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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

AUG 0 3 1992

MEMORANDUM

SUBJECT: Petitions for Tolerances for Sulfosate (Touchdown®; EPA Reg. 10182-276) in/on Whole Grapes and Dried Pomace, Resulting from the Use of Touchdown® Concentrate (EPA Reg. No. 10182-276) and Touchdown® 6 (EPA Reg. No. 10182-324) and Labels Review.

Tox. Chem. No. 893C
PD No. 128501
Project No. 1-0534A
ID No. 1H05606
Submission No. S389301
DP Barcode No. D160550, D160473

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

FROM: Nguyen B. Thoa, Ph.D. NBT 07/28/92
Section I, Toxicology Branch I
Health Effects Division (H7509C)

for THRU: Roger L. Gardner, Section Head Pamela M. Hurley 07/30/92
Section I, Toxicology Branch I
Health Effects Division (H7509C) KB 8/3/92

I. Actions Requested:

ICI Americas, Inc., Agricultural Products, Wilmington, Delaware, has submitted Petitions for tolerances for Sulfosate in/on the raw agricultural commodities Whole Grapes at 0.2 ppm (F Petition) and Dried Pomace at 0.4 ppm (H Petition). The proposed tolerances are for the combined residues of Sulfosate (Trimethylsulfonium carboxymethylaminomethylphosphonate) and its metabolite aminomethylphosphonic acid (AMPA) in/on whole grapes and dried pomace, resulting from the use of Touchdown® concentrate (EPA Reg. No. 10182-276) and Touchdown® 6 (EPA Reg. No. 10182-324).

The Petitioner also requests an amendment of the labels to add the new use on Grapes.

II. Conclusions:

A. The Toxicological Data Base on Sulfosate is incomplete and Toxicology Branch (TB) cannot act favorably on the requests for tolerances and amendment of labels. 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. 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.

III. Background:

Sulfosate is a nonselective foliar systemic herbicide used to control a broad spectrum of emerged weeds. The proposed use is for postemergence control of annual and perennial weeds in grape (any variety of table, wine, or raisin grape) vineyards.

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.

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. Grapes will be harvested 14 days from the last application.

Based on the results from 12 residue field trials conducted in the major grape growing States of Arkansas, California, New York, South Carolina, and Utah, 1-2 broadcast applications of Touchdown® concentrate and/or Touchdown® 6, at rates from 4-8 lbs. a.i./A/application, will result in residues levels in/on whole grapes and dried pomace below the proposed tolerances.

IV. Toxicological Data Requirements (CFR 158.340)

A. Technical Sulfosate*:

Use Pattern: New chemical/Food and Feed Use

Last Updated: 07/27/92

| | | Required | Satisfied |
|---|---|---|---|
| 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 |

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* 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%) into various amounts of water.

\+ Sulfosate is a salt composed of one fixed tertiary sulfur cation (trimethylsulfonium) and one phosphonate anion (carboxy-methylaminomethylphosphonate).

++ 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.

IV. TOXICOLOGICAL PROFILE

Updated 07/27/92

SULFOSATE TECHNICAL:

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| 81-1 | Acute Oral Toxicity in Rats.<br>MRID 249802<br>STAUFFER CHEMICALS<br># T11185<br>November, 1982.<br><br>Acceptable | $LD_{50}$ = 748 mg/kg (males)<br>$LD_{50}$ = 755 mg/kg (females)<br>Doses used: 500, 550, 600, 700, 800, and 900 mg/kg by gavage<br>Signs: mild to severe depression, prostration, tremors, and slow/shallow respiration.<br>Product tested: SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 |
| 81-2 | Acute Dermal Toxicity in Rabbits<br>MRID 249802, 260508<br>Stauffer CHEMICALS<br># T-11185<br>November, 1982.<br><br>Acceptable | $LD_{50}$ > 2000 mg/kg (Both sexes; intact or abraded skin).<br>Doses used: 800 -2200 mg/kg.<br>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.<br>Product tested: SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 |
| 81-3 | Acute inhalation toxicity in rats<br>MRID 249802<br>Stauffer Chem No.<br>T-11084<br>November, 1982<br><br>Acceptable | $LC_{50}$ > 6.9 mg/L (both sexes, 4-hr, whole body exposure)<br>Actual chamber concentration:<br>6.9 mg/L<br>MMAD = 3.5 um at 64 min.<br>2.8 um at 184 min.<br>SIGNS: wet fur, salivation, chromorhinorrhea<br>Product tested: Sulfosate (62% a.i.)<br><br>TOXICITY CATEGORY 3 |

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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| 81-3 | Acute inhalation toxicity in rats<br>MRID 412359-01<br>ICI<br>No: CTL/P/2254<br>08/25/88<br><br>Unacceptable | $LC_{50}$> 5.18 mg/L (4-hr, nose only exposure)<br>Actual chamber concentration: 2.65-6.3 mg/L<br>MMAD: 4.56 ± 2.06 um<br>[20% ≤ 2.5 um (inhalable) & 3.9% ≤ 1 um (respirable)]<br>No mortality observed.<br>SIGNS: (CNS & Autonomic) salivation, splayed gait, head & paw flicking, tail erection, shaking,subdue behavior, slow/deep breathing, decrease response to sound. Effects subsided on day 2.<br>A limit test was not reached since only 3.9% of the aerolised sulfosate particles were of respirable size (EPA requires 25%).<br>Product tested: Sulfosate 57.6% a.i. and [redacted]<br>This study may be upgraded to acceptable when evidences are provided to show that optimum technology was used in generating the sulfosate containing aerosol.<br><br>TOXICITY CATEGORY: |
| 81-4 | Primary Eye Irritation in Rabbits<br>MRID 249802<br>STAUFFER CHEMICALS<br># T-11185<br>November, 1982.<br><br>Acceptable | No effect on cornea.<br>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.<br>Effects on eyes washed after 20-30 sec. exposure: mild conjunctivitis (3/3 rabbits) lasting 3 days.<br>Dose used: 0.1 ml SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 (based on mild irritation of conjunctiva). |



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

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| 82-1(b) | Subchronic feeding dog<br>MRID 412099-02/03<br>Stauffer Chem<br>No. T-11002<br>4-3-87<br><br>Acceptable | NOEL: 10 mg/kg/day (LDT)<br>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.<br>Doses tested: 0, 10, 25, and 50 mg/kg/day by gavage.<br>Dog's Strain: Beagle<br>Product tested: Sulfosate (19.2% a.i., 75.6% water). |
| 83-1a<br>83-2b | Feeding/Oncogenic (2-year) in Mice<br>MRID 402140-06<br>412099-07<br>Stauffer Chem<br>No. T-11813<br>4/3/87<br><br>Guideline | Oncogenic NOEL: >8000 ppm (HDT)<br>Systemic NOEL: 1000 ppm (MDT)<br>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).<br>Doses used: 0, 100, 1000, and 8000 ppm<br>Mice strain: Charles River<br>Test material: Sulfosate 56.17% a.i. |
| 83-1a<br>83-2a | Feeding/Oncogenic (2-year) in Rats<br>MRID 402140-07<br>412099-05<br>Stauffer Chem<br>No: T-11082<br>4/4/87<br><br>Guideline | Oncogenic NOEL: >1000 ppm (HDT)<br>Systemic NOEL: 100 ppm (LDT)<br>Systemic LOEL: 500 ppm (MDT) based on decreased levels of lactate dehydrogenase in males and females at 6 and 12 months.<br>Effects at 1000 ppm: Decreases in B.W.(both sexes) and increase incidences of chronic laryngeal and nasopharyngeal inflammation (males).<br>Doses used: 0, 100, 500, and 1000 ppm<br>Rats strain: Charles River CrL:CD (SD)BR.<br>Test material: Sulfosate 56.17% a.i. |



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| 83-1(b) | Chronic Feeding (1-year) in Dogs<br>MRID 402140-05<br><br>Stauffer Chem.<br>No: ECH T-11075<br>4/3/87<br><br>Minimum | Systemic NOEL: 10 mg/kg/day (MD)<br>Systemic LOEL: 50 mg/kg/day (HD) based on decreases in LDH.<br>Doses used: 0, 2, 10, and 50 mg/kg/day, by gavage.<br>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.<br>Dog's Strain: Beagle<br>Test material: Sulfosate 56.2% a.i. |
| 83-3(a) | Teratogenicity in Rats<br>MRID 249802<br>Stauffer Environ. Health Cen.<br>No: T-11050<br>November 1982<br><br>Guideline | Terato.NOEL: >333 mg/kg/day (HDT)<br>Fetotoxic NOEL: 100 mg/kg/day (MDT)<br>Fetotoxic LOEL: 333 mg/kg/day based on significant decreases in B.W.<br>Maternal NOEL: 100 mg/kg/day.<br>Maternal LOEL: 333 mg/kg/day based on significant decreases in B.W. and feed intake.<br>Effects at 333 mg/kg/day: Two deaths. Signs were significant increase in incidences of lethargy, salivation, and chromorhinorrhea.<br>Doses used: 0, 30, 100, and 333 mg/kg/day by gavage to S-D rats.<br>Test material: Sulfosate 19.2% a.i. |
| 83-3(b) | Teratogenicity in Rabbits<br>MRID 260966<br>Stauffer Chem.<br>No: T-11052<br>6/21/83<br><br>Guideline | Developmental NOEL: >100 mg/kg/day (HDT). A/D ratio= 10/<100= <0.1.<br>Maternal NOEL: <10 mg/kg/day (LDT) (Significant increase in incidences of diarrhea, head tilt, nasal discharge, wet stains on chin, red urine stain).<br>Effects at 100 mg/kg/day: 38% mortality, 36% spontaneous abortion, significant decrease in feed intake, and in number of live fetuses per litter.<br>Doses used: 0, 10, 40, and 100 mg/kg/day by gavage to Dla;(NZW)SPF rabbits.<br>Test material: Sulfosate 56.2% a.i. |

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

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| 84-2(a) | Gene Mutation (Forward Mut.) Mouse Lymphoma MRID 249802 Stauffer Chem T-10848 2/8/1982<br><br>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<br><br>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<br>Indicator cells: L5178Y($TK^{+}/^{-}$) mouse lymphoma cell line (Dr. Clive, RTP, No.Carolina).<br>Test material:Sulfosate 55.6% a.i.<br>Cytotoxic concentrations:<br>Unadjusted acidic medium: >5ul/ml pH adjusted medium: >7.75 ul/ml<br>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<br><br>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 ($LD_{50}$= 565 mg/kg). Test material: sulfosate 58.5% a.i. Pos. control: cyclophosphamide |

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| 84-2(b) | Mutagenicity (Micronucleus assay) Mouse bone marrow MRID 402140-04 412099-08 Stauffer Chem. No: EHC-T-12689 4/23/87<br><br>Acceptable | Test animals: Charles River D-1 str. Not mutagenic (did not induce any increase in the number of PCE containing micronuclei). Doses used: 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<br><br>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. Concentrations used: 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<br><br>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. Concentrations used: 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<br><br>Acceptable | pH of treatment medium was readjusted to 7.4-7.6 prior to testing. Not mutagenic (did not induce any structural chromosome abberrations 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. |

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| 84-2(b) | Mutagenicity (cytogenetic) Mouse Lymphoma MRID 260966 Stauffer Chem. No: EHC T-12662 12/19/82<br><br>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 $\leq$ 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<br><br>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. |



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| 85-1 | Metabolism in Rats<br>MRID 258398<br>Stauffer Chem.<br>PMS-148<br>2/4/85<br><br>Acceptable | Test material: (Methyl $^{14}C$) trimethylsulfonium Carboxymethylaminomethylphosphonate) 96.5% purity, 20 mci/mmol.<br>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.<br>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.<br>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.<br>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.<br>$^{14}CO_2$ in expired air was negligible.<br>Tissues residues were negligible: 0-0.148 (LD) and 0-10.6 ppm (HD) sulfosate equivalents.<br>The lack of metabolism may be explained by the hydrophilic nature of TMS ion.<br>Acute toxic effects at the HDT: lethargy, ataxia, slow/labored breathing, salivation, occasional tremors. Signs lessened after 24 hrs. |



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| 85-1 | Metabolism in Rats<br>MRID 412359-03<br>ICI Americas Inc.<br>No: T-12906<br>12/20/88<br><br>Acceptable | Test material: Trimethylsulfonium Carboxymethylaminomethylphosphonate $^{14}$C-radiolabeled on the anionic moity (Carboxymethylaminomethyl-phosphonate), 93.2% radiopurity, 9.8 mCi/mmol.<br>Identification of anion by TLC, autoradiograhy, and GC/MS.<br>Males and females S-D rats iv-treated with 25 mg/kg (LDT) test material excreted 90% of the administered dose in urine.<br>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).<br>Absorption was incomplete: only 47-57% of total radioactivity was recovered in urine. Fecal excretion was 36-42% of the administered dose.<br>Most of the recovered radioactivity was unmetabolized carboxymethyl-aminomethylphosphonate (80-90% of urine and 77-96% of feces total radioactivity).One fecal metabolite was aminomethylphoshonic 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.<br>$^{14}CO_2$ in expired air was negligible.<br>Combined tissue residues were only $\geq$0.32% of administered dose.<br>Carcasses contained 2.25% of the administered dose, most of it located in bones.<br>Acute toxic signs observed with the HD: lethargy, moderate/severe depression, tremors, dehydration, and reduced feed consumption. Signs lasted 72 hours. |

V. Data Gaps:

The following are data gaps for this action:

(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 (carboxymethylaminomethylphosphonate). 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 inhalation toxicity studies (MRIDs 249802, 260508, 412359-01).

4. In addition, TB will require a 28-Day Neurotoxicity/hen (82-5a) if the acute delayed Neurotoxicity/hen is positive.

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 carboxymethylamino-methylphosphonate, formerly SC-0024). Tolerances are however established for glyphosate (iso-propylamine salt of carboxymethylamino-methylphosphonate), 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 the technical product:

(1) Ataxia, tremors, mild to severe depression, prostration, slow/shallow respiration (oral route/rats, MRID 249802).

(2) Mild to severe depression (dermal route/rabbits, MRID 249802 & 260508).

(3) Splayed gait, head and paw flicking, shaking, subdued behavior, decrease response to sound, slow/deep breathing (inhalation route/rats, MRID 412359-01).

Neuropathology (White matter degeneration of the lumbar spinal cord) was observed in a chronic feeding/oncogenicity study in mice (MRID 402140-06 & 412099-07).

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 Abberrations/CHO cells) and T-11019 (Structural Chromosomal Abberrations/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 Abberrations/CHO cells), and T-12663 (Structural Chromosomal Abberrations/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 ≤ 30%). The various "technical grade sulfosates" used in the toxicological studies described above under "Toxicological Profile" are either



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an aqueous sulfosate concentrate containing 62% ai or aqueous dilutions of this concentrate to a.i. concentrations of 19.2, 52, and 56.17%.

XI. Relevant Consideration in setting the tolerances:

The dietary impact of the requested tolerances is addressed by the Tolerance Support Chemistry Branch (TSCB). See response to data package No. D160546.



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