457
DP Barcode No. D154588

TO: R. Taylor/E. Allan, PM Team # 25
Registration Division (H7505C)

FROM: Nguyen B. Thoa, Ph.D. *rd 07/28/92*
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Health Effects Division (H7509C)

jr THRU: Roger L. Gardner, Section Head *Pamela M. Kinley*
Section I, Toxicology Branch I *7/30/92*
Health Effects Division (H7509C) *K/B 3/3/92*

I. Actions Requested:

ICI Americas, Inc., Agricultural Products, Wilmington, Delaware, has submitted a Petition for tolerance for Sulfosate in/on the raw agricultural commodity Citrus fruits at 0.5 ppm. The proposed tolerance level is for the combined residues of Sulfosate (Trimethylsulfonium carboxymethylaminomethylphosphonate) and its metabolite aminomethylphosphonic acid (AMPA) in/on citrus fruits, resulting from the use of Touchdown® concentrate (EPA Reg. No. 10182-276), Touchdown® 6 (EPA Reg. No. 10182-324), and the formulation Touchdown® 4LCE (EPA reg. No. 10182-277).

RD also requests a review of the 3 proposed labels.



II. Conclusions:

- A. The Toxicological Data Base on Sulfosate is incomplete and Toxicology Branch (TB) cannot act favorably on the request for tolerance. The following are data gaps:
1. Acute delayed Neurotoxicity/hen (81-7a): Sulfosate is a salt with a 1:1 molar ratio of a tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethylphosphonate).
 2. Acute Neurotoxicity/mammals (81-7b): This test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.
 3. 90-Day Neurotoxicity/mammals (82-5b): Sulfosate has demonstrated neurotoxicity in acute oral, dermal and inhalation toxicity studies.
 4. Acute Inhalation toxicity study (81-3) with Touchdown 4LCE.
 5. In addition, TB will require a 28-Day Neurotoxicity/hen (82-5a) if the acute delayed Neurotoxicity/hen is positive.
- B. Sulfosate needs to be submitted to the HED RfD Mini Peer Review, for an RfD evaluation and toxicological assessments of its potential for inducing oncogenicity, developmental and neurotoxicity, before tolerances can be established.
- C. As far as TB is concerned, the proposed labels for Touchdown® concentrate, Touchdown® 6, and Touchdown® 4LCE are presently adequate. All three proposed labels bear the Hazard Signal Word "CAUTION", which properly reflects the acute Tox. Category III of both Sulfosate technical (Touchdown® concentrate and Touchdown® 6) and the formulation Touchdown® 4LCE (See Tox. Profile below). All three labels also bear the precautionary statement "KEEP OUT OF REACH OF CHILDREN". Additional label statements may be required, pending the results of an acute inhalation toxicity study with the formulated end-product and acute neurotoxicity studies (hen and mammals) with the technical grade (See Data Gaps below).
- D. Two formulations, Touchdown 4LC and 4LCE are included in the HED Tox one-liners. According to the data submitted in the Petition Package, the formulation involved in this petition is Touchdown 4LCE.

III. Background:

Sulfosate is a nonselective foliar systemic herbicide used to control a broad spectrum of emerged weeds. The proposed use is for the control of annual and perennial weeds in citrus (citron, grapefruit, kumquat, lemon, orange, tangelo, tangerine, and lime) groves.

Touchdown® concentrate (52.2% a.i.; 5.5 lbs. a.i./gallon) and Touchdown® 6 (57.6% a.i.; 6 lbs. a.i./gallon) are technical grade liquid concentrates. Touchdown® 4LCE is a liquid formulation containing 39.9% a.i. (4 lbs. a.i./gallon) and 60.1% inert ingredients which use were cleared by the Agency.

The petitioner proposes a postemergence application by broadcast, spot spray, and/or wiper equipment to actively growing weeds, at a maximum rate of 4 lbs. a.i./acre/year. Fruits will be harvested 14 days from the last application.

Based on the results from 16 residue field trials conducted in the major citrus growing States of California, Florida, and Texas, applications at twice the maximum proposed annual rate will result in residues levels in/on citrus fruits below the proposed tolerance level.

IV. Toxicological Data Requirements (CFR 158.340)

A. Technical Sulfosate*:

Use Pattern: New chemical/Food and Feed Use

Last Updated: 07/27/92

		<u>Required</u>	<u>Satisfied</u>
81-1	Acute Oral Toxicity	yes	yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
81-7a	Acute Delayed Neurotox/hen	Yes+	No
81-7b	Acute Neurotoxicity/mammals	Yes#	No
82-1a	90-Day Oral (rodent)	Yes	Yes
82-1b	90-Day Oral (non-rodent)	Yes	Yes
82-5a	28-Day Neurotoxicity/hen	++	
82-5b	90-Day Neurotoxicity/mammal	Yes##	No
83-1a	Chronic Toxicity (rodent)Yes	Yes	
83-1b	Chronic Toxicity (non-rodent)	Yes	Yes
83-2a	Oncogenicity study (rat)	Yes	Yes
83-2b	Oncogenicity study (mouse)	Yes	Yes
83-3a	Teratology (rat)	Yes	Yes
83-3b	Teratology (rabbit)	Yes	Yes
83-4	2-generation Reproduction (rat)	Yes	Yes
84-2a	Mutagenicity - Gene Mutations	Yes	Yes
84-2b	Mutagenicity - Structural Chromosomal Aberrations	Yes	Yes
84-4	Mutagenicity - Other Genetic Effects	Yes	Yes
85-1	Metabolism	Yes	Yes

* The percent a.i. of technical grade sulfosate may vary from 19.2 to 62.0%, as a result of diluting the technical grade with the highest obtainable a.i. concentration (62%) in various amounts of water.

+ Sulfosate is a salt composed of one fixed tertiary sulfur cation (trimethylsulfonium) and one phosphonate anion (carboxymethylaminomethylphosphonate).

++ May be required if the acute delayed neurotoxicity study in hen (81-7) is positive.

Required for all new pesticides in the near future

Sulfosate has demonstrated neurotoxicity in acute oral, dermal and inhalation toxicity studies.

B. Formulation Touchdown 4LCE (39.8% ai):

Use Pattern: New chemical/Food and Feed Use

Last Updated: 07/27/92

		<u>Required</u>	<u>Satisfied</u>
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	No
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-2	21-Day Dermal	Yes	Yes

IV. TOXICOLOGICAL PROFILE

Updated 07/27/92

SULFOSATE TECHNICAL:

- 81-1 Acute Oral Toxicity in Rats.
MRID 249802
STAUFFER CHEMICALS
T11185
November, 1982.

Acceptable
- LD₅₀ = 748 mg/kg (males)
LD₅₀ = 755 mg/kg (females)
Doses used: 500, 550, 600, 700, 800,
and 900 mg/kg by gavage
Signs: mild to severe depression,
prostration, tremors,
and slow/shallow respiration.
Product tested: SC-0224 62% a.i.
- TOXICITY CATEGORY: 3
- 81-2 Acute Dermal Toxicity in Rabbits
MRID 249802, 260508
Stauffer CHEMICALS
T-11185
November, 1982.

Acceptable
- LD₅₀ > 2000 mg/kg (Both sexes;
intact or abraded skin).
Doses used: 800 -2200 mg/kg.
Signs: Rabbits with abraded skin
showed mild to severe depression
at all doses levels and mild to
moderate erythema. Rabbits with skin
intact showed mild depression and
mild erythema.
Product tested: SC-0224 62% a.i.
- TOXICITY CATEGORY: 3
- 81-3 Acute inhalation toxicity in rats
MRID 249802
Stauffer Chem No.
T-11084
November, 1982

Acceptable
- LC₅₀ > 6.9 mg/L (both sexes, 4-hr,
whole body exposure)
Actual chamber concentration:
6.9 mg/L
MMAD = 3.5 um at 64 min.
2.8 um at 184 min.
SIGNS: wet fur, salivation,
chromorrhinorrhea
Product tested: Sulfosate (62% a.i.)
- TOXICITY CATEGORY 3

81-3

Acute inhalation
toxicity in rats
MRID 412359-01
ICI
No: CTL/P/2254
08/25/88

Unacceptable

LC₅₀ > 5.18 mg/L (4-hr, nose only
exposure)
Actual chamber concentration: 2.65-
6.3 mg/L
MMAD: 4.56 ± 2.06 um
[20% ≤ 2.5 um (inhalable) & 3.9% ≤ 1
um (respirable)]
No mortality observed.
SIGNS: (CNS & Autonomic) salivation,
splayed gait, head & paw flicking,
tail erection, shaking, subdued
behavior, slow/deep breathing,
decrease response to sound. Effects
subsided on day 2.
A limit test was not reached since
only 3.9% of the aerosolized sulfosate
particles were of respirable size
(EPA requires 25%).
Product tested: Sulfosate 57.6% a.i.
and [REDACTED]
This study may be upgraded to
acceptable when evidences are
provided to show that optimum
technology was used in generating
the sulfosate containing aerosol.

TOXICITY CATEGORY:

81-4

Primary Eye
Irritation in
Rabbits
MRID 249802
STAUFFER CHEMICALS
T-11185
November, 1982.

Acceptable

No effect on cornea.
Effects on unwashed eyes: mild
iritis (1/6 rabbits), and mild
conjunctivitis (6/6 rabbits) at 24
hr (Draize score). All effects
reversible by day 7.
Effects on eyes washed after 20-30
sec. exposure: mild conjunctivitis
(3/3 rabbits) lasting 3 days.
Dose used: 0.1 ml SC-0224 62% a.i.

TOXICITY CATEGORY: 3 (based on mild
irritation of conjunctiva).

INSERT INGREDIENT INFORMATION IS NOT INCLUDED

81-5	Primary Dermal Irritation in Rabbits MRID 249802 STAUFFER CHEMICALS # T-11185 November, 1982. Acceptable	24-hr exposure. <u>Effects at 24 hr:</u> intact and abraded skin showed mild erythema. Mild edema observed in 3/6 rabbits with skin abraded and 1/6 rabbits with skin intact. All dermal effects reversed within 72 hrs. <u>Primary Irritation Score:</u> 0.67. <u>Dose used:</u> 0.5 ml SC-0224 62% a.i.
TOXICITY CATEGORY: 4		
81-6	Dermal Sensitization in Guinea Pigs MRID 258398 Richmond Tox. Labs. # T-11269 October 12, 1984. Acceptable	SC-0224 Technical (56.3% a.i) is a mild skin sensitizer (Open Epicutaneous Test)
82-1(A)	Subchronic feeding rat MRID 412099-02 Stauffer Chem No. T-10888 4-3-87 Acceptable	<u>NOELs:</u> 800 ppm (MDT, 36 mg/kg/day) in males and 2000 ppm (HDT, 108 mg/kg/day) in females. <u>LOEL:</u> 2000 ppm (88 mg/kg/day) in males, based on a significant overall decrease in body weight gain (22% below controls). The HDT only caused sporadic and minimal decreases in body weight in females (secondary to a feed palability - related reduction in feed intake) and no significant overall decrease in B.W. gain. No significant changes were observed in clinical chemistry, hematology, urinalysis, organ weights, or macroscopic/microscopic histopathology. <u>Doses tested:</u> 0, 150, 350, 800, and 2000 ppm. <u>MTD was reached for males only.</u> Product tested: Sulfosate (19.2% a.i., 75.6% water)

82-
1(b)

Subchronic feeding
dog
MRID 412099-02/03
Stauffer Chem
No. T-11002
4-3-87

Acceptable

NOEL: 10 mg/kg/day (LDT)
LOEL: 50 mg/kg/day (HDT) based on
increase incidences and earlier
onset of emesis and salivation.
No changes in B.W., food
consumption, clinical chemistry,
hematology, urinalysis, organ
weights, or macroscopic/microscopic
histopathology were observed.
Doses tested: 0, 10, 25, and 50
mg/kg/day by gavage.
Dog's Strain: Beagle
Product tested: Sulfosate (19.2%
a.i., 75.6% water).

83-1a
83-2b

Feeding/Oncogenic
(2-year) in Mice
MRID 402140-06
412099-07
Stauffer Chem
No. T-11813
4/3/87

Guideline

Oncogenic NOEL: >8000 ppm (HDT)
Systemic NOEL: 1000 ppm (MDT)
Systemic LOEL: 8000 ppm based on
decreases in B.W. and feed
consumption (both sexes), increases
incidences of white matter
degeneration in lumbar spinal cord
(males only), and increase
incidences of duodenal epithelial
hyperplasia (females only).
Doses used: 0, 100, 1000, and 8000
ppm
Mice strain: Charles River
Test material: Sulfosate 56.17% a.i.

83-1a
83-2a

Feeding/Oncogenic
(2-year) in Rats
MRID 402140-07
412099-05
Stauffer Chem
No: T-11082
4/4/87

Guideline

Oncogenic NOEL: >1000 ppm (HDT)
Systemic NOEL: 100 ppm (LDT)
Systemic LOEL: 500 ppm (MDT) based
on decreased levels of lactate
dehydrogenase in males and females
at 6 and 12 months.
Effects at 1000 ppm: Decreases in
B.W.(both sexes) and increase
incidences of chronic laryngeal and
nasopharyngeal inflammation (males).
Doses used: 0, 100, 500, and 1000
ppm
Rats strain: Charles River CrL:CD
(SD)BR.
Test material: Sulfosate 56.17% a.i.

83-
1(b) Chronic Feeding
(1-year) in Dogs
MRID 402140-05

Stauffer Chem.
No: ECH T-11075
4/3/87

Minimum

Systemic NOEL: 10 mg/kg/day (MD)
Systemic LOEL: 50 mg/kg/day (HD)
based on decreases in LDH.
Doses used: 0, 2, 10, and 50
mg/kg/day, by gavage.
Selection of above dose range was
based on (i) a 28-Day oral gavage
study in which 150 mg/kg/day was
lethal within 3 days and 75
mg/kg/day produced emesis, and
(ii) a 90-Day study in which 50
mg/kg/day produced increase in
emesis and salivation.
Dog's Strain: Beagle
Test material: Sulfosate 56.2% a.i.

83-
3(a) Teratogenicity
in Rats
MRID 249802
Stauffer Environ.
Health Cen.
No: T-11050
November 1982

Guideline

Terato.NOEL: >333 mg/kg/day (HDT)
Fetotoxic NOEL: 100 mg/kg/day (MDT)
Fetotoxic LOEL: 333 mg/kg/day based
on significant decreases in B.W.
Maternal NOEL: 100 mg/kg/day.
Maternal LOEL: 333 mg/kg/day based
on significant decreases in B.W. and
feed intake.
Effects at 333 mg/kg/day: Two
deaths. Signs were significant
increase in incidences of lethargy,
salivation, and chromorrhinorrhea.
Doses used: 0, 30, 100, and 333
mg/kg/day by gavage to S-D rats.
Test material: Sulfosate 19.2% a.i.

83-
3(b) Teratogenicity
in Rabbits
MRID 260966
Stauffer Chem.
No: T-11052
6/21/83

Guideline

Developmental NOEL: >100 mg/kg/day
(HDT). A/D ratio= 10/<100= <0.1.
Maternal NOEL: <10 mg/kg/day (LDT)
(Significant increase in incidences
of diarrhea, head tilt, nasal
discharge, wet stains on chin, red
urine stain).
Effects at 100 mg/kg/day: 38%
mortality, 36% spontaneous abortion,
significant decrease in feed intake,
and in number of live fetuses per
litter.
Doses used: 0, 10, 40, and 100
mg/kg/day by gavage to D1a;(NZW)SPF
rabbits.
Test material: Sulfosate 56.2% a.i.

83-4	Reproduction (2-gen) in Rats MRID 258398 264429 Stauffer Chem. No: T-110-51 4/19/84 Guideline	<u>Reproductive NOEL:</u> >2000 ppm (HDT) <u>Systemic NOEL:</u> 150 ppm (LDT) <u>Systemic LOEL:</u> 800 ppm (MDT) based on reduced feed intake and B.W. in pups and parents, reduced absolute thymus weight (P1 M+F), increase platelet count (F2B adults, M+F). <u>Doses used:</u> 0, 150, 800, and 2000 ppm in Crl CD(SD)Br strain. Test material: sulfosate 19.2% a.i.
84- 2(a)	Mutagenicity Reverse mut. (Ames Test) in Salmon. Typhi. MRID 249802 Stauffer Chem. No:T-10487 1/19/82 Acceptable	<u>Not mutagenic</u> at concentrations of 0.12, 0.37, 1.11, 3.33, and 10 mg/plate without S9, and of 0.56, 1.11, 1.67, 3.33, 5.0, 10, and 15 mg/plate with S9. <u>Tester Bacteria:</u> TA1535, TA1537, TA1538, TA98, and TA100 from Dr. Ames. <u>Pos. controls:</u> Na azide, 9- aminoacridine (9-AA), 2- nitrofluorene (2-NF), and 2-aminoanthracene (2-AA). Test material:sulfosate 90% a.i (estimated purity).
84- 2(a)	Mutagenicity Reverse mut. (Ames Test) in Salmon. Typhi. MRID 260966 Stauffer Chem. No: T-12660 9/25/85 Acceptable	<u>Not mutagenic</u> at concentrations of 2.5, 5, 10, 20, and 40 ul/plate, with or without S9. <u>Tester Bacteria:</u> TA1535, TA1537, TA 98, and TA100. <u>Pos. controls:</u> Na azide, 9-AA, 2-NF. <u>Cytotoxic Dose:</u> HDT Test material: Sulfosate 55.6% a.i.
84- 2(a)	Gene Mutation (SLRL) in Drosophila melanoga MRID 249802 Litton Bionetics No: 22169 6/13/82 Acceptable	<u>Not mutagenic</u> at doses of 25 and 50 mg/ml in "Sex linked recessive lethal test". <u>Pos. control:</u> EMS

84-
2(a)

Gene Mutation
(Forward Mut.)
Mouse Lymphoma
MRID 249802
Stauffer Chem
T-10848
2/8/1982

Acceptable

Not mutagenic without S9.
Significant reproducible increase in mutation frequency in presence of S9. Test medium pH not mentioned but was probably in the acid range.
Indicator cells: L5178Y (TK⁺/)
mouse lymphoma cell line from Dr. Clive, RTP, No. Carolina).
Concentrations used: 0.38, 0.75, 1.50, 3, 6, 8, 8.5, 9, and 10 mg/ml in presence of S9, and 0.38, 0.75, 1.5, 3, 6, 7, 8, 9, and 10 mg/ml w/o S9.
Cytotoxic concentrations: >7 mg/ml

84-
2(a)

Gene Mutation
(forward mut.)
Mouse Lymphoma
MRID 260966
Stauffer Chem.
No. T-12661
12/19/1985

Acceptable

Introduction of sulfosate in the test incubation medium reduced its pH to an acid range (5.67 -7.07).
Under this experimental condition, sulfosate was positively mutagenic both in the presence of S9, at concentrations of 3-5 ul test material/ml, or without S9, at concentrations of 3.5 to 5ul/ml).
When the pH of test incubation medium was readjusted to a physiological level of 7.4 (Addendum of 3/20,1987), concentrations from 5 to 10 ul/ml lost their mutagenic effect
Indicator cells: L5178Y(TK⁺/)
mouse lymphoma cell line (Dr. Clive, RTP, No. Carolina).
Test material: Sulfosate 55.6% a.i.
Cytotoxic concentrations:
Unadjusted acidic medium: >5ul/ml pH
adjusted medium: >7.75 ul/ml
Pos. controls: N-Nitrosodimethylamine (DMN) with S9 and Ethylmethanesulfonate (EMS) wo S9.

84-
2(b)

Mutagenicity
Cytogenetic
Rat bone marrow
MRID 249802
Stauffer Chem.
No: T-10884
september 1982

Acceptable

Test animals: 6-wk old
CD-Crl:CoBScd(SD)BR male rats.
Not mutagenic (did not induce any structural chromosome aberrations in rats' bone marrow cells.
Doses used: 21, 63, and 188 mg/kg (LD₅₀= 565 mg/kg).
Test material: sulfosate 58.5% a.i.
Pos. control: cyclophosphamide

84- 2(b)	<p>Mutagenicity (Micronucleus assay) Mouse bone marrow MRID 402140-04 412099-08 Stauffer Chem. No: EHC-T-12689 4/23/87</p> <p>Acceptable</p>	<p>Test animals: Charles River D-1 str. <u>Not mutagenic</u> (did not induce any increase in the number of PCE containing micronuclei). <u>Doses used:</u> 700, 900, and 1100 mg/kg in males and 400, 600, and 800 mg/kg in females, based on results of a range finding study in which doses >1400 mg/kg killed 3/3 males within 48 hrs and doses >1000 mg/kg killed 2/3 females.</p>
84- 2(b)	<p>Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-10875 7/6/1982</p> <p>Acceptable</p>	<p><u>Positive mutagenicity (induces structural chromosomal aberration in CHO cells both in the absence of S9, at the concentration of 4 mg/ml, and in its presence, at concentrations of 10 and 12 mg/ml.</u> Sister chromatid exchange (SCE) was not determined. <u>Concentrations used:</u> 2, 4, and 6 mg/ml w/o S9 and 2, 4, 6, 8, 10, and 12 mg/ml with S9. Test material: Sulfosate 58.5% a.i.</p>
84-2(b)	<p>Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-11019 7/22/82</p> <p>Acceptable</p>	<p><u>Positive mutagenicity (Induces structural chromosomal aberration in CHO cells both in the absence of S9, at concentrations of 6-8 ul/ml, and in its presence, at 1-8 ul/ml.</u> <u>No increase in SCE was observed.</u> <u>Concentrations used:</u> 2, 4, 6, 8, 10, and 12 ul/ml. Test material: Sulfosate 72% a.i.</p>
84- 2(b)	<p>Mutagenicity (cytogenetic) in CHO cells MRID 260966 Stauffer Chem. No: EHC T-12663 12/18/1985</p> <p>Acceptable</p>	<p>pH of treatment medium was readjusted to 7.4-7.6 prior to testing. <u>Not mutagenic (did not induce any structural chromosome aberrations in CHO cells or any increase in SCE) at concentrations of 4-10 ul/ml, with or w/o S9.</u> <u>Cytotoxic concentrations:</u> None <u>Pos. controls:</u> Mitomycin C and Cyclophosphamide. Test material: sulfosate 55.6% a.i.</p>

84-
2(b)

Mutagenicity
(cytogenetic)
Mouse Lymphoma
MRID 260966
Stauffer Chem.
No: EHC T-12662
12/19/82

Acceptable

Indicator cells: L 5178Y (TK⁺/-) mouse lymphoma cell line from Dr. Clive, RTP, No. Carolina).
Sulfosate concentrations of 5 ul/ml (w/o S9) and >3 ul/ml (w S9) induced chromosomal aberrations in the mouse lymphoma cells and increased the number of SCEs when the pH of the test medium was not readjusted (5.62-7.07). When the pH was readjusted to 7.4 concentrations from 4-10 ul/ml were not mutagenic.
Cytotoxic concentrations: >5 ul/ml at acidic pH, and ≤ 10 ul/ml at physiological pH.
Pos. controls: Ethyl methane-sulfonate & N-nitrosodimethylamine.
Test material: 55.6% a.i.

84-4

Mutagenicity
BALB/3T cells
(morphological
transformation)
MRID 249802
Stauffer Chem.
No: T-10849
1/4/82

Acceptable

Indicator cells: 1-1 subclone of clone A-31 of BALB/3T3 mouse cells from Dr. Kanunaga (NCI).
Not mutagenic (did not induce an increase in the number of transformed foci)
Concentrations used: 0.313, 0.625, 1.25, 2.5, and 5 mg/ml .
Cytotoxic concentrations: >3 mg/ml
Test material: sulfosate 90% estimated purity.

85-1

Metabolism
in Rats
MRID 258398
Stauffer Chem.
PMS-148
2/4/85

Acceptable

Test material: (Methyl ^{14}C)
trimethylsulfonium
Carboxymethylaminomethylphosphonate)
96.5% purity, 20 mci/mmol.
Identification of the (Methyl ^{14}C)
trimethylsulfonium ion (^{14}C -TMS) in
urine and fecal extracts done by
TLC, GC/MS, autoradiography, and K
iodoplatinate spray.

After oral administration of 35
mg/kg (LDT) or 350 mg/kg (HDT) test
material to S-D rats of both sexes,
the ^{14}C -TMS ion is rapidly and
almost completely absorbed from the
GI tract and rapidly excreted
unmetabolized mostly via the kidney.
Urine recovery of ^{14}C (expressed as
% of administered dose were: 80.8-
95% at 24 hr and 91.4-98.5 at 120
hr. Most (95.3-97%) of the total
radioactivity was unmetabolized ^{14}C -
TMS ion.

Fecal recovery of ^{14}C (expressed as
% of administered dose were: 0.72-
4.03% at 24 hr and 0.95-7.19% at 120
hr. All the radioactivity was
unmetabolized ^{14}C -TMS ion.

$^{14}\text{CO}_2$ in expired air was negligible.
Tissues residues were negligible:
0-0.148 (LD) and 0-10.6 ppm (HD)
sulfosate equivalents.

The lack of metabolism may be
explained by the hydrophilic nature
of TMS ion.

Acute toxic effects at the HDT:
lethargy, ataxia, slow/labored
breathing, salivation, occasional
tremors. Signs lessened after 24
hrs.

85-1

Metabolism
in Rats
MRID 412359-03
ICI Americas Inc.
No: T-12906
12/20/88

Acceptable

Test material: Trimethylsulfonium
Carboxymethylaminomethylphosphonate
¹⁴C-radiolabeled on the anionic
moiety (Carboxymethylaminomethyl-
phosphonate), 93.2% radiopurity, 9.8
mCi/mmol.

Identification of anion by TLC,
autoradiography, and GC/MS.

Males and females S-D rats iv-
treated with 25 mg/kg (LDT) test
material excreted 90% of the
administered dose in urine.

After oral administration of the LDT
or the HDT (250 mg/kg), the test
material was rapidly excreted in
urine and feces (70-82% of the total
radioactivity administered was
excreted within 24 hrs, and 85-94%
within 120 hrs).

Absorption was incomplete: only 47-
57% of total radioactivity was
recovered in urine. Fecal excretion
was 36-42% of the administered dose.
Most of the recovered radioactivity
was unmetabolized carboxymethyl-
aminomethylphosphonate (80-90% of
urine and 77-96% of feces total
radioactivity). One fecal metabolite
was aminomethylphosphonic acid (8.5%
of total fecal radioactivity in
female rats dosed repeatedly (14
single daily LD of unlabeled test
material followed by a single LD of
labeled test material).

¹⁴CO₂ in expired air was negligible.
Combined tissue residues were only
≥0.32% of administered dose.

Carcasses contained 2.25% of the
administered dose, most of it
located in bones.

Acute toxic signs observed with the
HD: lethargy, moderate/severe
depression, tremors, dehydration,
and reduced feed consumption. Signs
lasted 72 hours.

IV. TOXICOLOGICAL PROFILE

Updated 3/05/91

FORMULATION TOUCHDOWN 4LCE (39.8% a.i.):

- | | | |
|------|---|---|
| 81-1 | Acute Oral Toxicity
in Rats.
MRID 408938-02
STAUFFER CHEMICALS
T12589
2/12, 1987.

Acceptable | LD ₅₀ = 1760 mg/kg (males)
LD ₅₀ = 1298 mg/kg (females)
SIGNS: depression, hypersensitivity
to touch and sound.
NECROPSY: dark livers, spleens,
and/or lungs, and test-like material
in GI tract.

TOXICITY CATEGORY: 3 |
| 81-2 | Acute Dermal
Toxicity in Rabbits
MRID 408938-02
Stauffer CHEMICALS
T-12589
November, 1987.

Acceptable | LD ₅₀ > 2000 mg/kg (Both sexes)
SIGNS: mild depression and diarrhea.

TOXICITY CATEGORY: 3 |
| 81-3 | Acute inhalation
toxicity in rats
MRID 408938-03
Stauffer Chem No.
T-12983
6/22/1987

Unacceptable | A respirable aerosol could not be
generated: the test material was
highly viscous and formed excessive
foam. Registrant was advised to
pursue additional testing. Ways to
reduce foaming were suggested
(Dilute test material, reduce
surfactants) as well as ways to
improve particulation (form dense
fog and run through a cyclone
separator to remove large
particles).

TOXICITY CATEGORY: Not classified |

81-4	Primary Eye Irritation in Rabbits MRID 408938-02 STAUFFER CHEMICALS # T-12589 2/12/1987.	<u>Unwashed eyes:</u> Moderate iritis, and mild to moderate conjunctival irritation. Effects cleared by day 7. <u>Eyes washed:</u> (Exposure of 20-30 sec.) Mild to moderate conjunctival irritation. Dose: 0.1 ml (pH of test material= 5.85). TOXICITY CATEGORY: 3
	Acceptable	
81-5	Primary Dermal Irritation in Rabbits MRID 408398-02 STAUFFER CHEMICALS # T-12589 2/12/1987	Non-irritating (4-hr exposure) TOXICITY CATEGORY: 4
	Acceptable	
81-6	Dermal Sensitization in Guinea Pigs MRID 408398-04 Stauffer Chem. No.T-12588 8/4/1987	Not a skin sensitizer (Modified Buehler test).
	Acceptable	
82-2	21-Day Dermal in Rats MRID 412099-04 Ciba-Geigy Corp. No: CTL/P/2496, LR0535 7/7/89	Doses: 25, 250, 1000 mg/kg/day (6hr/day/21 days) in 0.0021, 0.0027, and 0.0826 ml/100 g B.W. NOEL= 250 mg/kg (MDT) EFFECTS: dermal irritation in HDT males (dermal histology was normal). Slight increase in testes weight at 25 and 1000 mg/kg/day with normal histology. Occasional sciatic nerve fiber degeneration (1 male and 2 fem. out of a total of 10) at 1000 mg/kg/day.
	Acceptable	

V. Data Gaps:

A. With Tech. Sulfosate:

- (1) Acute delayed Neurotoxicity/hen (81-7a): Sulfosate (formerly SC-0224) is a salt composed of a fixed tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethyl-phosphonate). Phosphonate containing OPs are known to cause acute delayed neurotoxicity (DS Barrett & al in "A Review of organophosphorus ester-induced delayed neurotoxicity", Vet. Hum. Toxicol., 27, (1), feb. 1987.
2. Acute Neurotoxicity/mammals (81-7b): This test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.
3. 90-Day Neurotoxicity/mammals (82-5b): Sulfosate has demonstrated neurotoxicity in acute oral, dermal and acute toxicity studies (MRIDs 249802, 260508, 412359-01)
4. Acute Inhalation toxicity study (81-3) with Touchdown 4LCE.
5. In addition, TB will require a 28-Day Neurotoxicity/hen (82-5a) if the acute delayed Neurotoxicity/hen is positive.

B. With The Formulation Touchdown 4LCE:

An acute Inhalation toxicity study is required.

VI. Action Taken to Obtain Additional Information or Clarification:

RD has been notified of the Data Gaps cited above.

VII. Established Tolerances:

There are no existing tolerances for the pesticide sulfosate (trimethylsulfonium carboxymethylaminomethylphosphonate, formerly SC-0024). Tolerances are however established for glyphosate (iso-propylamine salt of carboxymethylaminomethylphosphonate), a pesticide closely related in chemical structure to sulfosate (40 CFR 180.364).

VIII. Reference Dose (RfD):

There are no defined RfD for sulfosate.

IX. Pending Regulatory Actions:

HED is not aware of any pending regulatory action against the registration of this pesticide.

X. Toxicological Issues Pertinent to Granting this Request:

- A. Sulfosate's potential for neurotoxicity is of concern. The following neurotoxic symptoms were observed in acute oral, dermal, or inhalation studies with both the technical product and the formulation:
- (1) Ataxia, tremors, mild to severe depression, prostration (oral route, tech. product, MRID 249802) and depression, ataxia, prostration, tremors (oral route, 4LC, MRID 249803) in rats.
 - (2) Mild to severe depression (dermal route,, tech. sulfosate, MRID 249802 & 260508) and mild to severe depression, prostration, and tremors (dermal route, 4LC, MRID 249803) in rabbits.
 - (3) Splayed gait, head and paw flicking, shaking, subdued behavior, decrease response to sound (inha. route, tech. sulfosate, MRID 412359-01) and reduced activity, prostration (inha. route, 4LC, MRID 258398) in rats.
- C. The following neurohistopatology were also observed in subchronic and chronic/oncogenicity studies:
- (1) White matter degeneration of the lumbar spinal cord of male mice (oncogenic study, MRID 402140-06 & 412099-07).
 - (2) Sciatic nerve degeneration (21-Day dermal, 4LCE, MRID 412099-04).

Organophosphorus Compounds are known to cause neurotoxicity. Sulfosate is a organophosphonate. Several pesticides belonging to this group of chemicals are also known to cause acute delayed neurotoxicity in the hen and in humans.

- B. In some of the in-vitro mutagenicity tests conducted in 1982, Sulfosate induced a false positive mutagenic effect. These studies included MRID 249802, studies Nos. T-10848 (Forward mutation/Mouse Lymphoma cells), T-10875 (Structural Chromosomal Abberations/CHO cells) and T-11019 (Structural Chromosomal Abberations/CHO cells). A common feature of these tests was that the pHs of the test incubation media were acidic (pH 5.67 -7.07) due to the addition of sulfosate. These positive results were no longer observed [see MRID 260966, studies Nos. T-12661 (Forward Mutation/Mouse Lymphoma cells), T-12662 (Structural

Chromosomal Abberations/CHO cells), and T-12663 (Structural Chromosomal Abberations/Mouse Lymphoma cells)] when the pH was readjusted to a more physiological level (7.4) before the conduct of the mutagenicity test.

C. Composition of Technical Grade Sulfosate

Technical sulfosate is usually supplied as an aqueous solution containing about 52% active ingredinet. The very viscous nature of sulfosate precludes the practical manufacture of a technical grade with a standard a.i. content (sulfosate forms an intractable glass-like product if its water content is $\leq 30\%$). The various "technical grade sulfosates" used in the toxicological studies described under "Toxicological Profile" above are either an aqueous sulfosate concentrate containing 62% ai or aqueous dilutions of this concentrate to ai concentrations of 19.2, 52, and 56.17%.

XI. Relevant Consideration in setting the tolerance:

The dietary impact of the requested tolerances is addressed by the Tolerance Support Chemistry Branch (TSCB). See response to data package No. D154589.