

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
BRODIFACOUM

Chemical Code # 2049, Tolerance # 50164

SB 950 # 536

January 10, 2001, revised May 28, 2002 and April 4, 2005

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file ¹
Chronic toxicity, dog:	Data gap, no study on file ¹
Oncogenicity, rat:	Data gap, no study on file ¹
Oncogenicity, mouse:	Data gap, no study on file ¹
Reproduction, rat:	Data gap, no study on file ¹
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no 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 effects
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 091344 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T050404

Revised by J. Gee, January 10, 2001, May 28, 2002 and April 4, 2004

Used as an anticoagulant rodenticide.

¹ In a memorandum dated June 4, 2003, the Office of Environmental Health Hazard Assessment concurred with the Department of Pesticide Regulation that these studies are not required at this time under SB950 data requirements.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

** 50164 – 028, -058 046780, 180809 “Brodifacoum: Teratogenicity study in the rat.” (M. C. E. Hodge, P. B. Banham, D. Richards, T. M Weight and J. Wilson, ICI, Central Toxicology Laboratory, Report no. CTL/P/437, January 22, 1980, reformatted 4/25/90). Groups of 30 Wistar derived pregnant rats were given brodifacoum (92.5%) by oral gavage at doses of 0 (10% ethanol), 0.001, 0.01 or 0.02 mg/kg, days 6 through 15 of gestation. Analytical values were lower than nominal values. Due to the mixed-up pages and missing pages, an independent evaluation of record 046780 was not possible. Evaluated as unacceptable but possibly upgradeable with submission of the full report. (Gee, 1/8/01) Record 180809 contains the complete report with individual data and appendices. The study has been evaluated as ACCEPTABLE with no adverse effects. The maternal NOEL = 0.001 mg/kg/day based on blood in the uterus of 1 female at 0.01 mg/kg/day and 3 females at 0.02 mg/kg/day. The developmental NOEL \geq 0.02 mg/kg/day. (Gee, 5/28/02)

TERATOLOGY, RABBIT

** 50164 – 028, 057 046781, 180808 “Brodifacoum: Teratogenicity study in the rabbit.” (M. C. E. Hodge, P. B. Banham, D. Richards and T. M Weight, ICI, Central Toxicology Laboratory, report no CTL/P/459, January 30, 1980; reformatted by S. Palmer, 4/25/90) Fifteen Dutch rabbits per group were given brodifacoum (92.5%) by oral gavage at doses of 0 (5% ethanol), 0.001, 0.002 or 0.005 mg/kg with a second negative control group given Tween 80 as a control for ethanol. Dosing was from day 6 through day 18 of gestation. There were 21

mortalities with 10 in the high dose group associated with hemorrhaging. There was no evidence in the report of developmental toxicity.. Maternal NOEL = 0.002 mg/kg (mortality, (10/15) and internal hemorrhage); developmental NOEL = 0.002 mg/kg (no developmental effects but hemorrhagic implants in 1 doe at 0.005 mg/kg/day). No individual data were included in the initial submission (046781). Only half of the fetuses were given a skeletal exam and the other half a visceral exam. Evaluated as unacceptable and not upgradeable. (Gee, 1/8/01). A reformatted version of the study was submitted in record 180808, which included appendices of individual data, as requested. A cover letter discussed the timing of the conduct of the study as before finalization of current-type guidelines when it was acceptable to examine half of the fetuses for skeletal and half for visceral effects. In view of the overall lack of fetal findings, the study has been upgraded to ACCEPTABLE status with that deficiency. (Gee, 5/24/02)

GENE MUTATION

** 031 088829 Callander, R. D. "Brodifacoum - An Evaluation in the Salmonella Mutagenicity Assay." (ICI Central Toxicology Laboratory, UK, Report No: C.L./P/949. 6/29/84.) Brodifacoum, purity 92.5%, was evaluated for mutagenic potential at concentrations of 0, 4, 100, 500 or 2500 up/plate (with metabolic activation [S-9 Mix]) after 72 hours exposure of Salmonella typhimurium strains TA 98, TA100, TA1535, TA1537 and TA1538. Three trials with triplicate plates per concentration. ACCEPTABLE. No significant increase in revertants. (Kishiyama and Gee, 1/8/01)

50164- 028 046783 Trueman, R.W. "An Examination of brodifacoum for Potential Carcinogenicity using Two In Vitro Assays of Potential Carcinogenicity." (ICI, Central Toxicology Laboratory, Report Number CTL/R/481. March 9, 1979.) BRODIFACOUM, purity 92.5%, was evaluated for mutagenicity potential at concentrations of 0 (DMSO), 4, 20, 100, 500 or 2500 µg/plate (with metabolic activation only) after 72 hours exposure to Salmonella typhimurium strains TA 98, TA100, TA1535, TA1537 and TA1538. Triplicate plates per concentration with two trials. Positive controls were functional. No evidence of mutagenicity. UNACCEPTABLE. Not upgradeable (no trial without activation.) (Kishiyama and Gee, 1/10/01).

CHROMOSOME EFFECTS

** 032 091344 Mackay, J. M. "Brodifacoum: An Evaluation in the *In Vitro* Cytogenetic Assay in Human Lymphocytes". (ICI Central Toxicology Laboratory, Report Number CTL/P/3109. August 16, 1990.) Brodifacoum, purity 97.6%, was evaluated for genotoxicity potential at concentrations of 0, 5, 10 and 50 µg/ml using human lymphocytes [in whole blood] from 2 donors (1/sex) with and without rat liver metabolic activation. After approximately 44 hours in culture with phytohemagglutinin, brodifacoum was added for an exposure period of 3 hours. Incubation was continued for a total of 72 hours before harvest. 1000 lymphocytes were scored for mitotic index. Brodifacoum at 50 µg/ml decreased the mitotic activity. One hundred metaphases per culture per concentration were analyzed by chromosomal aberrations. At all doses tested, there was no increase in the frequency of chromosomal aberrations. ACCEPTABLE. (Kishiyama and Gee, 1/5/01)

DNA DAMAGE

** 50164-028 046782 "An evaluation of brodifacoum in the mouse micronucleus test." (T. Sheldon, C. R. Richardson and J. Shaw, ICI, Central Toxicology Laboratory, report no. CTL/P/1006, 11/28/84) Brodifacoum (96%) was given as a single intraperitoneal injection to C57BL/6J mice at 0 (corn oil), 0.187 or 0.30 mg/kg. Five per sex were sacrificed at 24, 48 and 72 hours along with the positive control, cyclophosphamide. The doses were estimated to be 50% and 80% of the median lethal dose in 7 days (MLD7) based on a preliminary study included in the report. It was unclear how many polychromatic erythrocytes per animal were scored and how many slides per sacrifice time were prepared. No increases in micronuclei or effect on percentage of polychromatic erythrocytes were reported. Cyclophosphamide was functional. Initially evaluated as not acceptable due to missing information about scoring but possibly upgradeable. (Gee, 1/9/01) A letter from Syngenta, dated April 24, 2001, clarified the scoring as 500 PCEs per animal, although the results were presented as per 1000. Although the number scored was less than currently recommended, the study has been upgraded to ACCEPTABLE status with this deficiency noted. No adverse effect. (Gee, 5/28/02).

50164 - 028 046784 Trueman, R. W. "An Examination of Brodifacoum for Potential Carcinogenicity using Two In Vitro Assays of Potential Carcinogenicity." [Cell transformation] (ICI, Central Toxicology Laboratory, Report Number CTL/R/481. March 9, 1979.) BRODIFACOUM, purity 92.5%, was incubated at concentrations of 0 (DMSO), 0.12, 1.2, 12, 120 and 1200 µg/ml for a 4 hour exposure of BHK21/C13 cells in suspension. Cells were collected, then resuspended in growth medium with agar. Cells were incubated in the semi-soft agar for 14 - 21 days for transformation assay and in parallel for 6 - 9 days for survival. All exposures were in the presence of S9 activation. The positive control was benzidine at concentrations of 0.25, 2.5, 25, 250 or 2500 µg/ml and was functional. Survival was determined with 4 replicate plates and transformation with duplicate plates except for DMSO, which had 4 plates. There was no evidence of mutagenicity. The LD50 was calculated to be 20 µg/ml with brodifacoum. There was 59% survival at 12 µg/ml and 8% at 120 µg/ml. UNACCEPTABLE. Not upgradeable (inadequate number of replicates) (Kishiyama and Gee, 1/10/01)

NEUROTOXICITY

Not required at this time.