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

CASWELL FILE

OCT - 5 1995

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 5H05727; 5F04554; 010182-00324. Touchdown® Herbicide.  
Application for Amended Registration for Use on Apples,  
Crabapples, Loquat, Pear, Quince and Wheat

PC Code 128501  
Tox. Chem. No. 893C

Project Nos. D217444, D217454,  
D217460

Submission Nos. S490509, S490506,  
S490457

TO: Terri Stowe, PM Team # 25  
Registration Division (7505C)

FROM: Pamela M. Hurley, Toxicologist  
Section I, Toxicology Branch I  
Health Effects Division (7509C)

*Pamela M. Hurley*  
8/30/95

THRU: Roger L. Gardner, Section Head  
Section I, Toxicology Branch I  
Health Effects Division (7509C)

*Roger Gardner*  
9/22/95  
*M. Lopez* 10/3/95

Background and Request:

Zeneca Ag Products has submitted an application for amended registration for use of Touchdown® Herbicide on pome fruit and wheat. Section F of the application (the proposed tolerance) was not submitted to the Toxicology Branch, but it is assumed that the tolerances will be for glyphosate-trimesium in or on the selected commodities. The submitted label for pome fruit and wheat is for Touchdown® Herbicide, containing 57.6% active ingredient. It contains 6 pounds active ingredient per gallon. It is to be applied as a broadcast and/or a spot spray. The herbicide may also be applied using a wiper or "wick" applicator. TB-I has been asked to determine whether or not the toxicology data base supports these requested tolerances.

Toxicology Branch Response:

TB-I has determined that the toxicology data base for this chemical is complete. TB-I has no objection to granting the application for amended registration for use of Touchdown® Herbicide on pome fruit and wheat, provided that the tolerances are for glyphosate-trimesium in or on the selected commodities.

The following summarizes the toxicity testing requirements for the requested uses and tolerances. A Toxicity Profile is attached for the technical material.

Data Requirements (CFR 158.135):

Technical: Glyphosate Trimesium

Use Pattern: Herbicide; broadcast and/or spot spray; wiper or "wick" applicator.

Action Type: Amended Registration

Last Updated: 08/22/94

		<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
81-7	Acute Delayed Neurotoxicity	Yes	Yes
81-8	Acute Mammalian Neurotoxicity	Yes	Yes
82-1(a)	Subchronic Oral (rodent)	Yes	Yes
82-1(b)	Subchronic Oral (non-rodent)	Yes	Yes
82-2	21-Day Dermal	Yes	Yes
82-7	Subchronic Mammalian Neurotoxicity	Yes	Yes
83-1(a)	Chronic Toxicity (rodent)	Yes	Yes
83-1(b)	Chronic Toxicity (nonrodent)	Yes	Yes
83-2	Oncogenicity (mouse)	Yes	Yes
83-5	Oncogenicity (rat)	Yes	Yes
83-3(a)	Teratology (first species)	Yes	Yes
83-3(b)	Teratology (second species)	Yes	Yes
83-4	Multigeneration Reproduction	Yes	Yes
84-2(a)	Mutagenicity - Gene Mutation	Yes	Yes
84-2(b)	Mutagenicity - Structural Chromosomal Aberrations	Yes	Yes
84-2(c)	Mutagenicity - Other Genotoxic Effects	Yes	Yes
85-1	Metabolism	Yes	Yes

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SULFOSATE (Caswell No. 893C; PD No. 128501)

SULFOSATE TECHNICAL (52% a.i.)

Updated 08/22/94

- 81-1 Acute Oral Toxicity in Rats.  
MRID 249802  
STAUFFER CHEMICALS  
# T11185  
November, 1982.  
Acceptable
- LD<sub>50</sub> = 748 mg/kg (males)  
LD<sub>50</sub> = 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
- LD<sub>50</sub> > 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
- LC<sub>50</sub> > 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,  
chromorhinorrhea  
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

LC<sub>50</sub> > 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 aerolised 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).

81-5

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

Acceptable

24-hr exposure.

Effects at 24 hr: 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.

Primary Irritation Score: 0.67.

Dose used: 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)

81-7 Acute Delayed  
Neurotoxicity Study  
in Hens  
MRID 431512-01  
ICI Toxicology Labs  
CA/# T-12324;  
4/18/89

Core Minimum

NOEL: for systemic toxicity: 500  
mg/kg  
LEL: for systemic toxicity: 5000  
mg/kg

Effects: Administered by gavage at 0, 500 or 5000 mg/kg in 5 ml/kg water. TOCP (500 mg/kg) was positive control. 6 hens/group in control groups, 8 hens/group in treated groups. Each animal dosed twice during study; day 1 & day 22. Each animal evaluated up to day 41 (or 42). 500 mg/kg: diarrhea for 2-3 days, starting a few days after each dosing. 5000 mg/kg: diarrhea, changes in comb appearance, early ↓ food consumption & ↓ in egg production observed. No indications of neurotoxicity were observed. The positive control indicated the appropriate clinical signs of toxicity, increased ataxia and microscopic observations for an organophosphate. Study is core minimum because it was conducted prior to the publication of the new neurotoxicity guidelines which were published in 1991.

81-8 Acute Mammalian  
Neurotoxicity Study  
in Rats  
MRID 431323-01  
Zeneca Central Tox.  
Labs  
#'s AR5425;  
CTL/P/3813  
2/15/93

Core Guideline

NOEL: 100 mg/kg  
LEL: 300 mg/kg

Effects: Alpk:APfSD rats. Doses: 0, 30, 100 or 300 mg/kg. Positive control data provided. 300 mg/kg: death, ptosis, ↓ activity, ↓ splay reflex, upward curvature of spine, chromodacryorrhea, shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, staining around nose, ↓ bodyweight (σ), ↓ food consumption (σ), ↑ time to tail flick, ↓ landing foot splay, ↓ forelimb grip strength, ↓ hindlimb grip strength, ↓ motor activity. Effects reversible. No microscopic evidence of neurotoxicity. No indications of neurotoxicity below a lethal dose (300 mg/kg).

<p>82- 1(A)</p>	<p>Subchronic feeding rat MRID 412099-02 Stauffer Chem No. T-10888 4-3-87</p> <p>Acceptable</p>	<p><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)</p>
<p>82- 1(b)</p>	<p>Subchronic feeding dog MRID 412099-02/03 Stauffer Chem No. T-11002 4-3-87</p> <p>Acceptable</p>	<p><u>NOEL</u>: 10 mg/kg/day (MDT) <u>LOEL</u>: 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. <u>Doses tested</u>: 0, 2, 10, and 50 mg/kg/day by gavage. Dog's Strain: Beagle Product tested: Sulfosate (19.2% a.i., 75.6% water).</p>
<p>82-2</p>	<p>21-day dermal - rabbit MRID 408937-02 Hazleton No. HLA6142-107 3-1-88</p> <p>Guideline</p>	<p><u>Systemic NOEL</u>: 1000 mg/kg/day (HDT) Mild erythema at application sites in all treated groups. <u>Doses tested</u>: 0, 10, 100, and 1000 mg/kg/day 6 hrs/day; 5 days/week; 3 weeks. Product tested: Sulfosate (57.3% a.i.).</p>

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82-7 Subchronic  
mammalian  
neurotoxicity rat  
MRID 431512-02  
Zeneca Central Tox.  
Labs  
Study #'s PRO887;  
CTL/P/3831  
2/15/93

Core Guideline

NOEL: 600 ppm (47.6 mg/kg/day)  
LOEL: 2000 ppm (153.2 mg/kg/day)

Effects: Alpk:APfSD rats: 0, 200, 600 or 2000 ppm (0, 15.6, 47.6 or 153.2 mg/kg/day for males; 0, 18.2, 54.4 or 171.0 mg/kg/day for females) in diet for 90 days. 12/sex/dose group. Positive control data were provided. 2000 ppm: ↓ body weights, food consumption & utilization, ↓ mean forelimb grip strength values (♀). No microscopic evidence of neurotoxicity. Evidence for neurotoxicity is not clear.

83-1a Feeding/Oncogenic  
83-2b (2-year) in Mice  
MRID 402140-06  
412099-07  
Stauffer Chem  
No. T-11813  
4/3/87

Guideline

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). Not oncogenic at dose levels up to and including 8000 ppm. Highest dose level may have been excessive.  
Doses used: 0, 100, 1000, and 8000 ppm  
Mice strain: Charles River  
Test material: Sulfosate 56.17% a.i.

83-1a Feeding/Oncogenic  
83-2a (2-year) in Rats  
MRID 402140-07  
412099-05  
Stauffer Chem  
No: T-11082  
4/4/87

Guideline

Systemic NOEL: 1000 ppm (HDT)  
There were decreases in bodyweight (both sexes) and increased incidences of chronic laryngeal and nasopharyngeal inflammation (males). Bodyweight decrease was considered to be secondary to reduction in food consumption. However, study was acceptable because top dose may be approaching at least 1/2 of an adequate dose for carcinogenicity testing (based on results from subchronic, reproduction studies). Not oncogenic at any level tested.  
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

Minimum

Developmental NOEL: 100 mg/kg/day  
Developmental LOEL: 333 mg/kg/day  
based on significant decreases in  
fetal bodyweight

Maternal NOEL: 100 mg/kg/day.

Maternal LOEL: 333 mg/kg/day based  
on undetermined deaths of 2 dams at  
HDT; decreases in bodyweight,  
bodyweight gain and feed intake;  
increased salivation,  
chromorrhinorrhea and lethargy (HDT).

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: 40 mg/kg/day  
Developmental LOEL: 100 mg/kg/day  
(reduction in number of live  
fetuses/doe, 4 abortions & having  
only 7 litters does not give  
sufficiently high # of animals to  
absolutely conclude that no  
developmental toxicity is occurring.

Maternal NOEL: 40 mg/kg/day (MDT)

Maternal LOEL: 100 mg/kg/day (HDT)

(6 deaths/17 pregnant does, 4  
abortions in 11 survivors, decreased  
body weight, body weight gain, food  
consumption).

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  
Accession Nos:  
258399 & 258399  
Stauffer Chem.  
No: T-110-51  
4/19/84

Guideline

Reproductive/Developmental NOEL:  
150 ppm (LDT)  
Reproductive/Developmental LOEL:  
800 ppm (MDT) based on decreased  
litter size in the F<sub>0a</sub> and F<sub>1b</sub>  
litters at 2000 ppm and on decreased  
mean pup weights during lactation in  
the second litters at 800 ppm and in  
all litters at 2000 ppm.  
Systemic NOEL: 150 ppm (LDT)  
Systemic LOEL: 800 ppm (MDT) based  
on reduced feed intake, body weights  
& body weight gains, reduced  
absolute and sometimes relative  
thymus, heart, liver & kidney  
weights.  
Doses used: 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

Not mutagenic 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.  
Tester Bacteria: TA1535, TA1537,  
TA1538, TA98, and TA100 from Dr.  
Ames.  
Pos. controls: 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

Not mutagenic at concentrations of  
2.5, 5, 10, 20, and 40 ul/plate,  
with or without S9.  
Tester Bacteria: TA1535, TA1537, TA  
98, and TA100.  
Pos. controls: Na azide, 9-AA, 2-NF.  
Cytotoxic Dose: 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

Not mutagenic at doses of 25 and 50  
mg/ml in "Sex linked recessive  
lethal test".  
Pos. control: 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<sup>+</sup>/-)  
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<sup>+</sup>/-)  
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-Nitrosodimethyl-  
amine (DMN) with S9 and Ethyl-  
methanesulfonate (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. <u>Doses used:</u> 21, 63, and 188 mg/kg (LD <sub>50</sub> = 565 mg/kg). Test material: sulfosate 58.5% a.i. <u>Pos. control:</u> cyclophosphamide
84- 2(b)	Mutagenicity (Micronucleus assay) Mouse bone marrow MRID 402140-04 412099-08 Stauffer Chem. No: EHC-T-12689 4/23/87  Acceptable	Test animals: Charles River D-1 str. Not mutagenic (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.
84- 2(b)	Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-10875 7/6/1982  Acceptable	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. 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.
84-2(b)	Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-11019 7/22/82  Acceptable	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. No increase in SCE was observed. <u>Concentrations used:</u> 2, 4, 6, 8, 10, and 12 ul/ml. Test material: Sulfosate 72% a.i.

84-  
2(b)

Mutagenicity  
(cytogenetic)  
in CHO cells  
MRID 260966  
Stauffer Chem.  
No: EHC T-12663  
12/18/1985

Acceptable

pH of treatment medium was readjusted to 7.4-7.6 prior to testing.

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.

Cytotoxic concentrations: None  
Pos. controls: Mitomycin C and Cyclophosphamide.

Test material: sulfosate 55.6% a.i.

84-  
2(b)

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

Acceptable

Indicator cells: L 5178Y (TK<sup>+</sup>/-) 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  $^{14}\text{C}$ )  
trimethylsulfonium  
Carboxymethylaminomethylphosphonate)  
96.5% purity, 20 mci/mmol.

Identification of the (Methyl  $^{14}\text{C}$ )  
trimethylsulfonium ion ( $^{14}\text{C}$ -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  $^{14}\text{C}$ -TMS ion is rapidly and  
almost completely absorbed from the  
GI tract and rapidly excreted  
unmetabolized mostly via the kidney.  
Urine recovery of  $^{14}\text{C}$  (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  $^{14}\text{C}$ -  
TMS ion.

Fecal recovery of  $^{14}\text{C}$  (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  $^{14}\text{C}$ -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  
<sup>14</sup>C-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).

<sup>14</sup>CO<sub>2</sub> 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.

Data Gaps: None

Actions Being Taken to Obtain Additional Information or Clarification: N/A

Reference Dose (RfD):

The recommended RfD (to the RfD Workgroup) is 0.1 mg/kg/day. This value was calculated by using the chronic dog feeding study NOEL of 10 mg/kg/day and a safety factor of 100. This RfD has been verified or approved by the Health Effects Division RfD Committee.

Less-than Lifetime Endpoints:

A risk assessment for acute dietary exposure is not required because no appropriate toxicological endpoints were found. The short term (1 to 7 Days) and the intermediate term occupational or residential (1 Week to Several Months) risk assessments are not required because when compared with the oral studies, the 21-day dermal studies indicate that there is not much dermal absorption.

Pending Regulatory Actions: None

Toxicologic Issues Pertinent to This Request:

This chemical has been classified as a Group E Carcinogen: no evidence of carcinogenicity in rat and mouse studies.

Technical sulfosate is usually supplied as an aqueous solution containing about 52% active ingredient. 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" in the "Toxicological Profile" above are either an aqueous sulfosate concentrate containing 62% a.i. or aqueous dilutions of this concentrate to a.i. concentrations of 19.2, 52 or 56.17%.

In some of the in vitro mutagenicity tests conducted in 1982, sulfosate induced a false positive mutagenic effect. These studies were submitted with accession number 249802 (study numbers T-10848 (forward mutation/mouse lymphoma cells), T-10875 (structural chromosomal aberrations/CHO cells) and T-11019 (structural chromosomal aberrations/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 [accession number 260966 (study numbers T-12661 (forward mutation/mouse lymphoma cells), T-12662 (structural chromosomal aberrations/CHO cells) and T-12663 (structural chromosomal

aberrations/mouse lymphoma cells)] when the pH was readjusted to a more physiological level (7.4) before the mutagenicity tests were conducted.