

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH**

**SUMMARY OF TOXICOLOGY DATA  
SULFOMETURON METHYL**

Chemical Code # 2149, Tolerance # 50294

SB 950 # 319

Original date: 11/12/02

**I. DATA GAP STATUS**

Chronic toxicity, rat:	Data gap, inadequate study, possible adverse effect indicated
Chronic toxicity, dog:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	Data gap, inadequate study, no adverse effect indicated
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	Data gap, inadequate study, no adverse effect indicated
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached.

All record numbers for the above study types through 129368 (Document No. 50294-056) were examined. Several older reports have record numbers > 900000. This Summary includes all relevant studies indexed by DPR as of 10/2/09.

In the 1-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: t20021112.wpd

Original by Aldous, 11/12/02.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

### COMBINED, RAT

**50294-012 and -013 037972 and 037973** “Long-Term Feeding Study in Rats with Benzoic Acid, 2-[[[(4,6-Dimethyl-2-Pyrimidinyl)amino]carbonyl]amino]-Sulfonyl]-, Methyl Ester (INT-5648), Final Report on the Feeding and Two-Generation Reproduction Study Conducted 1/27/81-2/24/83”, (Rickard, R. W., Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Company, Newark, DE, Report # 367-84, 12/27/84). [Combined Chronic/Oncogenicity Data Review]. Eighty CrI:CD®(SD)BR rats/sex/group received sulfometuron methyl in the diet at 0, 50, 500, and 5000 ppm in a 2-yr lifetime study (of these, 20 rats/sex/group were used for a reproduction “substudy” and were returned to this main study after weaning of the F1b litters). Estimated achieved doses were 2, 20, and 199 mg/kg/day in low to high dose males, and 3, 26, and 260 mg/kg/day in corresponding females. There were no clinical signs of toxicity. High dose female body weights were marginally decreased compared to controls (significant,  $p < 0.05$  at some time intervals), and food consumption was marginally decreased in those females. These are possible minor treatment effects. Apparent NOEL = 50 ppm, based primarily on fibrosis and hyperplasia in bile ducts in females (designated as a possible adverse effect). Males were unaffected at all dose levels tested. This study has several serious deficiencies, particularly (1) infections caused by *Corynebacterium kutscheri* killed 75 males and 13 females on study and (2) dose selection was poor. The use of 10-fold steps between doses offered very little hope of assessing dose-response relationships. Study deficiencies preclude an upgrade to acceptable status. Reviewed by C. Caraway and J. Gee on 5/23/86. Re-examined by H. Green and C. Aldous on 10/8/02.

50294-039 114877 Parts 1-3 of this volume contain individual pathology data for the rats in the chronic portion of 50294-012 037972, above. Aldous, 9/11/02.

50294-056 129368 (supplement dated 2/25/94) is a 3-month report, including hematology and clinical chemistry, of rats in the combined chronic/oncogenicity and reproduction study, above. Evidently no interim sacrifice occurred, and this report does not contain gross pathology or microscopic evaluations. There is no separate worksheet for this report. Aldous, 10/1/02.

50294-008 070157 A 2-page summary of subchronic and 1-generation reproduction studies related to Document Nos. 50294-012, -013, -036, -039, -056, and -011, above. No new worksheet. Aldous 10/1/02.

50294-003 904136 This volume contains only brief summaries of studies completed prior to 1982. This record apparently references Record No. 037972, above. Record No. 50294-003 904138 is Tab #7 in that volume: brief text with no data tables. There are no new data to review. Aldous, 10/2/02.

### CHRONIC TOXICITY, RAT

See Combined, Rat, above.

### CHRONIC TOXICITY, DOG

50294-037 114871 “One-Year Feeding Study in Dogs with Benzoic Acid, 2-[[[(4,6-Dimethyl-2-Pyrimidinyl)-Amino]Carbonyl]Amino]Sulfonyl]-, Methyl Ester [INT-5648]”, (Wood, C. K., F. O. O’Neal, H. J. Trochimowicz, and J. R. Gibson, Haskell Laboratory for Toxicology and Industrial Medicine, E. I. Du Pont de Nemours and Co., Newark, DE., Report # 482-82, 4/27/83; revised 5/10/83). Six beagles/sex/group received sulfometuron methyl (98.8%) in the diet at 0, 200, 1000, and 5000 ppm for 1 year. Estimated mean daily intakes were 0, 5, 28, and 153 mg/kg/day in M and 0, 5, 28, and 148 mg/kg/day in F. NOEL = 200 ppm (mild hematology changes in 1000 and 5000 ppm females and in 5000 ppm males: including reduced RBC counts, Hb, and HCT, and slightly elevated platelet counts). Modest but statistically significantly elevated liver weights in both sexes at 5000 ppm and approximately 2-fold increases in alkaline phosphatase were plausibly treatment-related. This study has major deficiencies. Ophthalmology was not performed. Also, there were no analyses of inorganic electrolytes in clinical chemistry evaluations. Since there are no data on the latter parameters in long-term studies in any species, the present study cannot be upgraded. No adverse effects are indicated. (H. Green and C. Aldous, 11/12/02).

50294-014 037974 Duplicate copy of 50294-037 114871 , above.

### ONCOGENICITY, RAT

(See combined, rat, above)

### ONCOGENICITY, MOUSE

50294-038 114875, 114873, “Oncogenicity Study with INT-5648, Long-Term Feeding Study in Mice”, (Abraham J. Tobia, Ph.D., E.I. du Pont de Nemours & Co., Haskell Laboratory, Newark, DE., Report # 355-87, final version 9/28/87). 80 CrI:CD<sup>®</sup>-1(ICR)BR mice per sex per group received sulfometuron methyl (98.1% purity) in the diet at concentrations of 0, 5, 20, 100, or 1000 ppm for 18 months. Estimated mean dietary intakes for 100 and 1000 ppm mice were 13 and 132 mg/kg/day (M) and 19 and 183 mg/kg/day (F). Apparent NOEL for females was 100 ppm [1-2 g b.w. decrement, often statistically significant during the course of the study, also decreased RBC parameters (RBC count, HCT, Hb) at 18 months, but not at 12 months or earlier, and increased incidence of the common end-stage pathology, amyloidosis, in multiple organs]. No oncogenicity was evident. Study is unacceptable and does not appear to be upgradeable. The high dose was too low to challenge males, but was in a toxic range for females. The mid-dose was placed 10-fold lower, making it difficult to assess dose-response relationships. It is not clear whether investigators examined multiple sections of brain and spinal cord. Analyses of dosed diets showed serious errors in preparation, although not at the 1000 ppm level. A copy of the subchronic study is requested if the registrant seeks to rebut acceptability status. H. Green and C. Aldous, 11/12/02.

## REPRODUCTION, RAT

50294-012 and -013 037972 and 037973 “Final Report on the Feeding and Two-Generation Reproduction Study Conducted 1/27/81 – 2/24/83”, (Rickard, R.W., Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Company, Newark, DE, Report # 367-84, 12/27/84). [Reproduction Data Review] Twenty CrI:CD®(SD)BR rats/sex/group received sulfometuron methyl in the diet at 0, 50, 500, and 5000 ppm through 2 generations with 2 litters per generation as a “substudy” of the combined chronic/oncogenicity study with the same record numbers. Treatment began 90 days prior to mating for each generation. Thus F0 parental rats were used for two mating periods, then kept on treatment until the end of the 2-yr lifetime study. Study remains unacceptable, as previously assessed. The 1986 review noted that the high dose selection was not justified, as 5000 ppm did not show definitive toxicity. The 2002 review is in general agreement on dosing justification, although there was slight evidence of decreased food consumption and decreased body weight (statistically non-significant) in 5000 ppm females, and litter sizes at birth were slightly reduced in 2 of the 4 littering periods. Histopathology was limited to (1) F0 parents at 2-yr study termination and (2) selected F2b weanlings. F1b parental rats were discarded without necropsy after rearing the F2b litters, thus there were no microscopic examinations of rats of reproductively viable age. Eighty-four out of the 640 rats of the main study (which included the F0 reproduction study rats) died of a respiratory infectious process, which occurred after the F0 parental mating periods, but before necropsies of F0 rats. Several items relating to the dams were not evaluated, including duration of gestation, food consumption and body weights during gestation and lactation periods, clinical signs during these same periods, and gross necropsies or histopathology of F1b parental rats. Apparent NOEL's are 500 ppm for parental and reproductive toxicity, based on non-significant, but possibly treatment-related effects (above). Initial submissions were reviewed by C. Caraway and J. Gee, 5/23/86. These and subsequently submitted data were examined by H. Green and C. Aldous between 9/11/02 and 10/7/02.

50294-011 027170 This is the text of 50294-012 037972 through p. 46, excluding data tables.

50294-039 114877 Part 4 of this volume contains mating data for both generations of parental rats, plus individual pathology data for F0 parental rats, which after being returned to the chronic portion comprised one-fourth of the rats in the report of 50294-012 and -013. Aldous, 10/7/02. (No separate worksheet: these data are cited as needed in the review of the above reproduction study).

50294-036 114869 This report provides an EPA “Acceptance Criteria” list, identifying which expected items for a reproduction study were available for Record No. 114877. Summaries of major indices and mean organ weights of F2b weanlings were provided. Pathology findings for the F0 adults and for the F2b weanlings were summarized. The registrant concluded that the discrepancies from current standards, based on the EPA “Acceptance Criteria” list, should not prevent agencies from accepting the reproduction study. DPR agrees that most discrepancies could be reconciled. The lack of histopathology on adults, treated for a generation and then observed in their reproductive prime stage of life, is a critical deficiency. Considering this record and a more recent record (50294-056 129368 - see under “Combined, Rat”, above)

containing limited subchronic data, the reproduction study remains unacceptable and does not appear to be upgradeable. A replacement or supplemental study is requested. Aldous, 11/12/02.

#### TERATOLOGY, RAT

50294-015 037979 Re-formatted and presented with greater detail in 50294-040 114880 and 114882 (the latter is a response to U.S. EPA acceptance criteria concerns). A summary is found in 50294-003 904137. "Teratogenicity Study by Diet in the Rat with Benzoic acid, 2-[[[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl]amino] sulfonyl]-, methyl ester," (M. H. Lu, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE). Report # 316-81, issued 6/5/81, revised 6/16/81. Twenty-five inseminated CrI: CD<sup>®</sup>(SD)BR dams/group received sulfometuron methyl in the diet at 50, 1000, and 5000 ppm on gestation days 6 through 15. There were 45 untreated controls. Maternal NOEL = 1000 ppm (slight reduction in maternal food consumption at 5000 ppm). Developmental NOEL = 1000 ppm (slight reduction in fetal body weights at 5000 ppm). There was no increase in fetal malformations or variations due to treatment. Study is not acceptable, and does not appear to be upgradeable for 2 major reasons (analysis of treated diet, and adequacy of high dose levels). Proper dosing was not adequately documented: the low dose group content of a.i. was 11-fold higher than nominal in the only sampling period at which all levels were sampled. Only diets at that dose level were subsequently sampled. The study was performed in 3 different runs, leaving considerable opportunity for similar mixing errors to have gone undetected. The high dose was not at the limit dose, and subchronic study data indicated that doses of at least 1000 mg/kg/day could have been tolerated. No adverse effects indicated. (H. Green and C. Aldous, 9/23/02).

#### TERATOLOGY, RABBIT

50294-040 114883 Serota, D. G. (study director and author of original report). "Phase 3 reformat of MRID 00078798 and related MRID 00078797: Teratology Study in Rabbits: H-13647-02: benzoic acid, 2-[[[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl]amino]-sulfonyl]-, methyl ester: HLO 331-81, Project No. 201-555." Hazleton Laboratories America, Inc. Final Report Date: 7/16/90 (reformatted version). Laboratory Study #: H-13647-02. Seventeen mature virgin NZW does/group were dosed by gavage (2 ml/kg suspension in 0.5% aqueous methylcellulose) at 0, 26, 90, and 252 mg/kg/day (assayed content) for nominal 30, 100, and 300 mg/kg/day groups in a standard teratology study. Maternal NOEL = 100 mg/kg/day (minor decrement in body weight gain during the dosing period). Developmental toxicity NOEL = 30 mg/kg/day (fused sternebrae). Report is not acceptable, but upgradeable. DPR requests information on (1) ages of does at start of dosing, (2) stability of dosing suspensions as prepared, for one week, refrigerated, (3) historical control data of the time frame of this study for fused sternebrae, and for ossification delays in sternebrae and vertebrae. Aldous, 11/12/02.

50294-040 114885 A summary of the EPA acceptance criteria for 50294-040 114883, in which the writers judged the primary study to be in compliance except for lack of food consumption data, which they considered not to have invalidated the study.

The pilot study for the above rabbit teratology study was summarized in Appendix B of 50294-040 114883. Reports 50294-015 037980 and 50294-040 115008 are exact duplicates of this same pilot study. Essential features of this pilot study were discussed in the review of the primary study.

50294-015 037981 is the original Hazleton report for the above rabbit teratology study, which is not as detailed as the primary record (114883).

50294-003 031867 is a brief summary of 50294-040 114883, above (no worksheet). 50294-003 031868 is a brief summary of the pilot study, detailed in Appendix B of the primary study report (see above). Aldous, 10/1/02.

### GENE MUTATION

\*\*50294-015, 003 037976, 904139, "Mutagenic Activity in the *Salmonella*/Microsome Assay", (James D. Taylor, E.I. du Pont de Nemours & Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Report # 271-79, 21 May 1979). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed in duplicate for 48 hours to sulfometuron methyl concentrations (95% purity) of 0 (DMSO), 50, 100, 250, 500, and 1000 : g/plate with activation, or to 0 (DMSO), 25, 50, 100, 250, and 500 : g/plate without activation for 48 hours in Trial 1. A lower exposure series was used in a second trial, reflecting toxicity at the higher dose levels in the first trial. Trial 2 exposures were 0, 2.5, 5, 10, 25, and 50 : g/plate with or without activation. Positive controls were functional. **Test article did not increase reversion rates. Acceptable.** (C. Caraway and J. Gee, 5/22/86).

\*\*50294-015, 041, 003 037977, 114172, 904140, "Chinese Hamster Ovary Cell Assay for Mutagenicity", (Kim Fitzpatrick, E.I. du Pont de Nemours & Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # 1074-80, 26 January 1981). Duplicate plates of Chinese hamster ovary cells (BH4 clone of the CHO-K1 cell line) were exposed in the presence (5-hour exposure) and absence (18-19 hour exposure) of activation to sulfometuron methyl (approximately 100% purity) concentrations of 0 (DMSO), 0.027, 0.27, 0.55, 0.82, and 1.1 mM in 2 trials. Higher concentrations were not soluble. Positive controls were functional. **Test article did not increase mutation frequency. Acceptable.** (C. Caraway and J. Gee, 5/21/86).

50294-041 114971 U.S. EPA acceptance criteria response to 50294-015 037977, above. No worksheet. Aldous, 10/1/02. 50294-041 114972 is a re-formatted version of 037977. No new worksheet is needed, as the study was accepted in the original review. Aldous, 10/1/02.

### CHROMOSOME EFFECTS

50294-015, 041 037978, 114973 (exact duplicate of 037978), 114974, "Mutagenicity Evaluation of H #13,647-03 in an *in Vitro* Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (Sheila M. Galloway, Litton Bionetics, Inc., Kensington, MD., Project # 20990, November 1981). Chinese hamster ovary cells (CHO-WBI) were exposed in the presence (2 hour exposure) and absence (8.5-10 hour

exposure) of activation to sulfometuron methyl concentrations of 0 (medium and DMSO), 3.0, 10.0, 30.0, 100.0, and 300.0 : g/ml. **An increase in chromosomal aberrations is not indicated. Unacceptable**, upgradeable. (The study needs justification for use of only 1 harvest interval and for using only a single trial.) (C. Caraway and J. Gee, 5/22/86).

50294-041 114974 U.S. EPA acceptance criteria response to 50294-015 037978, above. This response contains this statement on p. 7: "One trial with activation and one trial without activation were conducted. Duplicate independent cultures were not conducted, but this is a supplemental criteria and may not be required for every study. Since multiple concentrations gave no indication of a dose response or significant increase of a particular type of aberration, this study satisfies the guideline requirement." This statement was not provided to address the DPR concerns, and this record does not address another key issue raised in the original review, namely "A single time of harvest at 10-12 hours was used with no justification or comments on cell cycling." No DPR worksheet is required for this record. Aldous, 10/1/02.

#### DNA DAMAGE

\*\*50294-015, 041 037975, 114975, 114976, "Unscheduled DNA Synthesis/Rat Hepatocytes *in Vitro*", (Kevin T. McCooey, E.I. du Pont de Nemours & Company, Inc, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # 769-82, 12/8/82). Sulfometuron methyl purity was about 95%. Male Charles River/Sprague Dawley rats were the source of hepatocytes for the assay. Hepatocyte suspensions were seeded onto cover slips, which were exposed in duplicate in each of two trials, using sulfometuron methyl concentrations of 0 (DMSO),  $1 \times 10^{-5}$ ,  $1 \times 10^{-4}$ ,  $1 \times 10^{-3}$ ,  $1 \times 10^{-2}$ , 0.1, and 1.0 mM for 18 hours. UDS was quantified by assessing  $^3\text{H}$ -thymidine uptake by autoradiography. DMBA was a viable positive control. **Treatment caused no increases in unscheduled DNA synthesis. Acceptable.** (C. Caraway and J. Gee, 5/22/86).

#### NEUROTOXICITY

(This study type is not required at this time.)