

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLUVALINATE

SB 950-320, Tolerance # 50241

December 5, 1986

Revised 03/07/88

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect ^a
Chronic toxicity, dog:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effect ^a
Reproduction, rat:	No data gap, possible adverse effect ^b
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

^aPossible adverse effects are dermal lesions: no oncogenic response observed.

^bPossible adverse effects are dermal lesions: this study is not flagged for adverse reproductive effects.

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: SB320FLU.JAP2

Revised by Stanton Morris, 03/07/88

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

**** 063-071; 36956-36964** Oral Gavage Toxicity and Oncogenicity Study in rats(83-5); IRDC, 8/27/84; AA, 12/6/85;TRH, 8/13/86; Fluvalinate, Half-Resolved Technical, 89%; 0.25, 0.5, 1.0, 2.5, 10 mg/kg/day; NOEL 0.5 mg/kg/day (pharmacologic signs and plantar skin lesions) potential adverse health effect: paresthesia-pruritis-dermatitis complex. No oncogenic response observed; Study Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48731).

Note: Several supplementary studies are found in Document #50241-016 on the topic of pruritis and associated or resultant skin lesions. Apparently the pesticidally active isomer is primarily responsible for the symptoms. The test material appears to cause marked itching in rodents, as well as edema and erythema, which is reversible within 4 days. These studies appear to substantiate observations from previous chronic rodent studies, in which animals which were prevented from excessive scratching by clipping distal hindpaw phalanges generally demonstrated minimal skin lesions. The studies were surveyed by J. Carlisle and briefly summarized in File 1B:FLUVRTCX.320. Dr. Carlisle identified one study in that survey which referred to Worker Health and Safety Branch for evaluation.

CHRONIC TOXICITY, DOG

**** 50241-018&019, 993867&68;** "ZR 3210 Technical Six Month Subchronic Dog Study;" Elars Bioresearch Laboratories, 10/7/80 (QA signoff); fluvalinate technical, 93-94%, in corn oil by oral capsule at 50, 15, 5, 2, or 0 mg/kg/day to 6-11 sex/level for 6 months with interim sacrifice of 4/sex/level (except 2 mg/kg) at 3 months; MTD: emesis, loose stools, dehydration, and neurologic abnormalities verify MTD of 50 mg/kg/day, NOEL=5 mg/kg/day; **ADVERSE EFFECTS:** persistent pruritis with self-inflicted skin lesions, NOEL=2 mg/kg/day; decreased erythroid parameters and spleen weight, increased kidney and liver weight, overall NOEL=2 mg/kg/day. Unacceptable in prior review (JCC, 8/8/86, see below): inadequate treatment duration. ACCEPTABLE to fill chronic requirement upon second review - repeat would not give new information, change adverse effect or NOEL. Overall NOEL=2 mg/kg/day. HGM/FM, 1/4/88.

ONCOGENICITY, MOUSE

**** 058-062; 3142;** Two-year Dietary Toxicity and Oncogenicity Study in Mice with Half-Resolved ZR-3210 Technical (Fluvalinate)(83-2); IRDC, 1/12/84; AA, 12/5/85; JCC, 9/13/86; Half-resolved (alpha RS, 2R) Fluvalinate Technical(ZR-3210) 93.1%; 0, 2, 10, & 20 mg/kg/day; Possible adverse effect; Dermatitis due to auto-mutilation at 10 & 20 mg/kg/day. NOEL=2 mg/kg/day, based on dermatitis. Incomplete, unacceptable, not upgradeable as a chronic toxicity study due to lack of clinical chemistry, but acceptable as an oncology study. (Evaluation considers rebuttal comments and/or data form record 080:48732).

REPRODUCTION, RAT

**** 003; 993879;** Two Generation Reproduction, Rat; Racemic Fluvalinate Technical (83-4); IRDC, 8/81; AA, 8/12/85; JCC, 8/13/86; Fluvalinate (ZR-3210) technical racemic 93.8%; 0, 20, 100, 500 ppm in diet (250 & 1000 pilot only); Decreased F0 & F1 Body weight @250 ppm and above. Decreased fertility @ 500 ppm. Decreased pup viability @ 500 ppm. Skin and eye lesions @ 100 ppm. NOEL = 20 ppm based on general toxicity. No apparent specific reproductive effect. Study Acceptable. (Duplicate report begins in 024 #993881, and continues in Vol. 020))

TERATOLOGY, RAT

**** 024; 993877;** Teratology Study in Rats (83-3); ZR-3210 Technical; Hazleton, 5/5/80; AA, 8/23/85, JCC, 8/14/86; Fluvalinate Technical (Racemic) 93.8%; 0,2,10,50 mg/kg/day. Decreased maternal

and fetal weight, delayed ossification at 50 mg/kg (Increased variants @ 50 mg/kg) decreased viability 50 mg/kg. NOEL 10 mg/kg/day based on maternal and fetal toxicity at 50 mg/kg/day. Study Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48736).

TERATOLOGY, RABBIT

**** 005; 34980;** Teratology Study in Rabbits(83-3); Hazleton, 8/81; AA, 8/22/85; JCC, 8/13/86; Fluvalinate (ZR-3210) Half-Resolved Technical, 93.1%; 0,5,25,125 mg/kg/day. Decreased maternal body weight, decreased reproductive parameters, and increased anomalies at 125 mg/kg/day. NOEL for maternal and developmental toxicity = 25 mg/kg/day. Possible adverse effect due to severity and unusual nature of anomalies at 125 mg/kg/day. Study Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48737).

GENE MUTATION

An acceptable mouse lymphoma gene mutation assay with ZR-3210 Technical (Racemic) shows the induction of forward mutations with activation, while an incomplete, unacceptable mouse lymphoma gene mutation assay with Half-resolved Fluvalinate Technical was negative. Fluvalinate (at least ZR-3210 Technical, Racemic) must be considered potentially mutagenic.

**** 024; 993890;** Mouse Lymphoma Mutagenesis (84-2); (9/79, Litton Bionetics, Inc.); A.A.,8/23/85; BKD, 8/13/86; ZR-3210 Technical (Racemic), 93.2% purity; Mouse L5178Y TK+/-cells exposed for four hours to a range of dose levels from 0.0078 to 0.350 ul/ml. Three successful trials were done with activation and two without activation. Possible adverse effect: induction of forward mutations with activation. NOEL = 0.125 ul/ml. Complete. Study Acceptable. (Evaluation considers rebuttal comments and/or data from Document #50241-080, p. 9)

040; 3145; Mouse Lymphoma Mutagenesis (84-2); 3/2/84, Microbiological Associates; BKD, 8/11/86; Half-Resolved Fluvalinate Technical, Batch No. 8306-34B, 91% purity; Mouse L5178Y TK+/- cells exposed for four hours to 0.056, 0.075, 0.1, 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, or 0.75 ul/ml without activation, or 0.0036, 0.0048, 0.0063, 0.0084, 0.011, 0.015, 0.02, 0.027, 0.036, or 0.047 ul/ml with activation. No adverse effects. Incomplete. Not Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48742).

006; 993887; "Ames" Salmonella GNMU study (84-2); 10/ /80, Litton Bionetics; AA, 8/22/85 and BKD, 11/26/86 (Rebuttal response to Zoecon letter of 8/27/86). Fluvalinate, tech., 93.4% purity; 1, 10, 100, 500, 1000, 2500, 5000, and 10000 ug/plate with S9 activation. Duplicate plates, no confirmatory study. Negative result. Not Acceptable due to lack of confirmatory study. This study could be used to complement other comparable studies, if available, to provide an acceptable bacterial GNMU evaluation. (Evaluation considers rebuttal comments and/or data from record 080:48739).

CHROMOSOME

One sister chromatid exchange study (040:31444) is acceptable and shows no evidence of increased frequencies. A second study (024:993891) is incomplete and not acceptable, but does indicate weak induction of sister chromatid exchanges both with and without activation. Chromosome aberration induction cannot be evaluated in the study 024:993891 without activation because the positive control failed, but there was no evidence for mutagenesis with activation. Thus, the evidence is somewhat ambiguous, but since the negative study used far higher doses than the positive study and was acceptable, the test material is more likely not mutagenic. The data requirement for chromosomal effects is filled, and no adverse effect is indicated.

**** 040; 3144;** Sister Chromatid Exchange (84-3); Microbiological Associates, 3/24/84; AA,8/27/85;BKD, 8/12/86; Half-Resolved Fluvalinate Technical, Batch No. 8306-34B, 91% purity; Chinese hamster ovary cells exposed for two hours with activation or 24 hours without activation to

250, 500, 1000, or 2000 nl/ml. No adverse effect. Complete. Study Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48733).

024; 993891; Sister Chromatid Exchange (84-3,-4); and Chromosome Aberrations (84-3); Litton Bionetics, 9/79; BKD, 9/9/86; ZR 3210 Technical; Chinese Hamster Ovary (CHO) cells were dosed with 0.16, 0.80, 4.00, 20.00, 100.00 or 500.00 nl/ml with and without activation and scored for SCE and chromosome aberrations. In a second experiment CHO cells were dosed with 0.63, 1.25, 2.50, 5.00, 10.00 or 20.00 nl/ml with and without activation and scored for SCEs. The test material may weakly induce SCEs, both with and without activation. The major deficiency in this study is the failure of the positive control articles in the chromosome aberration assay without activation and the repeat SCE assay with activation. Incomplete. Unacceptable. (Evaluation considers rebuttal comments and/or data from record 080:48734).

DNA DAMAGE

** 006; 993888; (Litton Bionetics, Inc. 12/80) AA 8/22/85 & BKD 11/26/86. Cell transformation 844. Fluvalinate (90.5-94.1% purity) at 0, 0.1, 0.94, 1.875, 3.75, 7.50 ug/ml without metabolic activation in 3 day exposure of BALB/3T3 mouse cells. No evidence for transformation activity. Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48740).

An acceptable Unscheduled DNA synthesis study (040; 3146) was negative, as was an acceptable BALB/3T3 mouse cell transformation study without metabolic activation (006:999889) also appeared negative, however the study had deficiencies which rendered it not acceptable. The data requirement is filled, with no adverse effects are indicated.

** 040; 3146; Unscheduled DNA Synthesis (84-4); Microbiological Associates, 3/24/84; AA, 8/27/85; BKD, 8/8/86; Half-Resolved Fluvalinate Technical, Batch No. 8306-34B, 91% purity; 0, 5.0, 10, 50, 100, 500 nl/ml/plate for two hours with three replicate plates per treatment. No adverse effects. Study Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48735).

** 006; 993888; (Litton Bionetics, Inc. 12/80) AA 8/22/85 & BKD 11/26/86. Cell transformation 844. Fluvalinate (90.5-94.1% purity) at 0, 0.1, 0.94, 1.875, 3.75, 7.50 ug/ml without metabolic activation in 3 day exposure of BALB/3T3 mouse cells. No evidence for transformation activity. Acceptable. (Evaluation considers rebuttal comments and/or data from record 080:48740).

006; 993889; (Litton Bionetics, Inc. 12/80) AA 8/22/85 & BKD 11/26/86. Cell transformation 844. Fluvalinate (90.5-94.1% purity) at 1, 10, 50, 100, and 200 ug/ml with metabolic activation in exposure of BALB/3T3 mouse cells. No evidence for transformation activity. Unacceptable: Too few flasks per groups, especially in consideration of losses of some experimental units due to contamination. Study not upgradeable, but useful supplementary information in support of negative result in study 006:99388, above. Evaluation considers rebuttal comments and/or data from record 080:48741.

Neurotoxicity

072; 36965; (IRDC, 9/12/80) AA 12/5/85. "Acute delayed neurotoxicity study in hens". Fluvalinate, tech., 93.8% at 0, 1200, and 20000 mg/kg in single gavage dose to white leghorn chickens. Study negative, but inconclusive (positive controls not functional). Not upgradeable. CDFA does not require repeat of this study. (Evaluation considers rebuttal comments and/or data from record 080:48744).