CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA
GLYPHOSATE TRIMESIUM (formerly known as Sulfosate)

Chemical Code # 2327, Document Processing Number (DPN) # 51764
SB 950 # (N/A)

Original Date: 10/2/90
Revised Dates: 5/5/93, 8/21/15

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 158455 (Document No. 51764-075) were examined. This includes all relevant studies indexed by DPR as of 8/21/2015.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: t20150821
Revised by C. Aldous, 8/21/2015

NOTE: The following symbols may be used in the Table of Contents which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
(N/A) = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS 3
GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT 4
Acute oral toxicity, rat ** 4
Acute dermal toxicity ** 4
Acute inhalation toxicity, rat ** 5
Primary eye irritation, rabbit ** 5
Primary dermal irritation ** 5
Dermal sensitization (**, based on study 364–0471; 212679) 5
SUBCHRONIC STUDIES 6
Oral toxicity, rat: 6
Oral toxicity, non-rodent: ** 6
Dermal toxicity, 21/28-day or 90-day: ** 7
CHRONIC STUDIES 7
Combined (Chronic and Oncogenicity), rat ** 7
Chronic, dog ** 8
Oncogenicity, mouse ** 8
GENOTOXICITY 8
Bacterial reverse mutation assay ** 8
Mutagenicity: *In vitro* mammalian cell assay ** 9
Mutagenicity: *In vivo* cytogenetics (includes *in vitro*) ** 10
Mutagenicity: DNA Damage (no longer a required category) ** 11
REPRODUCTIVE TOXICITY, RAT ** † 12

DEVELOPMENTAL TOXICITY 12
Rat ** 12
Rabbit ** † 12
NEUROTOXICITY 13
Acute neurotoxicity, rat 13
90-day neurotoxicity, rat 13
Developmental neurotoxicity, rat 13
Delayed neurotoxicity, hen ** 13
IMMUNOTOXICITY 14
ENDOCRINE DISRUPTOR STUDIES 14
SUPPLEMENTAL STUDIES 14

METABOLISM AND PHARMACOKINETICS

** 022 90942; "ICIA-0224: Metabolism in Rats" (ICI Americas, Inc., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-12906, 12/20/88); rat; 851; nonlabeled ICIA-0224 technical (Lot# WRC-8865-20-01, 56.2%, w/w); 14C-radiolabeled ICIA-0224 (Lot# WRC-8917-23-01, 93.2%, w/w, 9.8 mCi/mmol); single oral dosing: 25 or 250 mg/kg to 5 rats/sex/dose, multiple oral dosing: 25 mg/kg to 5 rats/sex/day for 14 days, and single iv dosing: 25 mg/kg to 6M/5F; no unscheduled deaths reported; 87.5 - 96.9% of the administered dose recovered in all treatment groups by 120 hrs; following iv dosing, both males and females excreted 90% of the dose in the urine and 3-4% in feces indicating incomplete absorption by the oral route; single and multiple oral dosing at 25 mg/kg resulted in higher levels excreted in feces (35-54%) and less in urine (36-57%); multiple oral dosing did not produce any differences in rate, route of excretion, distribution and concentration of residual radioactivity; 250 mg/kg-treated males excreted greater percentage of dose in urine and less in feces than similarly dosed females; bone appears to be a site for bioaccumulation of ICIA-0224; **acceptable**; (Leung, 8/15/90).

022 90943; "Metabolism, Tissue Residue and Balance Studies of Orally Administered [Methyl 14C-]Trimethylsulfonium Carboxymethylamino- methylphosphonate (SC-0224) in Rats (Lab. Report No. PMS-148)" (Stauffer Chemical Co., Mtn. View Research Ctr., Mtn. View, CA, 3/5/85); rat; 851; [Methyl 14C-]Trimethylsulfonium Carboxymethylaminomethylphosphonate (Lot# WRC-7293-36; 96.5% purity, 20 mCi/mmol); oral; 35 or 350 mg/kg in distilled water to 3 rats/sex/dose; tissue residue ratios between the high and low doses for males and females (1.7 and 3.7 times, respectively) were greater than what would be expected with first order kinetics; this suggests that at 350 mg/kg either the excretion process is saturated or reabsorption of the test article in the kidney or GI tract; females tend to have higher tissue retention than males; necropsy did not reveal any abnormal findings; highest concentration of radioactivity was found along the paths of excretion (liver, kidneys, and bladder) and in the adrenals, thymus and stomach; at both doses the TMS ion accounted for >95% of the recovered radioactivity in urine; **supplemental**; (Leung, 8/17/90)

022 90944; "Metabolism, Balance and Tissue Distribution of Orally Administered [PM-13C,14C]SC-0224 in Rats, Lab. Report No. PMS-147, MRC-87-01" (Stauffer Chemical Co., Mtn. View Research Ctr., Mtn. View, CA, 2/9/87); rat; 851; [PM-14C]SC-0224 (Lot# WRC-7615-29-01, 30 mCi/mmol, 96.5% purity), [PM-13C]SC-0224 (Lot# F-396), nonlabeled SC-0224 technical (Lot# WRC-7466-14-01, 57%, w/w); single; oral: 25 mg/kg or 250 mg/kg to 3 rats/sex/dose, IP: 25 mg/kg to 3 males; rapid elimination after oral dosing with 72.8% and 76.8% (males and females, respectively) of the smaller dose and 72.9% and 68.5% of larger dose recovered in urine and feces in 24 hours; urinary excretion of the intraperitoneal dose of 25 mg/kg was 94.9% with only 3.2% in feces suggested poor absorption; bone contained the highest levels of tissue residues in males and females at both dose levels; 92.9% to 97.8% of total radioactivity in urine and feces was identified by TLC and 13C-NMR as unchanged parent anion, N-(carboxymethyl)aminomethanephosphonic acid; a minor component (2.0% to 3.5% of radioactivity) was identified as aminomethanephosphonic acid; **supplemental**; (Leung, 8/20,90).

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat **

011 90907, "Acute Toxicity Tests for SC-0224 Technical", (Stauffer Chemical Company, Richmond Toxicology Laboratory, Richmond, CA, Lab Report No. T-11185, 11/30/82); 811; rat; SC-0224 Technical (Lot No. 7981-12-01), purity = 62%, dosed as a mixture in water at a volume of 10 ml dosing mixture/kg; 0 (vehicle) (40M/40F), 500 (10M), 550 (10M/10F), 600 (20M), 700 (10M/10F), 800 (10M/10F), 900 (10M/10F) mg/kg; Mortality- male: 0/40, 0/10, 0/10, 5/20, 3/10, 6/10, 10/10, female: 0/40, 1/10, 5/10, 4/10, 9/10, respectively; Clinical Observations- depression, prostration, ptosis, slow and shallow respiration, tremors, ataxia, involuntary muscle contractions, chromodacryorrhea, piloerection, rough coat, tremors, red facial stains, convulsions; Necropsy- included darkened lungs, spleens, and black tipped kidneys; LD50 (M) = 748 (667-840), (F) = 755 (677-841) mg/kg; Toxicity Category III; **Acceptable. (Duncan, 7/9/90)

Acute dermal toxicity **

**51764-075; 158455; Acute Dermal Toxicity Study; 812; Rat; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Report No. CTL/P/5220; 10/15/96; 600 g/l SL Formulation (a.i. 48.1%); 5 animals/sex; Dose: 2000 mg/kg, 24 hour exposure, occlusive wrap; No mortality; Clinical Observations: slight skin irritation at the site of application; Necropsy: no treatment-related lesions; LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 12/12/97) [NOTE: This formulation at nearly Technical concentration is placed here to provide an "acceptable" study of this type.]

011 90908, "Acute Toxicity Tests for SC-0224 Technical", (Stauffer Chemical Company, Richmond Toxicology Laboratory, Richmond, CA, Lab Report No. T-11185, 11/30/82); 812; rabbit; SC-0224 Technical (Lot No. 7981-12-01), purity = 62%, applied neat; intact and abraded skin, 24-hour exposure; intact groups: 0 (sham), 2000 mg/kg; abraded groups: 0 (sham), 800, 900, 1000, 1200, 1600, 1900, 2200 mg/kg; 3 animals/sex in control groups, 4 animals/sex in treated groups; Mortality- male/intact: 0/3, 0/4; male/abraded: 0/3, 0/4, 0/4, 0/4, 2/4, 2/4, 2/4, 2/4; female/intact: 0/3, 0/4; female/abraded: 0/3, 0/4, 1/4, 1/4, 0/4, 1/4, 0/4, 1/4, respectively; Clinical Observations- included depression, tremors, salivation; erythema, edema at application

site; Necropsy- included pale lungs, discolored area on abdominal wall; LD50 and Toxicity Category cannot be determined; **Unacceptable,** and cannot be upgraded because group size was too small. (Duncan, 7/10/90)

Acute inhalation toxicity, rat **

011 90911, "ICIA 0224: 4-Hour Acute Inhalation Toxicity Study in the Rat", (ICI Central Toxicology Laboratory, Cheshire, UK, Lab Report No. CTL/P/2254 Revised, 8/25/88); ICIA 0224, technical grade (Reference No. SA 42/88), 57.6% sulfosate, used neat; 0 (air), 6.20 mg total particulates/l (gravimetric; equivalent to 5.18 mg ICIA 0224/l by chemical analysis); 5 animals/sex/dose level; liquid aerosol inhalation, nose-only, 4-h exposure; MMAD (GSD) = 4.56 (2.06) um, w/cascade impactor; no mortality; Clinical Observations- salivation, reduced response to sound, slow and deep breathing, splayed gait, head and paw flicking, tail erection, subdued behavior, shaking, abnormal respiratory noise, ungroomed appearance, piloerection; Necropsy- No gross abnormalities; LC50 (M/F) > 6.20 mg/l; Toxicity Category IV; **Acceptable. (Duncan, 7/10/90)

Primary eye irritation, rabbit **

011 90910 "Acute Toxicity Tests for SC-0224 Technical", (Stauffer Chemical Company, Richmond Toxicology Laboratory, Richmond, CA, Lab Report No. T-11185, 11/30/82); 814; rabbit; SC-0224 Technical (Lot No. 7981-12-01), purity = 62%, dosed neat; 0.1 ml/eye; 6 animals unwashed, 3 animals washed after 20-30 sec; examined at Days 1, 2, 3, 4, 7, 10, 11, and 14 (termination); UNWASHED- iritis (max. score = 1) which cleared by Day 7, and conjunctivitis (max. scores = 2/redn., 0/chem., 1/disch.), which cleared by Day 7; WASHED- conjunctivitis only (max. scores = 1/redn., 0/chem., 1/disch.) which cleared by Day 3; Toxicity Category III; **Acceptable. (Duncan, 7/10/90)

Primary dermal irritation **

011 90909, "Acute Toxicity Tests for SC-0224 Technical", (Stauffer Chemical Company, Richmond Toxicology Laboratory, Richmond, CA, Lab Report No. T-11185, 11/30/82); 815; rabbit; SC-0224 Technical (Lot No. 7981-12-01), purity = 62%, applied neat; intact and abraded skin, 24-hour exposure; 0.5 ml/site; one abraded, one intact site/animal, occlusive wrap; 4-h exposure (6 animals), 24-h exposure (6 animals); examined 4, 24, and 72 h after application in 4-h exposure group, and 24 and 72 h after application in 24-h exposure group; 4-h/Intact- no irritation; 4-h/Abraded- erythema of 0 or 1 at 4 and 24 h, and edema of 0 or 1 at 4 h, all sites clear at 72 h; 24-h/Intact- erythema of 0 or 1 at 24 and 72 h, and edema of 0 or 1 at 24 h; 24-h/Abraded- erythema of 1 or 2 and edema of 0 or 1 at 24 h, all sites clear at 72 h; Toxicity Category IV (based on 4-h exposure/intact skin data); **Acceptable. (Duncan, 7/10/90)

Dermal sensitization (**, based on study 364–0471; 212679)

NOTE: the following studies were submitted previously to DPR at a time when this study type was not reviewed by Human Health Assessment Branch. The above report is more relevant than the following studies, which were sent in support of Glyphosate Trimesium.

90915) Dermal sensitization test with SC-0224 4LC-E (Touchdown 4-LC) (51p.) ICI Americas Inc. Touchdown Concentrate and Touchdown 4-LC. Study Date: 08/01/1987. Document Number: 51764-0012.

##90912) Dermal Sensitization Test with SC-0224 Technical (Touchdown Concentrate) (50P.) ICI Americas Inc. Touchdown Concentrate and Touchdown 4-LC. Study Date: 10/01/1984 Document Number: 51764-0011.

SUBCHRONIC STUDIES

Oral toxicity, rat:

017 90920, "3-Week Dietary Range-finding Study with SC-0224 in Rats" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11048, 1/83); rat; SC-0224 technical (Lot #EHC 0355-25, 19.2% by weight) mixed in diet at 0, 150, 350, 800, 2000, and 5000 ppm (active ingredient) and given to 10 rats/sex/dose for 3 weeks; the mortality of 1 female at 800 ppm and 1 male at 5000 ppm prior to termination of study was not treatment-related; no toxicologically significant changes were reported with respect to clinical signs, gross necropsy, and blood chemistry; a reliable method for analysis of the test article in the diet was not fully developed; **supplemental**; (Leung, 7/30/90).

017 90921; "3-Month Dietary Toxicity Study with SC-0224 in Rats" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-10888, 4/3/87); 821; rat; SC-0224 technical (Lot #EHC 0355-25, 19.2% by weight) mixed in diet at 0, 150, 350, 800, and 2000 ppm (active ingredient) and given to 20 rats/sex/dose for 3 months; no mortality; males at 2000 ppm exhibited decrease in body weight gain ($p<0.05$, 24.3% of control) with decrease in mean food consumption ($p<0.05$); **no adverse effects indicated**; no toxicological significant changes attributed to SC-0224 were noted with respect to clinical signs, gross necropsy or histomorphologic observations; NOEL(M)= 800 ppm (decrease body weight gain), NOEL (F)=2000 ppm (no effects observed); palatability of mixed diet and food utilization not addressed; failure in selecting an appropriate dose level which elicits any signs of toxicity and permits identification of target organ(s); **not acceptable** and **not upgradeable**; (Leung, 7/31/90)

Oral toxicity, non-rodent: **

018 90922; "28 Day Range finding study with SC-0224 in Beagle Dogs" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T11001, 3/7/83); dog; SC-0224 technical (Lot #EHC 0355-25, 19.2%,w/w); water; oral gavage, males: 0, 36, 75, 150, 300, 450, and 600 mg/kg (active ingredient), females: 0, 5, 10, 20, 36, 75, and 150 mg/kg (active ingredient) for 28 days; 2-3 dogs/sex/dose; males treated at single doses >150 mg/kg exhibited mortality, emesis, coma, convulsions, and diaphragmatic breathing; after three doses females at the 150 mg/kg dose level exhibited similar signs of toxicity in addition to tremors, salivation, decrease activity and prostration; tremors and salivation were observed in females treated at 75 and 36 mg/kg; no microscopic evidence of central or peripheral nervous system damage; severe hepatocellular hydropic degeneration in livers of dogs that died after 1 or 3 doses of SC-0224; based on these observations dose levels of 0, 2, 10, and 50 mg/kg were selected for the subsequent 3-month subchronic study; **supplemental**; (Leung, 7/31/90).

** 018 90923; "Three Month Subchronic Oral Toxicity Study with SC-0224 in Beagle Dogs"(Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT., Lab. Report No. T-11002, 4/3/87); dog; 821; SC-0224 technical (Lot #EHC 0355-25, 19.2%, w/w); water; oral

gavage; 0, 2, 10, and 50 mg/kg (active ingredient) to 6 dogs/sex/dose once a day for 5 days/week for 3 months; **no adverse effects**; no mortality; no treatment-related effects on body weights, food consumption, gross necropsy findings or organ weights; no abnormal findings in urinalysis and fecal analysis; greater frequency and earlier onset of emesis and transient salivation at 50 mg/kg occurred before or after dosing; increases ($p<0.05$) in red blood cell cholinesterase (20.4% of control) in 50 mg/kg males at six weeks and in brain cholinesterase (20.8% of control) in 2 mg/kg males at termination were inconsistent and not toxicologically significant; NOEL(M/F) = 10 mg/kg (based on emesis at 50 mg/kg); study **acceptable**; (Leung, 8/2/90).

Dermal toxicity, 21/28-day or 90-day: **

** 019 90924; "21-Day Dermal Toxicity Study with SC-0224 Concentrate in Rabbits"(Hazleton Laboratories America, Inc., Madison, WI, Lab. Report No. T-13038, Lab. Project Id.# HLA-6142-107, 3/1/88); Hra:(NZW)SPF rabbit; 822; SC-0224 technical (Lot# WRC 10387-47-01, HLA# 70902074, 57.3%, w/w); dermal; 0 (vehicle), 10, 100, and 1000 mg/kg to 5 rabbits/sex/dose; 6 hours/day, 5 days/week, for at least 3 weeks; no mortality reported; no treatment-related effects on body weights, organ weights, food consumption, hematology or clinical chemistry noted; pustule/papule formation seen in the vehicle control group (2nd week to termination) as well as in the 10 and 1000 mg/kg treated groups (days 21-22); slight erythema seen in the 10-, 100-, and 1000-mg/kg groups and one male exhibited moderate erythema on days 9, 10, 11 in the 100 mg/kg group; necropsy and histopathologic exam did not reveal any abnormal findings; NOEL(M/F) = 1000 mg/kg (no observable effects); **not acceptable** but **possibly upgradeable** with analyses of dosing material for content; (Leung, 8/20/90). [NOTE: Despite the asterisks which precede this one-liner, this study may not have actually been upgraded to "acceptable" status. In any case, the following rat 21-day dermal study is acceptable, and fills this data requirement. Aldous, 8/21/15.]

** 013 90916; "ICIA0224 4LC-E: 21-Day Dermal Study in Rats" (ICI Central Toxicology Lab., Alderley Park, Cheshire, UK, Lab. Report No. CTL/P/2496, 7/7/89); Alpk:APfSD rat; 822; ICIA0224 4LC-E (batch number WF1005A/Lot WHF 2204, 39.8%, w/w); dermal; 0 (sham control), 25, 250, and 1000 mg/kg to 5 rats/sex/dose; 6 hrs/day for 21 days; occlusive; all rats survived to termination; minor changes in skin included scabbing, desquamation and macular erythema in 1000 mg/kg treated males; no treatment-related effects on body weights, food consumption, hematology or clinical chemistry; testes weights were higher in all treated groups than those in sham controls but was not toxicological significant in the absence of any histological changes; NOEL (M/F) = 1000 mg/kg (based on no observable effects); **acceptable**; (Leung, 8/21/90).

CHRONIC STUDIES

Combined (Chronic and Oncogenicity), rat **

** 015 90918; "Two Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Rats" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11082, 4/3/87); rat; 835; SC-0224 technical (Lot #EHC 0469-15, WRC# 8108-24-1; 56.2%, w/w); oral; untreated control (60M/60F), 0 (propylene glycol, 80M/80F), 100 (80M/80F), 500 (80M/80F) and 1000 (90M/90F) ppm (active ingredient); interim sacrifices at 6, 12, and 18 months using 10 rats/sex/dose; 10 extra rats/sex were sacrificed at the HDT at 12 months; **no**

adverse effects; mean body weights in the 1000 ppm-treated groups remained lower ($p<0.05$) than the control groups through 49 weeks in males (94.2% of control) and through 75 weeks in females (88.4% of control); no treatment-related effects on organ weight, food consumption, feed efficiency, survival, neoplastic and non-neoplastic lesions were reported; hematology and clinical chemistry did not indicate toxicity related to SC-0224; no indication of cholinesterase inhibition; NOEL (M/F) = 500 ppm (based on decreased body weight); study **acceptable**; (Leung, 8/9/90).

Chronic, dog **

** 023 90945; "One-Year Chronic Oral Toxicity Study with SC-0224 in Beagle Dogs" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT., Lab. Report No. T-11075, 4/3/87); dog; 831; SC-0224 technical (Lot #EHC 0469-15, WRC# 8108-24-1; 56.2%, w/w); water; oral gavage; 0, 2, 10, and 50 mg/kg (active ingredient) to 5 dogs/sex/dose once a day for 5 days/week for 1 year; **no adverse effects**; no mortality; no treatment-related effects were reported in body weight gain, food consumption, clinical observations, organ weights, and blood chemistry; transient salivation in females at 10 and 50 mg/kg; emesis noted in females at 50 mg/kg; renal tubular lipidosis in control- and SC-0224-treated dogs consistent with the tan discoloration within the cortico-medullary region of kidney was not considered to be of toxicological significance due to lack of function impairment; NOEL (M) = 50 mg/kg (no observable effects), NOEL (F) = 10 mg/kg (based on emesis at 50 mg/kg); study **acceptable**; (Leung, 8/2/90).

Oncogenicity, mouse **

** 015 90919; "Two Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Mice" (Stauffer Chemical Co., Environmental Health Ctr, Farmington, CT, Lab. Report No. T-11813, 4/3/87); mice; 835; SC-0224 technical (Lot# EHC 0586-08, WRC# JHC8865-20-1; 56.2%, w/w); oral; untreated control (60 M/60F), 0 (propylene glycol, 80M/80F), 100 (80M/80F), 1000 (80M/80F), 8000 (80M/80F) ppm (active ingredient); **no adverse effects**; decreased body weight gain throughout the study in 8000 ppm -treated males ($p<0.05$, 59.1% of control) and females ($p<0.01$, 49% of control) with reduction in food consumption ($p<0.05$, 96% and 92% of control for males and females, respectively); SC-0224 in diet did not produce oncogenicity or target organ toxicity; no gross pathologic evidence of treatment-related effects; histopathology exam did not reveal any compound-related non-neoplastic lesions; hematology and blood chemistry did not indicate toxicity related to SC-0224; no indication of dose-related cholinesterase inhibition; highest dose tested satisfies "limit" test requirements; NOEL (M/F) = 1000 ppm (based on decreased body weight gain); study **acceptable**; (Leung, 8/14/90).

GENOTOXICITY

Bacterial reverse mutation assay **

** 021 90928; "Mutagenicity Evaluation in Salmonella Typhimurium" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-10847, 1/19/82); SC-0224 technical (Lot# 7269-10, EHC-0293-13, 90% purity, w/w); tested with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100 with and without activation by Aroclor 1254- or phenobarbital-induced rat or mouse liver S9 fraction; triplicate plates; 1 and 4 trials for non-activated and activated systems, respectively; concentrations of 0 (water) and a dose range

of 0.1235 - 15.0 mg/plate; 48 hour incubation; no increase in reversion rate reported; **acceptable**; (Leung and Gee, 9/7/90).

** 021 90929; "Mutagenicity Evaluation in Salmonella Typhimurium" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11707, 11/19/82); SC-0224 technical (lot# 7981-12-1, EHC-0293-42, 62% purity, w/w); tested with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100 with and without activation by Aroclor 1254- or phenobarbital-induced rat or mouse liver S9 fraction; triplicate plates; 1 and 4 trials for non-activated and activated systems, respectively; concentrations of 0 (water), 0.62, 1.85, 5.56, 16.67, and 50.00 µl/plate; 48 hour incubation; signs of cytotoxicity seen at doses ≥ 5.56 µl/plate; no increase in revertants reported; **acceptable**; (Leung and Gee, 9/7/90).

** 021 90930; "Mutagenicity Evaluation in Salmonella Typhimurium" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-12660, 9/25/85); SC-0224 technical (lot# JHC-8865-20-1, EHC-0701-25, 55.6% purity, w/w); tested with Salmonella typhimurium strains TA-1535, TA-1537, TA-98, and TA-100 with and without activation by Aroclor-1254-induced mouse or rat liver S9 fraction; triplicate plates; single trial; concentrations of 0 (water), 2.5, 5, 10, 20, and 40 µl/plate; 48 hour incubation; signs of cytotoxicity at doses ≥ 20 µl/plate; cytotoxicity was decreased when increased amount of S9 was used (50 µl/plate vs. 20 µl/plate); reduction in revertant counts was seen only at 40 µl SC-0224/plate; no increase in revertants reported under any test conditions; **acceptable**; (Leung and Gee, 9/10/90).

021 90931; "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: A. Forward Mutation Assay" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-10848, 2/8/82); SC-0224 technical (lot# EHC-0293-13, 90% purity; lot# EHC-0293-21, 58.5% purity); tested with L5178Y TK+/- cell line with and without activation by Aroclor 1254-induced rat liver S9 fraction; replicates/dose not clear; two and three trials for non-activated and activated systems, respectively; concentrations of 0 (RPMI 1640), 0.375, 0.750, 1.5, 3, 6, 7, 8, 8.5, 9, 9.5, or 10 mg/ml; 4 hour exposure; **possible adverse effect indicated**; dose-related and reproducible increase in mutation frequency in the presence of activation by Aroclor 1254 rat liver S9 fraction; number of replicates/dose not known, not able to determine whether the increase in mutation frequency is either compound-related or due to abnormal exposure conditions (acidic pH and increased osmolality); **not acceptable** but **possibly upgradeable** with clarification of above issues; (Leung and Gee, 9/11/90).

Mutagenicity: *In vitro* mammalian cell assay **

** 021 90932; "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test: Forward Mutation Assay" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No., T-12661, 12/19/85); SC-0224 technical (lot# 8865-20-1, EHC-0701-25, 55.6% purity, w/w); tested with L5178Y TK+/- cell line with and without activation by Aroclor 1254-induced rat liver S9 fraction; 2 replicates/dose; 3 and 1 trials with and without pH adjustment to 7.2-7.5, respectively; 0 (Fischer's Medium), and over a dose range of 1.0 - 10.0 µl/ml; 4 hour exposure; **no adverse effects**; acidic pH (<6.5) induced non-specific increases in mutant frequency in the absence and presence of S9 activation; SC-0224 retested with controls and dose levels adjusted to pH 7.2-7.5 indicated reduced cytotoxicity with no increase in mutant frequency; additional tests conducted at dose range of 4 - 10 µl/ml in order to address the effect

of increased osmolality at high doses with pH adjustment did not produce an increase in mutant frequency; **acceptable**; (Leung and Gee, 9/11/90).

021 90940; "Mutagenicity Evaluation of SC-0224 in the Sex-linked Recessive Lethal Test in Drosophila Melanogaster" (Litton Bionetics, Inc., Kensington, MD, Lab. Report No. T-10886, 7/9/82); SC-0224 (lot# 6481-48-3, 58.5% purity); 0 (1% sucrose), 25, and 50 mg/ml, and ethylmethane sulfonate (0.005 M); 50 male Drosophila Melanogaster (Oregon-R strain) flies/dose; oral route; single 24 hour exposure; positive control functional; **no adverse effects indicated**; SC-0224 did not induce any significant increases in mutant frequencies except for the positive control group; doses not justified, only 2 concentrations used, no confirming trial; inadequate number of treated males used in each dose level and negative control; **unacceptable** and **not upgradeable**; (Leung and Gee, 9/20/90).

Mutagenicity: *In vivo* cytogenetics (includes *in vitro*) **

** 021 90935; "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-12662, 12/19/85); SC-0224 technical (lot# JHC-8865-20-1, EHC-0701-25,. 55.6% purity, w/w); tested with L5178Y TK+/- cell line in the presence or absence of activation by Aroclor 1254-induced rat liver S9 fraction; 2 replicates/dose; trials: 2 trials without pH adjustment, 1 trial with pH adjustment to 7.2 - 7.5; 0 (Fischer's medium) and a range of doses: 1 - 5 µl/ml (without pH adjustment), 1 - 10 µl/ml (with pH adjustment); SC-0224 induced structural aberrations and SCE in the presence or absence of an activating system in which culture conditions became acidic; at physiological pH levels, no structural aberrations or SCE were reported; **no adverse effects**; **acceptable**; (Leung and Gee, 9/14/90).

** 021 90936; "Mutagenicity Evaluation in Chinese Hamster Ovary Cytogenetic Assay" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-12663, 12/18/85); SC-0224 technical (lot# JHC-8865-20-1, EHC-0701-25, 55.6% purity, w/w); tested in Chinese hamster ovary cells with or without activation by Aroclor 1254-induced rat liver S9 fraction; 2 replicates/dose; 1 trial; 4 hour exposure; concentrations 0 (William's Medium E) and a dose range of 4 - 10 µl/ml; 50 cells/dose scored for chromosomal aberrations and 50 cells/dose scored for sister chromatid exchange (SCE); pH readjusted to 7.4 - 7.6; **no adverse effects**; SC-0224 not toxic to cells in the dose range tested; SC-0224 did not induce chromosomal aberrations or an increase in SCE in the presence or absence of activation; **acceptable**; (Leung and Gee, 9/17/90).

021 90933; "Mutagenicity Evaluation in Chinese Hamster Ovary Cytogenetic Assay"(Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No.T-10875, 7/6/82); SC-0224 technical (lot# 6841-48-3, EHC-0293-21, 58.5% purity, w/w); tested in Chinese Hamster Ovary cells with and without activation by Aroclor 1254-induced rat liver S9 fraction; 50 cells/dose scored for chromosomal aberrations; number of replicate cultures unclear; single trial; concentrations 0 (Ham's F-12 Medium) and a dose range of 2 - 12 mg/ml; 2- and 10- hour exposure with and without S9 activation, respectively; **possible adverse effect indicated**; non-activated assay exhibit increase ($p<0.05$) in aberrations at 4 mg/ml, but was not dose-related; in the presence of activation by S9 fraction: significant increases ($p<0.05$) in aberrations at 8, 10, and 12 mg/ml; positive control in the presence of activation not functional, number of replicate

cultures unclear; inadequate number of cells scored; **unacceptable** and **not upgradeable**; (Leung and Gee; 9/12/90).

021 90934; "Mutagenicity Evaluation in Chinese Hamster Ovary Cytogenetic Assay" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No.T-11019, 7/22/82); SC-0224 technical (lot# WRC-7466-18-01, EHC-0293-27, 72% purity, w/w); tested in Chinese hamster ovary cells with activation by Aroclor 1254-induced rat liver S9 fraction; 50 cells/dose scored for chromosomal aberrations and 3-20 cells/dose scored for sister chromatid exchange; number of replicates cultures unclear; single trial; concentrations 0 (F-12 medium) a dose range of 1-8 µl/ml; 2 hours exposure; **possible adverse effects indicated**: significant increases ($p<0.01$) in aberrations reported at doses $\geq$ 6 µl/ml; no significant increases in sister chromatid exchange (SCE) reported; cytotoxicity observed at doses $\geq$ 7 µl/ml; number of replicate cultures/dose unclear, inadequate number of cells scored, positive control not functional in SCE study, and testing in non-activating system not performed; **unacceptable** and **not upgradeable**; (Leung and Gee, 9/13/90).

021 90938; "Mutagenicity Evaluation in Bone Marrow Cytogenetic Analysis in Rats" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report. No. T-10884, 9/9/82); SC-0224 technical (lot# 6841-48-3, EHC-0293-21, 58.5% purity, w/w); tested in Sprague-Dawley male rats; oral; single or five consecutive daily doses: 0 (distilled water), 21, 63, and 188 mg/kg; 8 rats/dose; 3 hours prior to sacrificing at 6, 12, 24, 48 hrs and 5 days, rats were treated with 4 mg/kg of colchicine (ip); 45-100 spreads read for each rat; positive control functional; **no adverse effects indicated**; none of the treatment doses induced chromosomal aberrations that was significantly different from the control; use of males only, inadequate dose selection and no indication if doses were adjusted for purity; **unacceptable** but **possibly upgradeable** with additional information to justify the use of male rats, and to eliminate the above deficiencies; (Leung, 9/18/90).

021 90939; "Mutagenicity Evaluation in Bone Marrow Micronucleus" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-12689, 4/23/87); SC-0224 technical (lot# JHC-8865-20-1, EHC-0701-25, 55.3% purity, w/w); single oral (males: 0, 700, 900, and 1100 mg/kg; females: 0, 400, 600, and 800 mg/kg), cyclophosphamide (100 - 250 mg/kg, positive control); 5 CD-1 mice/sex/dose; bone marrow samples taken at 24, 48, and 72 hrs after dosing and 48 hrs after dosing for the positive control; positive control functional; **no adverse effects indicated**; SC-0224 does not induce any significant increases in micronuclei frequency; individual data for females at the 48th hour sacrifice (second trial) is missing in the appendix; **unacceptable** but may be **upgradeable** with submission of missing data in appendix; (Leung and Gee, 9/19/90).

Mutagenicity: DNA Damage (no longer a required category) **

** 021 90937; "Morphological transformation of BALB/3T3 Cells"(Stauffer Chemical Co., Environmental Health Ctr, Farmington, CT, Lab. Report No. T-10849, 1/4/82); SC-0224 technical (lot# 7269-10, EHC-0293-13, 90% purity, w/w); tested with BALB/3T3 mouse cells without activation; 0 (EMEM), 0.313, 0.625, 1.25, 2.50, and 5.00 mg/ml; 15 flasks/dose; 1 trial; 3-day exposure followed by washing and a 4-6 week incubation; reduction in clonal survival at doses $\geq$ 3 mg/ml; **no adverse effects**; no increase in transformed foci over control levels was reported; **acceptable**; (Leung and Gee, 9/18/90).

** 021 90941; "ICIA0224: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes In Vivo" (ICI Central Toxicology Lab., Alderley Park, UK, Lab. Report No. CTL/P/2789, 2/7/90) ICIA0224 (lot# Y06380/001/002, 57.6%, w/w); tested in Alpk:APfSD male rat hepatocytes; 3-5 rats/dose; 0 (corn oil), 150, 300, and 600 mg/kg; rats sacrificed at 4 and 12 hours post-treatment; cells labelled in vitro 4 hours with 3H-Tdr and chased overnight; UDS by autoradiography; 50 cells scored on each of two slides for each rat; positive control functional; **no adverse effects**; treatment with ICIA0224 did not result in any significant increase in UDS activity in rat hepatocytes either at 150, 300, or 600 mg/kg, or at either time point; **acceptable**; (Leung and Gee, 9/20/90).

REPRODUCTIVE TOXICITY, RAT ** †

**** 014 90917**; "Two-Generation Reproduction Study in Rats" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11051, 4/19/84); [Crl CD(SD)BR] rat; 834; SC-0224 technical (Lot# EHC-0355-25, 19.2%, w/w); oral diet; 0, 150, 800, and 2000 ppm active ingredient to 30 females/dose; **adverse effects:** postnatal growth retardation; reduction in mean maternal body weight at 800 and 2000 ppm ($p<0.01$, 90% and 84% of control, respectively) with a decrease ($p<0.05$, 86% and 80% of control, respectively) in feed intake for P-1 females during reproductive phase; pup weights were reduced ($0.01 \leq p < 0.05$) after lactational day 7 at 2000 ppm for all litters and for both second litters at 800 ppm; no evidence of altered intrauterine development, increased stillbirths, or pup anomalies; NOEL = 150 ppm or 7.5 mg/kg/day (based on postnatal growth retardation, reduced feed intakes and body weights in parents and pups); **acceptable**; (Leung and Chernoff, 9/5/90).

DEVELOPMENTAL TOXICITY

Rat **

** 020 90925; "A Teratology Study in CD Rats with SC-0224" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11050, 11/5/82); rat; 833; SC-0224 (Lot# EHC-0355-25, 19.2%, w/w); oral intubation; 0, 30, 100, 333 mg/kg active ingredient to 25-26 females/dose on days 6 through 20 of gestation; **no adverse effects**; three females in the 333 mg/kg/day group were found dead before scheduled sacrifice; clinical observations and necropsy findings indicated trauma during dosing in one female and reddened lungs and darkened cortico-medullary junctions in the kidneys in two other females; maternal effects included significant decrease in body weight gain ($p<0.05$, 57.5% of control), increase incidence ($p<0.05$) of chromorhinorrhea, lethargic and salivation at 333 mg/kg/day; decrease in mean fetal weight ($p<0.05$, 84% of control) at 333 mg/kg/day; no evidence of structural teratogenicity; Maternal NOEL = Developmental NOEL = 100 mg/kg/day (based on decrease maternal weight gain and mean fetal weight; **acceptable**; (Leung and Chernoff, 8/24/90).

Rabbit ** †

**** 020 90927**; "A Teratology Study in New Zealand White Rabbits with SC-0224" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-11052, 12/5/85); rabbit; 833; SC-0224 technical (Lot# EHC-0469-15,56.2%, w/w); oral gavage; 13 consecutive

daily doses of 0 (water), 10, 40, and 100 mg/kg/day to 15 females/dose on days 7 through 19 of gestation; 6 additional females were assigned to highest dose; **adverse effects**; 100 mg/kg: 6 deaths in 17 pregnant females and 4 abortions in 11 survivors, and significant ($p<0.05$) maternal body weight loss (-0.3 kg) during dosing (days 7-21) with concomitant reduction in food consumption were reported; 40 mg/kg: reduction in food consumption on days 7-14 ($p<0.05$, 79.5% of control); clinical signs indicate anorexia, diarrhea, and lethargy; no significant differences in mean fetal weight or fetal anomalies; no malformed fetuses were reported in the conceptuses aborted; Maternal NOEL=40 mg/kg/day (unscheduled deaths); Developmental NOEL = 40 mg/kg/day (based on aborted conceptuses at HDT); **acceptable**; (Leung and Chernoff, 8/28/90).

020 90926; "A Range-Finding Teratology Study in New Zealand White Rabbits" (Stauffer Chemical Co., Environmental Health Ctr., Farmington, CT, Lab. Report No. T-1105A, 3/31/83); rat; SC-0224 technical (Lot# EHC-0355-25, 19.2%, w/w); oral intubation for 13 consecutive days at 0, 25, 100, and 400 mg/kg/day SC-0224 to 5 rabbits/dose; 400 mg/kg: one of five rabbits survived the first day and dosing at this level was discontinued after the first day; two females which died did not exhibit any clinical signs prior to death and a third female was lethargic after dosing and became ataxic and convulsive; 100 mg/kg: transient reduction in gastrointestinal and urinary tract motility; occurrence of transient absence of defecation and urination observed in low dose and control-treated females suggests that it may be stress-related rather than a sign of toxicity; **supplemental**; (Leung, 8/27/90).

NEUROTOXICITY

Acute neurotoxicity, rat

90-day neurotoxicity, rat

Developmental neurotoxicity, rat

Delayed neurotoxicity, hen **

**51764-038 120443, "Acute Delayed Neurotoxicity of ICIA-0224", (L. C. Mutter, ICI Americas, Inc., Toxicology Laboratory, Western Research Center, Richmond, CA., Report # T-12324, 18 April 1989). Technical ICIA-0224 (N-(phosphono-methyl) glycine, sulfonium salt) with 56.9% purity by weight was used as test article. [The a.i. is now designated glyphosate-trimesium]. Six to 8 White Leghorn (Hy-Line strain) hens per group were treated twice by gavage with a three week interval at concentrations of 0, 500, or 5000 mg/kg a.i. Positive

controls received 500 mg/kg TOCP. Hens were killed 3 weeks following the second administration. No absolute NOEL was obtained (transient, dose-related diarrhea in both glyphosate-trimesium groups). Common signs in 5000 mg/kg glyphosate-trimesium hens included transient decrements in food consumption for a few days after each dosing, associated with minor temporary b.w. decrements, also transient decrements in egg productivity. There was no acute delayed neurotoxicity associated with glyphosate-trimesium. Study is **acceptable**. **No adverse effects**. (H. Green and C. Aldous, 5/5/93).

51764-024; 90946; "SC-0224 Technical: Effect On Rat Cholinesterases," Neurotoxicity testing; Rat; Stauffer Chemical Company, Richmond, CA, Report # T-11220, 6/20/83; SC-0224 Technical (Lot # 7981-12-01, purity=62%) mixed in distilled water; animals dosed orally by gavage (1 group of 5 males: 1 single dose of 645 mg/kg; 3 groups of 5 females: single doses of 645, 968, 1290 mg/kg); mortalities- males: 0/5; females: 0/5, 1/5, 3/5; observations- no effect on brain, erythrocyte, or plasma cholinesterase levels in all treated groups at 4 hrs and in the 968 mg/kg female group at 1 and 2 hrs; animals in 645 mg/kg group appeared normal before sacrifice, animals in 968 mg/kg group exhibited mild behavioral depression and slight drop in body temperatures, and animals in 1290 mg/kg group exhibited marked behavioral depression accompanied by marked reduction of body temperature; Supplemental. (Corlett, 9/6/90).

IMMUNOTOXICITY

ENDOCRINE DISRUPTOR STUDIES

SUPPLEMENTAL STUDIES