

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ESBIOTHRIN

Chemical Code # 4040, Tolerance # 52103
SB 950 # not assigned
Original date October 3, 1997

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through doc. # 52103-010, rec. # 112053 and doc. # 113-019, rec. # 933396 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: t971003

Revised by Stanton Morris 10/03/97

NOTE: EPA guidelines for reregistration of allethrin stereoisomers was published on March 24, 1988.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

The U.S.E.P.A. classifies the allethrin stereoisomers as five different active ingredients:

- 1) Allethrin (Pynamin*)
- 2) D-cis, trans allethrin (D-allethrin, Pynamine-forte*)
- 3) Bioallethrin (D-trans allethrin)
- 4) S-biothrin
- 5) Esbiothrin*

Only studies conducted with esbiothrin are evaluated below.

COMBINED, RAT

52103-010; 112053; "Combined Chronic Toxicity/Oncogenicity Study by Repeated Dietary Administration to Rats (104 Weeks)," Laboratory Study Number 2253 TCR, RBC Study No. RBT-86-120; A. Simonnard; Centre International de Toxicologie, Missery France; 3/9/90. Groups of 80 Sprague Dawley Crl-CD-SD (BR) rats/sex were fed dietary mixtures of esbiothrin (control no. 6B0342, 93.8% purity) at 0, 0, 0, 100, 500, 1500, or 4500 ppm for 104 weeks. Ten rats/sex/group were sacrificed at 52 weeks. Twenty rats/sex/group were sacrificed at 104 weeks of which 10 rats/sex/group were used for hematology, biochemical, and urinalysis evaluation at 13, 26, 52, 78, and 104 weeks and all surviving animals of the 0 and 4500 ppm groups were given ophthalmology exams at 0, 51, and 103 weeks. The remaining 50 rats/sex/group were sacrificed at 104 weeks. Gross and histopathology examinations were done on all rats. Treatment-related effects were decreased body weight gains in females at 1500 and 4500 ppm and males at 4500 ppm; increased serum aminotransferases in both sexes at 1500 and 4500 ppm; increased serum cholesterol levels in both sexes at 4500 ppm; and increased liver weights, hepatic cell hypertrophy, focal cell degeneration, and necrosis in both sexes at 1500 and 4500 ppm (NOEL = 500 ppm). There was no treatment-related increase in neoplastic findings. No adverse effect was indicated. The study is unacceptable but possibly upgradeable with submission of an adequate rationale for the doses used (J. Kishiyama and S. Morris, 9/18/97).

CHRONIC TOXICITY, RAT

See combined rat.

CHRONIC TOXICITY, DOG

52103-007; 112048; "Toxicity study in Beagle Dogs by Repeated Oral Administration in Diet for 52 Weeks," study number 2181 TCC; D. Petra; Centre International de Toxicologie, Miserey, France; 10/28/87. Groups of 4 adult beagle dogs/sex were fed dietary mixtures of esbiothrin (lot # 6B0342, 93.8%) for 52 weeks at 0, 80, 400, or 2000 ppm. Behavioral, clinical signs, and food consumption were observed daily and body weights were measured weekly. Ophthalmological testing was done predose and week 52. Hematology, blood chemistry, and urinalysis were done predose and at weeks 26 and 52. At 52 weeks all animals were sacrificed, organs weighed, and a full gross and partial histopathology performed on each animal. Treatment-related effects included increased liver weights in both sexes at 2000 ppm; increased thyroid weights in males at 80 and 400 ppm and both sexes at 2000 ppm; enlarged mandibular glands in males at 80,

400, and 2000 ppm; increased serum cholesterol in both sexes at 2000 ppm; and liver discoloration and brown intracellular pigmentation in males at 80 and 400 ppm and both sexes at 2000 ppm (NOEL \leq 80 ppm). No adverse effect was indicated. The study is unacceptable but possibly upgradeable with submission of an adequate rationale for the doses used (J. Kishiyama and S. Morris, 8/22/97).

ONCOGENICITY, RAT

See combined rat.

ONCOGENICITY, MOUSE

52103-009; 112052; "102-Week Dietary Carcinogenicity Study in Mice," Laboratory Study Number 1669 TCS; A. Simonnard; Centre International de Toxicologie, Miserey, France; 4/11/90. Five groups of 50 CD1 Crl mice/sex were fed esbiothrin (control no. 6B0342, 93.8% purity) in the diet for 102 weeks at 0, 0, 50, 250, or 1250 ppm. Group mean exposures in males and females were, respectively, 0, 0, 8.4, 41.9, or 214.3 and 0, 0, 10.2, 49.7, or 249.6 mg/kg/day. There were no treatment-related clinical signs, incidences of tumors, mortality, changes in food consumption or body weight, hematology, non-neoplastic lesions, or neoplastic lesions. A treatment-related increase in male liver weights was seen at 1250 ppm (NOEL = 250 ppm). No adverse effect was indicated. The study is unacceptable but possibly upgradeable with submissions of an adequate rationale for the doses used and Laboratory Study Number 1767 TSS (J. Kishiyama and S. Morris, 9/15/97).

REPRODUCTION, RAT

52103-008; 112051; "Two-generation Reproduction Toxicity Study in Rats," Study No. 1690; M.H. Savary; Centre International de Toxicologie, Miserey, France; 1/29/88. Esbiothrin (lots 6 B 0342 and 6 L 1365, 97.5% purity) was continuously fed in the diet at 0, 0, 70, 200, 600, or 1800 ppm to groups of 25 Sprague-Dawley rats/sex/generation/dose for two generations (F0, F1) with one litter (F1, F2) per generation. F0 adults were exposed for 8 weeks then paired to produce the F1 litters. F1 pups were culled at post-partum day 4, treated for 14 weeks after weaning then paired to produce the F2 litters. F2 pups were culled at post partum day 4 and the remainder sacrificed on day 21. F0 and F1 males were sacrificed after mating. F0 and F1 females were treated through pregnancy and lactation and then sacrificed. Clinical signs, body weight, food consumption, and reproductive performance were recorded for F0 and F1 adult animals. Litters were examined for viability, body weight gain, and physical and behavioral development. The reproductive organs of the 0, 70, and 1800 ppm F0 and F1 adults were examined at term for gross and microscopic pathology. There were no treatment-related effects on adults or reproductive performance (parental NOEL \geq 1800 ppm). A **possible adverse effect** was indicated by treatment-related effects were seen in F1 pups: decreased body weight gain at 1800 ppm and viability at 70, 200, 600, and 1800 ppm (developmental NOEL < 70 ppm). These effects were not seen in the F2 pups. The study is unacceptable but possibly upgradeable by submission of an adequate rationale for the dose selection. (J. Kishiyama and S. Morris, 6/5/97).

TERATOLOGY, RAT

113-019; 933396; "Esbiol Teratological Test Results: Effect on the Rat Fetus of Orally

Administering Esbiol." (Roussel UCLAF, 2-75) Esbiol, no purity stated, given by oral gavage in olive oil to Wistar rats in a teratology study at 0.025, 0.05 and 0.1 ml/kg. Number per group is not stated. UNACCEPTABLE. Incomplete - tables and figures are not included. Number of rats per group is unclear. No data are included. Insufficient information for independent assessment of effects. **Possible adverse effect** indicated: the report states that "...transformation of lumbar into thoracic vertebrae..." was dose related. Apostolou, 7-2-85 and Gee, 11-12-87.

** 52103-005; 112046; "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Esbiothrin Technical Administered Orally via Gavage to CrI:CD[®]BR VAF/Plus[®] Presumed Pregnant Rats," ARGUS 718-001; E. A. Lochry; Argus Research Laboratories, Inc., Horsham, PA; 8/31/90. Groups of 25 presumed pregnant rats were given esbiothrin technical (lot 9N031B3, analytical purity 96%, 5 ml/kg corn oil vehicle) by oral gavage on gestation days 6 through 15 at 0, 5, 25, or 125 mg/kg/day (doses adjusted to 95.2% purity). The rats were sacrificed on gestation day 20 and each uterus and fetus weighed and examined. Recorded variables included number and placement of fetuses, number of corpora lutea, fetal sex and gross external, soft tissue and/or skeletal alterations. Treatment-related maternal effects at 125 mg/kg/day included: death (1/25), increased tremors, body jerks and hypersensitivity to sound, urine-stained abdominal fur, and chromorrhinorrhea (maternal NOEL = 25 mg/kg/day). There were no treatment-related uterine or fetal effects or gross external, soft tissue or skeletal malformations of the fetus (developmental NOEL \geq 125 mg/kg/day). No adverse effect was indicated. The study is acceptable (J. Kishiyama and S. Morris, 7/17/97).

52103-005; 112046 (pp. 373 - 430); "Dose-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Esbiothrin Technical Administered Orally via Gavage to CrI:CD[®]BR VAF/Plus[®] Presumed Pregnant Rats (Pilot Study)," ARGUS 718-001P; E. A. Lochry; Argus Research Laboratories, Inc., Horsham, PA; 1/31/90. Groups of 8 presumed pregnant rats were given esbiothrin technical (lot 9N031B3, analytical purity 96%, 5 ml/kg corn oil vehicle) by oral gavage on gestation days 6 through 15 at 0, 25, 50, 100, 200, or 500 mg/kg/day (doses adjusted to 95.2% purity). The rats were sacrificed on gestation day 20 and each uterus and fetus weighed and examined. Recorded variables included number and placement of fetuses, number of corpora lutea, fetal sex, and gross external alterations. Treatment-related maternal effects included: death at 200 (2/8) and 400 mg/kg/day (8/8); increased body jerks and tremors at 100, 200, and 400 mg/kg/day; increased urine stained abdominal fur and excess salivation at 200 and 400 mg/kg/day, decreased body weight gain and feed consumption at 25, 50, 100, 200, and 400 mg/kg/day; and decreased gravid uterine weights at 200 mg/kg/day. There were no treatment-related effects on conceptuses (J. Kishiyama and S. Morris, 7/17/97).

Summary: No data have been submitted to corroborate the finding of a possible adverse effect in the unacceptable study at DPR rec. # 933396. The data gap is filled by the adequate study at DPR rec. # 112046 which did not indicate a possible adverse effect (S. Morris, 10/3/97).

TERATOLOGY, RABBIT

** 52103-006; 112047; "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Esbiothrin Technical Administered Orally Via Stomach Tube to New Zealand White Rabbits," ARGUS 718-002; A. M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; 8/31/90. Groups of 20 pregnant Hra: (NZW) SPF female rabbits were given

technical esbiothrin (lots 9N0317B3 [95.2%], 9N0947B3 [94.6%]; aqueous 0.5% (w/w) methylcellulose vehicle) by oral gavage at 0, 30, 100, or 300 mg/kg/day (adjusted for purity) on gestation days 6 through 18. On gestation day 29 the surviving dams were sacrificed, the uteri were removed, weighed, and examined, and the number of corpora lutea were counted. Fetuses were weighed and examined for sex and gross, soft tissue, and skeletal alterations. Treatment-related maternal effects at 300 mg/kg/day included death (4/20), reduced food consumption, and transient post dosing clinical signs of tremors, decreased motor activity, ataxia, impaired righting reflex, and excess saliva. There were no treatment-related effects on reproductive or developmental variables or fetal abnormalities (maternal NOEL \leq 100 mg/kg/day, developmental NOEL \geq 300 mg/kg/day. No adverse effect is indicated. The study is acceptable (J. Kishiyama and S. Morris, 7/22/97).

GENE MUTATION

52103-004;112039; "Detection of a Mutagenic Potency with a Bacterial Test," RBT-84-108; J. F. Chantot and B. Vannier; Centre de Recherches ROUSSEL UCLAF, Romainville, France; April 4, 1984. Reverse mutation at the histidine locus of *Salmonella typhimurium* was estimated by measuring the frequency of prototrophic colonies arising from histidine auxotrophic strains (TA 1535, TA 100, TA 1537, TA 1538, TA 98) exposed for 2 or 3 days to esbiothrin (batch No. OLO 925, unstated purity, DMSO solvent) at 0, 100, 500, 1000, or 5000 μ g/plate with or without metabolic activation (S-9, microsomes from Aroclor 1254-induced rat livers). There were 2 trials with 2 plates/dose/strain/trial. There was no treatment-related increase in prototrophic colonies. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analytical data for the test material and exposure solutions (J. Kishiyama and S. Morris, 5/21/97).

52103-004; 112041; "An Assessment of the Mutagenic Potential of Esbiothrin using an *In Vitro* Mammalian Cell Test System," RSL 642/8442; Margaret Richold *et al.*; Huntingdon Research Centre, Cambridgeshire, England; 7/9/84. The mutation rate of the thymidine kinase locus from heterozygous to thymidine kinase deficient was measured in mouse lymphoma L5178Y cells in the presence of esbiothrin (purity and lot no. not stated, DMSO solvent) without metabolic activation at 0, 30, 35, 40, 45, 50, 55, 60, 70, or 80 μ g/ml (multiple trials) or with S-9 metabolic activation (9000 g supernatant of Aroclor-induced Sprague-Dawley CD rat liver homogenate) at 45, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, or 120 μ g/ml (multiple trials). Four suspensions of 6×10^6 cells/exposure level were incubated with the test material for 3 hours with or without S-9, washed, resuspended and incubated for 48 hours. Duplicate cultures were washed, pooled, and incubated for 48 hours. 10^6 cells were plated in triplicate in the presence of trifluorothymidine (TFT, 4 μ g/ml) and incubated for 12 days. The mutation rate was estimated by counting TFT-resistant colonies. A possible adverse effect was indicated by treatment-related increases in mutation rate without S-9 at 45 and 50 μ g/ml and for all doses with S-9. The study is unacceptable but possibly upgradeable with submission of an adequate certificate of purity (J. Kishiyama and S. Morris, 10/2/97).

CHROMOSOME EFFECTS

52103-004; 112040; "Esbiothrin, Detection of Mutagenic Potency, Micronucleus Test in the Mouse"; B. Vannier and R. Fournex; Centre de Recherches ROUSSEL UCLAF, Romainville, France; 3/21/84. Groups of 5 mice/sex were given esbiothrin (batch No. 3 L 1577, purity not stated, corn oil vehicle) at 180 mg/kg by single oral gavage and sacrificed 24, 48, or 72 hours

later. Bone marrow smears were collected, stained, and ratios determined of polychromatic / normochromatic erythrocytes and micronuclei / 1000 polychromatic erythrocytes. There was no treatment-related effect on micronuclei frequency. The positive controls were adequate. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analytical data for the test material and an adequate rationale for the doses used (S. Morris and J. Gee, 7/3/97).

DNA DAMAGE

52103-004; 112045; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes," Study No. T8283.380; R.D. Curren; Microbiological Associates, Inc., Rockville, MD; 12/15/88. Three replicate plates of 5×10^5 primary hepatocytes from adult male Fisher 344 rats were treated with esbiothrin (lot 11418-RL, 95.7% purity) at 0, 0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03, or 0.1 $\mu\text{l}/\text{plate}$ and ^{13}H -thymidine at 10 $\mu\text{Ci}/\text{ml}$. After 18 to 20 hours the cells were washed, fixed, autoradiographed, and stained. Unscheduled DNA synthesis (UDS) was measured by estimating ^{13}H -thymidine incorporation into nuclear material by microscopic inspection of autoradiographs for grains in the nuclear versus cytoplasmic regions of 50 nuclei per replicate plate. There was no treatment-related increase in UDS. No adverse effect was indicated. The study was unacceptable but possibly upgradeable by submissions of adequate rationales for the doses used, cell viability data criteria, and deviations from protocol (J. Kishiyama and S. Morris, 6/11/97).

NEUROTOXICITY

Not required at this time.

These documents were reviewed.

52103-004	112039
52103-004	112040
52103-004	112041
52103-004	112045
52103-005	112046
52103-006	112047
52103-007	112048
52103-008	112051
52103-009	112052
52103-010	112053
113-019	933396