

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FENVALERATE and ESFENVALERATE

NOTE: All new data supporting Fenvalerate registration utilize Esfenvalerate. Synonyms for Esfenvalerate, an A-a-isomer-enriched Fenvalerate technical material, include S-1844, MO 70616, and SS-Pydrin.

SB-950 data for esfenvalerate or fenvalerate are organized together in this Summary, since several of the fenvalerate studies support both active ingredients. Racemic fenvalerate contains substantial amounts of an isomer which has a toxicity profile quite different from the insecticidally active, primary component of esfenvalerate; therefore esfenvalerate studies cannot appropriately be applied to support racemic fenvalerate registration (see rebuttal document of 1/17/95 and the DPR response). Aldous, 5/2/95.

Fenvalerate Chemical Code # 001963, Tolerance # 00379, SB 950 # 230
Esfenvalerate Chemical Code # 2321, Tolerance # 51722

Original date 1/27/87

Revised 2/23/88, 10/26/93, 3/16/94, 9/7/94, 5/2/95, 12/03/98, 2/21/01, and 5/16/01

I.A. DATA GAP STATUS

ESFENVALERATE

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, possible adverse effect (not oncogenicity)
Reproduction, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Teratology, rat:	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 effect
Neurotoxicity:	No data gap, no adverse effect

I.B. DATA GAP STATUS

FENVALERATE

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	Data gap, no chronic study
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated
Teratology, rodent:	Data gap, inadequate study, no adverse effect indicated*
Gene mutation:	Data gap, inadequate studies, no adverse effect indicated
Chromosome effects:	Data gap, inadequate studies, no adverse effect indicated
DNA damage:	Data gap, inadequate studies, no adverse effect indicated
Neurotoxicity:	No data gap, possible adverse effect**

* A mouse teratology study has been submitted (not acceptable as presented).

**Not a required test type under SB-950. Several studies in several species have been submitted. Most studies involve rats. Generally the test article was racemic fenvalerate. No studies submitted as of December 1998 utilized the active ingredient Esfenvalerate. Very high doses of fenvalerate in a 4-week repeat-dose rat study elicited neurological functional and histopathological changes (not TOCP-type delayed distal neuropathy). Aldous, 5/2/95, 12/3/98.

Esfenvalerate and fenvalerate toxicology one-liners are attached.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t010516.doc
Revised by Duncan, 5/16/01.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT (studies supporting both active ingredients)

379-070 to 379-073 037090-037093 (The "Principal Study": Additional data considered were studies 379-074:37094 and Document Nos. 379-075 to 379-078, Record Nos. 037087 and 037095-037098). "Lifetime feeding study in rats: SD-43775 Technical" (Title of "principal study"). Principle study by Litton Bionetics, April, 1978, LBI Project No. 2541. All three studies were by diet incorporation, each study with untreated controls: treated groups received 1, 5, 25, and 250 ppm (principal study), or 1000 ppm (ancillary Litton study in Vol. 074), or 50, 150, 500, or 1500 ppm (Sumitomo study in Vols. 075-078). The latter study involved "Japanese Wistar SLC" rats: the two Litton studies used Charles Rivers Sprague-Dawley derived "CD" rats. A letter (D.C. Donovan of Du Pont to F. Bundock of DPR, dated Oct. 8, 1993) stated that the rats for the two Litton studies were both performed with "CRL COBS CD SD BR outbred albino rats from the Wilmington Massachusetts facility". Purity was reported to be 98% (of racemic fenvalerate) in the Litton studies. Original review cited a "possible adverse effect", based on the original diagnosis of five subcutaneous spindle cell sarcomas in 1000 ppm males (Vol. 074) vs. none in concurrent controls. Re-evaluations of original slides plus multiple additional sections of each of the lesions led to the conclusion that the majority of the tumors were fibrosarcomas. The incidence of these tumors was similar to background incidence, and the new information led to removal of the "possible adverse effect" flag (see review for Document No. 379-166, Record No. 124280). The general systemic NOEL for fenvalerate = 250 ppm [based on infiltration of various phagocytic cells, often containing brown pigment at 500 and 1500 ppm in Sumitomo study (Vols. 075-078). There were marked weight gain decrements, transient hind limb weakness, and other signs at 1000 ppm in ancillary Litton study (Vol. 74)]. The NOEL for esfenvalerate comes from a subchronic study (Record No. 130648). This NOEL is 125 ppm, based on neurological effects at higher dose levels (see re-evaluation discussion in Record No. 129492 review). Prior to the July 1994 reviews, the NOEL for esfenvalerate was considered to be 62 ppm (based on granulomatous lesions at 250 ppm for fenvalerate). Each individual study, when considered separately, was unacceptable in May, 1986 reviews by C. Aldous. Taken together, the three studies were upgraded in the 1993 review to **acceptable to fill the chronic and oncogenicity data requirements. **No adverse effects.** C. Aldous, 12/30/87, 8/25/93, 7/11/94.

379-166 124280 (additional information relating to the 1979 Litton Bionetics study, 379-074:037094). This supplement was written by L.A. Malley representing E. I. du Pont de Nemours & Co. Date of the present supplement was 6/28/93. The present volume discussed issues about acceptability of the two Litton rat lifetime dietary studies (comprising DPR Document Nos. 379-070 to 379-074), however acceptability issues do not need DPR review, since this study has already been accepted. The primary remaining concern was whether the apparent increase in subcutaneous "spindle cell sarcomas" in 1000 ppm rats was a treatment effect. Three pathologists independently re-evaluated the lesions, and their consensus diagnosis was that the 5 tumors consisted of 3 fibroadenomas, 1 liposarcoma, and 1 malignant mixed mammary tumor. Neither the total incidence of fibroadenomas nor total incidence of all subcutaneous sarcomas in 1000 ppm males indicates a treatment effect. The data support removing the "possible adverse effect", which was previously applied to the rat dietary "combined" studies based on "spindle cell sarcoma" incidence. The NOEL for rat chronic effects was set at 62 ppm for esfenvalerate in the 8/25/93 review by Aldous (however see revised NOEL for esfenvalerate in the first paragraph following "Combined, Rat" on p. 2 of the 1994 Summary).

379-027 983654 Summary of 37090-3.

379-038 25840 12 month interim data for 37090-3.

379-074 037094 "Lifetime Feeding Study in Rats", SD 43775 Technical (Fenvalerate) Final Report, (10/79, Litton Bionetics 20733-01) [Ancillary study to 37090-3] Fenvalerate, 98%, at 0 and 1000 ppm in diet. No NOEL observed in the present study (significant weight gain decrements in both sexes, transient hind-limb weakness in males, decreased hemoglobin and hematocrits in females at term, increased incidence of subcutaneous spindle cell sarcomas in males. NOT INDEPENDENTLY ACCEPTABLE, BUT CONTRIBUTES TO FULFILLMENT OF DATA REQUIREMENT FOR COMBINED RAT STUDY. C. Aldous, 5/13/86. [Re-examined in context of overall rat combined study evaluation, with new information showing spindle cell tumors not to be treatment effects, see 070-073:37090-37093, above].

379-075 to 379-078 037087, 037095-037098 "Two Year Chronic Toxicity Study of S5602 (Fenvalerate) In Rats" (4/20/81, Sumitomo AT-10-0278) Fenvalerate, 93.4%; 0, 50, 150, 500 and 1500 ppm in diet. General systemic NOEL = 150 ppm (infiltration of various phagocytic cell types in lymph nodes, liver, lung, adrenals, and spleen; often such cells containing brown pigment); UNACCEPTABLE, NOT UPGRADEABLE: Pulmonary disease epidemic substantially reduced animal numbers and confounded results; insufficient clinical chemistry/-hematology data sampling intervals. Study contributes to fulfillment of data requirement for combined rat study, largely because ophthalmology was performed [See 070-073:37090-37093, above]. NOTE: increased incidence in testicular interstitial cell tumors was originally observed by investigators at 500 and 1500 ppm in this study. Examination of confounding effects in this study and consideration of results of the two Litton chronic/oncogenicity studies (Vols. 70-74) does not support such tumors as being treatment effects [See review by C. Aldous, 5/8/86, and 1/27/86 Fenvalerate toxicology summary]. "One-liner" update by C. Aldous, 12/23/87, [Re-examined in context of overall rat combined study evaluation, see 070-073:37090-37093, above].

379-038 983652 Summary of #37087, Sumitomo #AT-10-0278.

379-172 129492 "Nature of microgranulomatous lesions observed in chronic rodent studies with Fenvalerate", (a review of submitted studies by Malley, L.A., and Mullin, L.S.), 3/16/94. Consideration of this record in light of the other records on rodent chronic and subchronic studies suggests revisions of chronic **esfenvalerate** toxicity NOEL's for mice and rats to 50 ppm and 125 ppm, respectively. For both species, the NOEL's are based on neurological changes. Aldous, 7/11/94. (See comments under "Oncogenicity, Mice", below).

CHRONIC TOXICITY, RAT

(see also under rat, combined studies, above)

SUBCHRONIC STUDIES (using esfenvalerate, supporting esfenvalerate only)

379-117 056372 "Subchronic feeding study of MO70616 in the rat", T.P.S., Inc., Mt. Vernon, Indiana, Feb. 1986 [T.P.S. Study No. 227A-101-030-84, Sponsor I.D. No. WTP 252]. [A previous worksheet was done by J. Berliner in Nov., 1987]. Report was re-examined to note effects on clinical signs, possible peripheral nerve histopathology, or other factors influencing the NOEL. 30 S-D rats/sex/group were dosed with 0, 50, 150, 300, or 500 ppm technical MO 70616 ("98.7% of the parent isomers of which 84% is the A alpha isomer") in diet. Clinical signs of "jerky leg movements" were common at 300 ppm in both sexes. An additional common finding at 500 ppm in both sexes was "unsteady gait". "Hypersensitivity to sounds" and "body tremors" were occasionally seen in high dose females. Seven high dose females died or were killed in extremis, with deaths attributed to treatment. One 150 ppm male had "jerky leg movements", making a conservative NOEL of 50 ppm. Significant b.w. decrements were seen in both sexes at 500 ppm only ($p < 0.01$). Slight hypertrophy of parotid

salivary gland parenchyma were seen at 300 to 500 ppm males and females, and slight hypertrophy of pituitary pars intermedia was observed in some male 500 ppm rats. There were no other histopathological changes evident in nervous tissues, although brain, spinal cord, sciatic nerves, tibial nerve, plantar nerves, and right median nerve had been examined. Useful information, suggesting that neurological signs did not result from microscopically evident changes in nerves. Aldous, 8/30/93 (no additional worksheet).

379-176 130648 Larson, D.M., "13-Week dietary admix study of MO 70616 Technical in rats", T.P.S., Inc., 4/14/87. Sponsor ID No. WTP 374. Groups of 25 S-D rats/sex were dosed for 7 (10/sex/group) or 13 wk (15/sex/group). Dose levels were 0, 75, 100, 125, and 300 ppm. Most parameters of a standard subchronic study were evaluated, except for histopathology, for which a relatively high NOEL had been previously established. NOEL = 125 ppm, based primarily on neurological effects ("jerky leg movements" in both sexes, and "hyperactive" behavior in females). There were also small reductions of body weight and minor organ weight changes (the most noteworthy change being increased relative kidney weights in both sexes). Study is acceptable in conjunction with the earlier 3-month rat study (Document No. 379-117, DPR Record No. 056372). This study complements Record No. 056372, and provides a higher NOEL for the most sensitive indicators of compound toxicity, which were neurological changes. No "adverse effect" is indicated. Aldous, 9/7/94.

056; 179224; "Esfenvalerate Technical: Repeated Dose Dermal Toxicity 21-Day Study in Rats" (D. Delker; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; DuPont-4228; 11/28/00); Esfenvalerate (Batch No. YB656-84; purity = 97.3% - 98.5%) was applied undiluted at 40-50°C to the skin at doses of 0 (deionized water), 25, 125, 500, and 1000 mg/kg/day to groups of 10 Crl:CD (IGS)BR rats/sex/dose level for 21 days; a neurobehavioral test battery was conducted prior to treatment and during week 3; increased dermal lesions and corneal opacity were observed in most treated groups but were considered to be caused by scratching; abnormal gait was the most sensitive indicator of toxicity and was observed in 125, 500, and 1000 mg/kg/day males and females, more frequently during the first week of the study than the last week; other neurotoxicity parameters were observed in treated females, but not males: hyperactivity, hyperreactivity, vocalization, and increased motor activity; NOEL (M and F) = 25 mg/kg/day (based on abnormal hindlimb gait); **Acceptable. (Duncan, 5/1/01)

OLDER RODENT CHRONIC STUDIES USING FENVALERATE: NOT UPGRADEABLE

MOUSE

083-4 37104-7 "Chronic Toxicity and Potential Carcinogenicity Study in the Mouse Technical SD 43775" (7/79, Litton Bionetics #20738) Fenvalerate, technical: 0, 10, 50, 250, and 1250 ppm in diet; **Possible adverse effect indicated:** NOEL = 10 ppm (Granulomata and macrophage hypertrophy with syncytium formation in lymph nodes; dose-related increase in phagocytic cell infiltration, syncytium formation, giant cells, etc. at higher dosages in lymphoid and other tissues). No oncogenicity observed; Complete, UNACCEPTABLE - excessive tissue losses due to cannibalism, autolysis; no hematology during course of study; useful data to help characterize mouse oncogenicity potential. Aldous, 5/20/86. (See section for Mouse Oncogenicity below).

HAMSTER

085-7 37108-37111 and 37114 (feed analysis) "Lifetime Feeding Study in Hamsters: SD 43775 Technical" (11/77 [revised 2/78], Litton Bionetics #2542) Fenvalerate, Technical, 98% at 0, 1, 5, 25, and 250 ppm in diet; deficiencies of study did not allow establishment of a NOEL: no apparent toxicity or oncogenicity in dosage range tested (up to 250 ppm). UNACCEPTABLE, not upgradeable. No further information requested (Excessive disease, doses apparently too low). C. Aldous, 5/14/86.

027 983648 Summary of 085/087:37108-37111.

027 25839 12 month interim report of 085/087:37108-37111.

RAT

069 37088 "Fifteen-Month Chronic Toxicity Study of S5602 (Fenvalerate) In Rats" Chronic 831 Rat (12/14/77, Sumitomo AT-70-0175) Fenvalerate, technical; 0, 50, 150, 500, and 1500 ppm in diet; NOEL = 500 ppm (reduced weight gain in both sexes, reduced serum cholinesterase in females, and "hypersensitivity" [presumed to mean abnormal responses to sensory stimuli] in males); Incomplete, UNACCEPTABLE, not upgradeable - too few animals, no necropsy data for on-study deaths. (Data gap subsequently filled, see "combined, rat", above). C. Aldous, 5/7/86.

027 31739 Summary of #069:37088, above.

CHRONIC TOXICITY, DOG

(The single guideline study supports esfenvalerate only)

379-119 056377 "One-year Oral Study in Dogs with MO 70616 Technical". Hazleton Study No. 6160-103, 8/21/86. A-alpha-enriched fenvalerate technical, [esfenvalerate], 98.7% purity, in the diet to 6 beagles/sex/level at 200, 100, 50, 25, or 0 ppm for 1 year. In-life phase was 1/24/85 to 1/31/86. **No adverse effects. Guideline study except that the high dose was not clearly adequate and feed was occasionally offered slightly beyond period of documented stability of test article in diet. Initially considered unacceptable, but upgradeable upon submission of complete pilot study and data to show sufficient stability of a.i. in diet (Martz, 10/27/87). Several studies have been reviewed which relate to these issues. A 3-week dog esfenvalerate study (Record No. 061505) found ataxia in all 500 ppm dogs and in one 300 ppm dog. Tremors and/or fasciculations were common at 500 ppm. There were marked body weight and food consumption decrements at 500 ppm. The NOEL from that study was 100 ppm for clinical observations. This short-term study supports the choice of dose levels in the chronic study. Record No. 061638 showed content of diets at intervals of no more than 6 wk over the course of the study to be consistently close to nominal levels. Record No. 061637 showed good stability of esfenvalerate at room temperature in diet over the range tested (up to 8 wk). Record No. 124957 gave mean dietary intake of 200 ppm esfenvalerate as 5.01 to 5.62 mg/kg/day over the duration of the chronic study in males and females, respectively. These additional data allow an upgrade of Record No. 056377 to **acceptable** status. Aldous, 8/23/93.

379-167 124957, Malley, L.A., additional data to study 379-119:056377. "Supplement 2 to: One-year oral study in dogs with MO 70616 technical", Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, 3/10/88. Daily intake of male and female dogs in Record No. 056377 based on 1-year mean of weekly means, was 5.01 and 5.62 mg/kg/day, respectively. Useful additional data. Aldous, 8/23/93.

379-126 61633 exact duplicate of 379-119 056377, above.

379-125 061505 "Probe study in dogs with MO 70616 technical", Study No. 6160-101, Hazleton Laboratories America, Inc., Madison, 5/30/85. Two beagles/sex/group were dosed in diet with 0, 100, 300, or 500 ppm esfenvalerate for 3 weeks. Body weights dropped 1.4 and 1.1 kg in high dose males and females during the first week, and body weights at this dose remained low through the study. Food consumption of high dose dogs was reduced 40% or more in both sexes at 500 ppm. Limited food consumption data suggested modest reductions at 300 ppm also. Ataxia was noted in one male 300 ppm dog at day 19 only. Ataxia was seen in all 500 ppm dogs. First notations of ataxia were at or after day 18. Tremors and/or fasciculations were observed in 3 of the 4 high dose dogs. All of these signs were noted during or shortly after eating. There were no gross pathological changes. Histopathology was not assessed in this study. Adrenal weights were elevated, dose-related, in 300 and 500 ppm females. These data demonstrate that a high dose for a chronic study should be well under 500 ppm. Useful data relevant to assessment of chronic study. Aldous, 8/23/93.

379-167 124958 Text of report is exact duplicate of 379-125 061505, above.

379-127 061637 dog diet data relevant to chronic study 379-119:056377. Schultz, D.R., "Analyses and stability of 25, 50, 100, and 200 part-per-million concentrations of MO 70616 on canine diet -- WTP-270, One Year Feeding Test", Shell Development Co., Biological Sciences Research Center Modesto, CA., 4/23/85. Stability of esfenvalerate was determined in dog diet for periods of up to 8 weeks. There was no change in total fenvalerate content nor in relative amounts of the 4 isomers of fenvalerate over a period of at least 8 weeks in dog diet at room temperature. Useful data in support of the chronic study. Aldous, 8/20/93.

379-127 061638 dog diet data relevant to chronic study 379-119:056377. Schultz, D.R., "Determination of MO 70616 contents of feeds fed to dogs during one year test (WTP-270); Preparations of 2-12-85, 3-6-85, 4-16-85, 5-30-85, 7-6-85, 8-20-85, 10-1-85, 11-12-85 and 12-24-85". Shell Development Co., Biological Sciences Research Center Modesto, CA., 2/26/86. Assays of combined fenvalerate isomers were consistently close to target at the above sampling periods. Twice during the feeding study, diets were evaluated for contents of the individual isomers of fenvalerate. There was no evidence of altered levels of esfenvalerate or associated isomers over the course of the study. Aldous, 8/20/93.

379-038 983649 Summary of 1981 6-month dog study **using unresolved fenvalerate**. Dose levels of 0, 250, 500, and 1000 ppm in diets. No NOEL established: neurologic signs were reported to be dose-related, and manifest to a small degree even at the lowest dose. Observations included irregular posture, exaggerated head movements, trunkal ataxia. One high dose male was sacrificed moribund at week 24 with "hyperactivity, twitching, and severe convulsions". There were no positive histopathological findings correlated with the observed clinical signs. Increased retinal vessel tortuosity reported at 500 to 1000 ppm. Incomplete, not acceptable in lieu of a chronic study. No adverse effects indicated, since neurologic effects are already widely recognized as associated with test article. A more definitive study 119:56377, above, exists for the "Asana" product (also called esfenvalerate, fenvalerate enriched the active A-alpha isomer). No worksheet exists for this study, since it is not a chronic study. One-liner by C. Aldous, 12/24/87.

ONCOGENICITY, RAT
(see combined rat, above)

ONCOGENICITY, MOUSE
(studies relating to both esfenvalerate and fenvalerate)

NOTE: This section contains studies on racemic fenvalerate, on esfenvalerate, and comparative effects of two or several isomers of fenvalerate. Studies **do not** indicate oncogenicity. Previous DPR evaluations considered findings of granulomatous lesions in various tissues following treatment with racemic fenvalerate or of one of its isomers (the Ba form) to indicate a "possible adverse effect", because of the low NOEL for that effect. Studies using esfenvalerate, particularly the recent 18-month oncogenicity study (Record No. 154590), demonstrate that the granulomatous lesions are not important findings with this refined active ingredient. Esfenvalerate does, however, cause mice to scratch themselves in response to apparent skin irritation, leading to local inflammation and infections. The above study shows a sharp dose-response over the entire range tested (35 to 350 ppm). This response was considered to indicate a "possible adverse effect", due to a lack of a NOEL and a relatively low LOEL for the skin lesions. It is likely that clinical experience in humans is a better source for evaluation of associated human dermal response than these mouse studies. Aldous, 12/03/98.

379-183 154590 Ross, P. E., "Oncogenicity study with DPX-YB656-84: Eighteen-month feeding study in mice", Haskell Laboratory, Newark, DE, 4/3/97. Haskell Laboratory Report No. 853-95. Eighty Crl:CD-17BR mice/sex/group were dosed in diet with 0, 35, 150, or 350 ppm esfenvalerate (84.8% S,S isomer; 98.8% total fenvalerate isomers) in an 18-mo study. Skin irritation, common in this class of chemicals, led to self-trauma and associated infection, which was serious enough that the 350 ppm group was terminated by study day 58. Other groups continued for the 18-month course of study, however survival was reduced in 150 ppm mice in association with self-trauma. Parameters measured included clinical observations, hematology, and histopathology of the three surviving dose groups. No NOEL was found (modest levels of skin erosion/ulceration or deformity/inflammation of the ears were found at the lowest dose tested). These lesions and the associated secondary changes (including particularly splenic enlargement and extramedullary hematopoiesis, bone marrow and mandibular lymph node hyperplasia) had a sharp dose/response relationship. Survival was markedly affected at 150 ppm, but there was no increased mortality at 35 ppm. There was **no oncogenic response**. The lack of a NOEL and relatively low LOEL for the above skin lesions may be called a "possible adverse effect". This outcome is of questionable regulatory importance, since the extent of skin irritation elicited by esfenvalerate is probably best evaluated through clinical experience. Granulomatous lesions, which were seen in several tissues following treatment with racemic fenvalerate at low dose levels, were not seen in this study. This suggests that the S,S isomer did not cause this response. Valid supplemental data. Aldous, 12/3/98.

****081-082:37101-37103 and 079-080:37099-37100.** Evaluation of these two studies together indicates that there were sufficient numbers of animals "at risk" at or near to an "MTD" to constitute a valid study. There is no oncogenic response. Some items originally requested on one or the other of the two CDFA reviews of May, 1986 are not critical information for evaluation as an oncogenicity study, as indicated in this 1/6/87 review. The most important information needed was Appendix N of the report, which was supplied in Record No. 129493, below (analyses of treated diets and compound stability data). The data base is now **acceptable** for the fenvalerate mouse oncogenicity data requirement. A "**possible adverse effect**" exists for fenvalerate, based on the granulomatous lesions seen in several tissues at low dose levels. An ongoing mouse oncogenicity study with esfenvalerate will allow a re-examination of the chronic effects of the active ingredient in current use. Aldous, 1/6/88 and 7/13/94. (See individual 1-liners below).

081-2 37101-3 "Lifespan Chronic Toxicity Study of S5602 in Mice" (4/20/81, Sumitomo #AT-10-0286) Fenvalerate, technical, 91.4% purity at 0, 10, 30, 100, and 300 ppm in diet, to ddy mice for 20 months; NOEL = 10 ppm (based on **slight** degree of giant cell infiltration in mesenteric lymph node in 30 ppm males and females; Dose-related infiltrations or proliferations of phagocytic cells or aggregations of such cells in liver, spleen, and lymph nodes observed at 100 ppm and above). See above for upgraded acceptability status. C. Aldous, 5/16/86 (acceptability status upgraded 7/13/94).

379-173 129493 (diet analysis relevant to 379-081:037101, specifically Appendix N, "Determination of S5602 in diet", which was cited but not included in that report). This appendix provided analysis method for fenvalerate, evidence of stability of prepared diet (10 ppm) for up to 6 wk under refrigeration, and analyses for 10 and 300 ppm levels at 44 "times of diet preparation". The last 14 analyses included also 30 and 100 ppm diets. Nearly all assayed values were within an acceptable range. This submission addresses the most essential missing information requested for an update of fenvalerate study 037101 (see 1-liner for that study). Aldous, 7/13/94.

379-174 129494 Kaneko, H., Matsuo, M., and Miyamoto, J., "Differential metabolism of fenvalerate and granuloma formation. I. Identification of a cholesterol ester derived from a specific chiral isomer of fenvalerate", *Toxicol. Appl. Pharmacol.* 83:148-156 (1986). Test animals were male ddY mice and (to a limited extent) male S-D rats. The four isomers of fenvalerate were used (Aa, Aβ, Ba, and Bβ). Six days after a single po dose in either rats or mice, tissue levels in adrenals, heart, kidneys, liver, lung, mesenteric lymph nodes, spleen, and testes were much higher following Ba administration compared to either of the other 3 isomers (over 10-fold in many cases). Mice on a continuous diet of 500 ppm of either Aa, Ba, or Bβ chlorophenyl-¹⁴C-labeled isomers were killed after either 1 or 2 wk, and tissues were analyzed for (1) total labeled metabolites and (2) lipophilic metabolites. Tissues retained much more of the Ba isomer than either of the other isomers. A large part of the activity in tissues of mice exposed to Ba was lipophilic (compared to typically non-detectable lipophilic residues in other groups). Duration of exposure did not appear to affect labeled residue content. The lipid-soluble residue was identified as the cholesterol ester of the chlorophenyl carboxylic acid portion of the Ba parent molecule. (See also "Part II" of this series, immediately following this paper). Aldous, 6/1/94.

379-177 130649 Okuno, Y., Seki, T., Ito, S., Kaneko, H., Watanabe, T., Yamada, T., and Miyamoto, J., "Differential metabolism of fenvalerate and granuloma formation. II. Toxicological significance of a lipophilic conjugate from fenvalerate", *Toxicol. Appl. Pharmacol.* 83:157-169 (1986). Male ddY mice were about 5 wk old when placed on these studies. Primary treatments involved either dietary dosing with fenvalerate or its isomers for up to 1 year, or single iv doses with cholesterol conjugates of fenvalerate metabolites. Primary objectives were to study histopathology changes, including subcellular structures and autoradiographic localization of label following injection of fenvalerate, or fenvalerate metabolite-cholesterol conjugates. Granulomatous changes, such as the granuloma formations and giant cells observed in fenvalerate studies, were shown to be exclusively due to one isomer of technical fenvalerate [the Ba or 2R,aS form]. These changes were also elicited by fenvalerate metabolite-cholesterol conjugates, suggesting that these conjugates are involved in the granulomatous changes. Administration of tritiated Ba fenvalerate isomer, or of cholesterol conjugates of fenvalerate metabolites, led to concentrations of radiolabel in the giant cells upon autoradiography. EM studies showed crystalline structures in these cells, plausibly formed from cholesterol conjugates of the Ba isomer of fenvalerate. The modern technical material, esfenvalerate, is substantially enriched in the insecticidally active ingredient [the Aa or 2S,aS isomer], so that the percent of the Ba isomer is an order of magnitude smaller than that of older a.i. (racemic fenvalerate). It is therefore appropriate to consider findings of granulomatous changes in fenvalerate studies as "not relevant" with respect to toxicity evaluation of esfenvalerate. Aldous, 7/5/94.

379-179 130652 Ito, S. et al., "Reversibility of granulomatous changes in ddy mice fed S-5602", Sumitomo Chemical Co., Ltd., April, 1980. From 90 to 150 ddy mice/sex/group were dosed with 0,

1000, or 3000 ppm in diet for 6 weeks, then taken off treatment for up to one year. Interim sacrifices occurred at weeks 4 and 6 of treatment, and months 1, 3, 6, 9, and 12 of the recovery phase. No NOEL was sought or achieved in this study. Study was designed to evaluate recovery from known histopathologic changes at dose levels known to elicit changes. This is not a FIFRA-mandated study, but is sufficiently rigorous for the purpose of the study. During the post-treatment period, there were various degrees of recovery from treatment-associated changes in the tissues previously shown to develop granulomatous lesions. Aldous, 9/7/94.

379-178 130651 Okuno, Y. and Miyamoto, J., "Comment on granulomatous changes in ddy mice treated with S5602 for 18 months", Sumitomo Chemical Co. report dated 2/13/78. The granulomatous changes seen in the chronic mouse studies appear to result from leukocytes responding to the presence of certain foreign chemicals in the tissues. These changes have been reported in response to several drugs and metallic compounds. There are clinical data showing that these changes are reversible in liver and lymph node tissues in humans, after removal of the stimulatory chemicals. Elevated liver enzyme activities were associated with the more severe grades of granulomatous responses in the fenvalerate mouse chronic studies, suggesting that tissue damage may have occurred. The above comments provide useful information. No new data are provided, and there is no DPR worksheet. Aldous, 7/8/94.

038 983650 Summary of 081-082:37101-37103, reviewed by J. Wong 6-17-85.

079-80 37099-37100 "18 Month Chronic Toxicity Study of S5602 in Mice" (12/29/77 Sumitomo #AT-70-0176) Fenvalerate, apparently technical (97.7% purity); at 0, 100, 300, 1000, and 3000 ppm in diets of ddY mice; No NOEL observed; Dose-related giant cell infiltrates or granulomas observed in lymph nodes or liver of both sexes, occasionally down to the lowest dosage level (100 ppm). Misc. increases in serum enzymes at 1000 ppm and above. "Hypersensitivity" (sensory hyper-reactivity) noted at 1000 ppm and above. Increased mortality and apparent anemia at 3000 ppm; Incomplete UNACCEPTABLE, not upgradeable - too few animals used and high mortality; insufficient hematology and clinical chemistry. C. Aldous, 5/12/86.

038 983682 "Reversibility of Granulomatous Changes in DDY Mice Fed Fenvalerate." (Shell Development Company Technical Information Record No. WRC-529). Brief description of histology data concerning a recovery study in which mice were dosed with 0, 1000, or 3000 ppm fenvalerate (= two highest dosages in study 079/080:37099-37100), then killed at 4, 6, 10, 19, 32, 44 and 58 week intervals. Investigators indicate that histopathological changes "were not progressive and, in fact, diminished with time". Investigators' conclusions only: no data provided. Incomplete, UNACCEPTABLE (potentially useful information). (No CDFA worksheet. One-liner by C. Aldous, 12/24/87).

027 983653 Summary of 37099-100.

027 983629, 983630, 983646 025841 Misc. references to mouse chronic or oncogenicity studies. Brief summaries, no data.

379-175 129495 Koyama, Y., "Comparative subacute toxicity in B6C3F₁ mice treated with S-1844 and S-5602 for 3 months", Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Hyogo, Japan, 12/28/85. Twelve mice/sex were dosed with 50, 150, or 500 ppm esfenvalerate, or with 2000 ppm fenvalerate, or with control diets in a standard subchronic study design. The NOEL for esfenvalerate was 50 ppm, based on decreased glucose and triglyceride levels in plasma of 150 ppm males. The latter dose did not cause associated changes in body weights, clinical signs, or histopathology, and is considered the NOAEL. No NOEL was sought for fenvalerate, since only a single (MTD) dose was used. Common findings in 500 ppm esfenvalerate and 2000 ppm fenvalerate mice included: small decrements in b.w., despite normal food consumption; neurologic signs

such as fibrillation, tremor, and convulsion; scratching, with associated alopecia and skin lesions such as dermatitis and ulceration; lymphatic changes, such as lymphoid hyperplasia and lymphadenitis, often in association with regional dermal lesions; a general decrease in circulating glucose, cholesterol, triglycerides, phospholipids, and albumin; and an increase in circulating enzymes, not accompanied by major histopathologic changes in liver, kidney, or other plausible target organs. Microgranulomas and giant cell infiltration were commonly found in liver, spleen, and lymph nodes of males and females, exclusively in 2000 ppm fenvalerate mice. The study indicates a "possible adverse effect", based mainly on the neurological findings noted above. **Acceptable**. Aldous, Sept. 7, 1994.

REPRODUCTION, RAT

(The single acceptable study supports esfenvalerate only)

51722-020 134163 Biegel, L.B., "Reproductive and fertility effects with DPX-YB656-84: Multigeneration reproduction study in rats", Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Dec. 1, 1994. CrI:CD7BR rats (30/sex/group) consumed 0, 75, 100, or 350 ppm DPX-YB656-84 [Esfenvalerate: 98.8% total fenvalerate isomers, enriched in the S,S isomer (84.8%)] in diets in the F0 generation. High pup mortality of 350 ppm F1 lactating pups prompted reduction of the high dose to 150 ppm at weaning of F1 rats selected as parental animals. Continued mortality of F1 parental high dose animals during early phases of the pre-mating period led to a loss of this treatment group due to infections secondary to extensive scratching of irritated skin, despite therapeutic application of Vitamin E oil to all rats on study. High mortality of F1 rats compared to F0 rats seemed to reflect high dermal and dietary exposure of F1 pups during early postnatal development, compared to F0 animals, which were first exposed at day 65 or later. There was no NOEL for effects on F1 males during the pre-mating period (slight increase in skin sores at 75 ppm). Sores and scabs were common and dose-related at 100 to 350 ppm, attributed to irritation of the skin, particularly of the head, neck, shoulders, and back. "Abnormal gait or mobility" was commonly observed among 350 ppm adults. These signs, plus other neurologic effects (such as tremors, seizures, vocalizations, spasms, and rolling behaviors) were commonly seen among young high dose F1 rats (despite reduction of the high dose level to 150 ppm), particularly early in the pre-mating period. The reproductive NOEL = 75 ppm (primarily based on minor pup body weight decrements in F1 and F2 lactating pups). F1 pups at 350 ppm suffered high neonatal mortalities and marked body weight gain decrements. A NOEL for effects other than those evidently related to skin irritability is 100 ppm. **Acceptable. No adverse reproductive effects were noted. The lack of a definitive NOEL for clinical signs is relevant for subacute or acute effects risk assessment. Aldous, 5/2/95.

088:37112-37116. "Three-generation reproduction study in rats: SD-43775". Litton Bionetics, date with current revisions Feb., 1978. SD-43775 (Technical Fenvalerate, 98% purity). 0, 1, 5, 25, and 250 ppm in diets of Sprague-Dawley rats for three generations (2 litters/generation). Apparent general toxicity NOEL = 25 ppm (slight weight losses in F_{2B} adults, slight increase of "mottled kidneys" in gross exams of adult males at necropsy). Apparent reproductive effects NOEL = 250 ppm (HDT). NOT ACCEPTABLE, NOT UPGRADEABLE (dose levels not justified, no histological exams of adults). C. Aldous, 12/9/86.

027 983657 "Summary Interim Report On Rat Reproduction Study -With 43775 Technical." Summary of one of the above interim reports

027 25836 "Summary, Special Studies For SD 43775 (Fenvalerate): Reproduction (Rat)." Summary only of #37112-16

REPRODUCTION, MOUSE

027 31737 "Special Studies For SD 43775: Reproduction In Mice." Summary only, extension of teratogenicity study, does not meet guidelines.

TERATOLOGY, RAT

(The acceptable study supports only esfenvalerate)

51722-017 130363 Nemec, M.D., "A developmental toxicity study of S-1844 in rats", WIL Research Laboratories, Inc., Project No. WIL-118010, Jan. 10, 1991. CD rats, 25/dose group, were gavage dosed with 0 (5 ml/kg corn oil vehicle), 2.5, 5, 10, or 20 mg/kg/day of 97.1% purity S-1844 (Sumitomo designation for esfenvalerate) on p.c. days 6-15. Maternal NOEL < 2.5 mg/kg/day, based on transient neurological signs such as "erratic jerking and extension of forelimbs", atypical head movements, and excessive grooming at all dose levels tested. A conservative NOEL for more persistent maternal effects is 5 mg/kg/day, based on very minor decrements in maternal food consumption and/or body weight gain. A conservative NOEL for developmental effects is 10 mg/kg/day, based on a small increase in incidence of 14th rudimentary rib. The 1994 review considered study to indicate a "possible adverse effect" due to marked maternal toxicity: however see change below. Study is **acceptable, with no adverse effects. Aldous, 9/6/94, 3/8/95.

[No Record or Document # given: rebuttal ID# is SBDR-151161-E] Addendum to Document No. 51722-017, Record No. 130363 [above]. Original review flagged study as indicating a "possible adverse effect", due to lack of a NOEL for maternal toxicity, and a comparatively low LEL for maternal toxicity. A pilot developmental toxicity study was undertaken by Haskell Laboratories under comparable conditions, finding a NOEL of 3 mg/kg/day. The studies can be taken together to provide a "highest NOEL below the lowest LEL" of 2 mg/kg/day for maternal toxicity. This NOEL is based on transient neurological effects: non-transient effects were limited to higher dose levels and were of minor consequence. There is no need to consider the studies to indicate a "possible adverse effect" (status change). Aldous, March 8, 1995.

51722-015 130361 Murray, S.M., "Pilot developmental toxicity study of DPX-YB656-84 in rats", Haskell Laboratory, 3/31/94. DPX-YB656-84 is du Pont's Esfenvalerate, similar in isomeric content to Shell and Sumitomo products. This technical was assayed at 98.8% total fenvalerate isomers, and 84.8% S,S isomer. Doses of 0, 1, 2, 3, 4, 5, or 20 mg/kg/day were given by gavage in 10 ml/kg cottonseed oil to 15 Crl:CD7BR rats/group during gestation days 7-16. Modest, but statistically significant decrements in b.w. were noted at 20 mg/kg/day during days 7-9, and the b.w. gain of that group trailed significantly behind other groups during the treatment period. This was accompanied by a modest (not statistically significant) decrement in feed consumption. The maternal NOEL is 3 mg/kg/day, based on clinical observations of "abnormal gait or mobility" (page 19 states that rats were observed "pushing their chins along the cage floor"). Study was originally considered to indicate a "possible adverse effect", however see clarification of 3/8/95, above. Common high dose findings included diarrhea and tremors (4 females). There were no developmental effects. Useful data; suitable for a pilot study. Aldous, 9/6/94, 3/8/95.

NOTE: The following preliminary information was submitted to U.S. EPA and to DPR to indicate a "possible adverse effect".

51722-013 128565 This is not a study, but rather a memo entitled: "Information submitted in accordance with FIFRA Section 6(a)(2) report of studies with Esfenvalerate (CAS #66230-04-4) Asana7 XL (EPA Reg. No. 352-515)" submitted by E. I. du Pont de Nemours & Co. regarding clinical signs noted in a Sumitomo rat teratology study and in 2 du Pont pilot studies. The memo notes maternal toxicity (behavioral changes) at low dose levels. The essential studies have since been received and reviewed (see especially Record No. 130363). Aldous, 9/7/94.

TERATOLOGY, RABBIT
(Acceptable study or studies support esfenvalerate only)

51722-018 130364 Nemec, M.D., "A developmental toxicity study of S-1844 in rabbits", WIL Research Laboratories, Inc., 10/10/90. Mated NZW rabbits, 20/group, were dosed with 0, 3, 10, or 20 mg/kg/day esfenvalerate in 0.5 ml/kg corn oil. Purity was stated to be 97.1%. Test article was identified as Lot No. 71219, however isomer composition was not given. There was no maternal NOEL identified in this study. The most characteristic findings at 3 mg/kg/day were erratic jerking and extension of forelimbs, and excessive grooming. Many does in the two higher dose groups displayed a side-to-side head movement, whereas some signs such as tremors and ataxia were limited to the 20 mg/kg/day group. This study was classified as indicating a "possible adverse effect" in the 1994 review due to transient maternal toxicity, but this classification was changed in 1995, as indicated in the next paragraph. A maternal NOEL of 2 mg/kg/day was found in the pilot study (Record No. 130362). Neither this study nor related studies have found anatomical changes associated with these behavioral changes. There was no evident developmental effect at any dose tested. **Acceptable, no adverse effects. Aldous, 9/6/94.

[No Record or Document # given: rebuttal ID# is SBDR-151161-E] Addendum to Document No. 51722-018, Record No. 130364, "A developmental toxicity study of S-1844 in rabbits", WIL Research Laboratories, Inc., 10/10/90. Original review flagged study as indicating a "possible adverse effect", due to a low NOEL for maternal toxicity [the NOEL of 2 mg/kg/day came from a pilot developmental toxicity study undertaken by Haskell Laboratories (Record No. 130362) under comparable conditions]. This NOEL is based on transient neurological effects (i.e. primarily limited to dosing days, and most prominent during the hours shortly after dosing): non-transient effects were limited to higher dose levels and were of minor consequence. There is no need to consider the studies to indicate a "possible adverse effect" (change of status). Aldous, March 8, 1995.

51722-013 128564 This is not a study, but rather a memo entitled: "Information submitted in accordance with FIFRA Section 6(a)(2) report of studies with Esfenvalerate (CAS #66230-04-4) Asana7 XL (EPA Reg. No. 352-515)" submitted by E. I. du Pont de Nemours & Co. regarding clinical signs noted in rabbit teratology studies and associated range-finding and pilot studies. Only summary data are presented in the memo, flagging the neurological symptoms in dams in Record Nos. 130362 and 130364 as "possible adverse effects". See other 1-liners in this section for details. Aldous, 7/13/94.

51722-016 130362 Murray, S.M., "Pilot developmental toxicity study of DPX-YB656-84 in rabbits", Haskell Laboratory, 4/15/94. DPX-YB656-84 is du Pont's Esfenvalerate, similar in isomeric content to Shell and Sumitomo products. This technical was assayed at 98.8% total fenvalerate isomers, and 84.8% S,S isomer. Doses of 0, 2, 3, 4, 4.5, 5, or 20 mg/kg/day were given by gavage in cottonseed oil to 14 NZW rabbits/group during gestation days 7-19. Highest dose group had a minor reduction in diet consumption (statistically significant on days 7-10), nevertheless there were no appreciable b.w. effects. The most prominent maternal effects were clinical signs such as "excessive grooming" and "paw shake" (both were seen at the LEL of 3 mg/kg/day, but the former was more prevalent). Head shaking became prominent at 5 to 20 mg/kg/day, and sores and scabs on skin were often seen at 20 mg/kg/day. There were no developmental effects. The 1994 review considered this study to indicate a "possible adverse effect" of minor importance, due to the relatively low maternal NOEL of 2 mg/kg/day. The "possible adverse effect" designation was removed in 1995 (see 1-liner to ID# is SBDR-151161-E, above). Useful data, valid as a pilot study. Aldous, 6/7/94, 3/8/95.

090:037125 "Toxicity of WL 43775 [Fenvalerate]: Teratological studies in rabbits given WL 43775 orally", Tunstall Laboratory, 10/75. Fenvalerate technical (97% purity). 0, 12.5, 25, and 50 mg/kg/day to banded Dutch rabbits. Apparent maternal and developmental NOEL = 50 mg/kg/day (no adverse effects). NOT ACCEPTABLE nor complete as written. Upgrade possible. C. Aldous 12/10/86.

027 25838 "Special Studies For SD 43775: Teratogenic (Rabbits) (Full Report In record # 37125 In Fenvalerate." Summary only of #37125.

TERATOLOGY, OTHER SPECIES

090:37126 "Teratogenic study on S5602 [fenvalerate] in mice", Sumitomo Chemical Co., 11/5/76. Technical S5602 (97.6% pure). 0, 5, 15, and 50 mg/kg/day by gavage in corn oil. Apparent developmental toxicity NOEL = 50 mg/kg/day (MTD). Apparent maternal toxicity NOEL = 15 mg/kg/day (multiple clinical signs). Not complete, NOT ACCEPTABLE, may be upgradeable. C. Aldous, 12/10/86.

027 31730 "Special Studies For SD 43775: Teratogenic (Mice)." Summary only of #37126. J. Wong 6/17/85.

GENE MUTATION

(Acceptable study or studies support esfenvalerate only)

**379-164 114917, "Reverse Mutation Test of S-1844 in Salmonella typhimurium and Escherichia coli", (S. Kogiso, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Japan, Lab. Proj. ID LLT-50-0009, Study No.: MUT 85066, 12/28/85). Test article was S-1844, also known as esfenvalerate (95.5% fenvalerate isomers, of which the active Aa isomer constituted 91.5%). S-1844 was evaluated for mutagenic potential at concentrations of 0, 15, 50, 500, 1500 and 5000 ug/plate using Salmonella typhimurium strains TA100, TA98, TA1535, TA1537 and TA1538 and Escherichia coli strain WP2_{uvrA} with and without metabolic activation (S-9 Mix). Test article exposure time was for 65 hours. Test article precipitation was observed at and above 1500 ug/plate without S-9 mix and at 5000 ug/plate with S-9 mix. The number of revertants did not increase with test article treatments. ACCEPTABLE. Kishiyama and Gee, 8/19/93.

**379-164 114918 "In Vitro Gene Mutation Test of S-1844 in V 79 Chinese Hamster Cells in Culture", (S. Kogiso, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Japan, Lab. Proj. ID LLT-50-0012, Study No.: MUT 85069, 12/28/85). Test article was S-1844, also known as esfenvalerate (95.5% fenvalerate isomers, of which the active Aa isomer constituted 91.5%). S-1844 was evaluated for mutagenicity at the HGPRT locus, using concentrations of 0 (DMSO), 10^{-5} , 3×10^{-5} , 10^{-4} and 3×10^{-4} M without S-9 mix and at 3×10^{-5} , 10^{-4} , 3×10^{-4} and 10^{-3} M with S-9 mix using Chinese Hamster lung cells (V 79). Test article exposure time was for 6 hours. Cell survival was 64% or less for the two higher dose groups and above 80% for the two lower dose groups. The number of mutant colonies did not increase with S-1844 treatments. ACCEPTABLE. Kishiyama and Gee, 8/19/93.

089 37124 "Studies on Mutagenicity of Some Pyrethrins on Salmonella Strains in the Presence of Mouse Hepatic S9 Fractions" (8/4/77, Sumitomo AT-70-0157). Fenvalerate, 95%; 0, 10, 100 or 1000 ug/plate, \pm mouse liver S9, 6 mouse strains; no increased reversion rate, 3 trials; Incomplete (missing data), UNACCEPTABLE, upgradeable J. Gee, 5/1/86.

027 31735 "Special Studies For SD 43775: Mutagenic Assays In Vitro Microbial Assays With Salmonella typhimurium." Salmonella - Summary only J. Wong, 6/17/86.

048 2056 Salmonella - "Absence Of A Mutagenic Effect-Rats." Summary only. J. Wong 6/17/85.

089 37121 "Studies On Mutagenicity Of S-5602 (Fenvalerate) With Bacterial Systems: Ames Test Using Salmonella typhimurium." Ames test - Summary only (1976, Sumitomo). J. Gee 5/1/86.

089 37122 "Studies On Mutagenicity Of S-5602 (Fenvalerate) With Bacterial Systems: Reverse Mutation Frequencies Using Salmonella typhimurium." (1976, Sumitomo). Summary only - reverse mutations w/ Salmonella.

CHROMOSOME EFFECTS
(Acceptable study or studies support esfenvalerate only)

**379-164 114919, "In Vitro Chromosomal Aberration Test of S-1844 in Chinese Hamster Ovary Cells (CHO-K1)", (S. Kogiso, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Japan, Lab. Proj. ID LLT-50-0010, Study No.: MUT 85070, 12/28/85). Test article was S-1844, also known as esfenvalerate (95.5% fenvalerate isomers, of which the active Aa isomer constituted 91.5%). S-1844 was evaluated for mutagenicity at concentrations of 0 (DMSO), 1×10^{-5} , 2×10^{-5} , 5×10^{-5} and 1×10^{-4} M without S-9 mix and at 0 (DMSO), 5×10^{-5} , 1×10^{-4} , 2×10^{-4} and 5×10^{-4} M with S-9 mix and using Chinese hamster ovary cells (CHO-K1). Test article exposure time was 6 hours with S-9 mix and 24 or 48 hours without S-9 mix. The numbers of cells with chromosomal aberrations did not increase with S-1844 treatments. ACCEPTABLE. Kishiyama and Gee, 8/19/93.

379-164 114920, "Micronucleus Test of S-1844 in Mouse Bone Marrow Cells", (S. Kogiso, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Japan, Lab. Proj. ID LLT-50-0011, Study No.: MUT 85067, 12/28/85). Test article was S-1844, also known as esfenvalerate (95.5% fenvalerate isomers, of which the active Aa isomer constituted 91.5%). A single peritoneal injection was given at concentrations of 0 (corn oil), 40, 80 or 150 mg/kg to each of six male mice/group for evaluating the effect on mammalian chromosomes *in vivo*. Bone marrow smears were evaluated after 24 hours for all groups and also 48 and 72 hours for the high dose group. There were no significant increases of micronucleated PCE's observed in any S-1844 treated groups. UNACCEPTABLE. Possibly upgradeable (needs justification for not including female mice in this study). Kishiyama and Gee, 8/19/93.

089 37117 "Toxicity Studies with WL 43775: Chromosome Studies on Bone Marrow Cells of Chinese Hamsters after 2 Daily Oral Doses" (10/75, Tunstall TLGR.0085.75). Fenvalerate, batch #6 (96%); 12/sex/group were given 0, 12.5 or 25 mg/kg or 50 mg/kg MMS by oral gavage twice at 24 hour intervals; 6/sex/group were killed at 8 and 24 hrs; no increase in aberrations due to fenvalerate is reported Incomplete (missing data), UNACCEPTABLE J. Gee, 5/14/86.

004/027 25362 "Toxicology Of SD 43775, Mutagenesis, Chromosome Abnormalities In Bone Marrow Cells Of Chinese Hamsters." Summary only of 37117. J. Wong 6/17/86.

089 37118 "Toxicity Studies with WL 43775: Dominant Lethal Assays in Male Mice after Single Oral Doses". (12/75, Tunstall TLGR.0101.75). Fenvalerate, batch #6 (96%). 11 males/treatment group and 33 controls were given 0 (DMSO), 25, 50 or 100 mg/kg by oral gavage, and mated 1:3 over 8 weekly intervals; no evidence of a dominant lethal effect. Incomplete (missing data), UNACCEPTABLE, possibly upgradeable. J. Gee, 5/14/86.

040/027 25361 "Toxicology of SD 43775, Mutagenesis, Dominant Lethal Mutation In Mice." Summary only of #37118. J. Wong 6/17/85

DNA DAMAGE
(Acceptable study or studies support esfenvalerate only)

**379-164 114921, "Unscheduled DNA Synthesis Assay of S-1844 in HeLa Cells", (S. Kogiso, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Japan, Lab. Proj. ID LLT-60-0022, Study No.: MUT 85068, 2/24/86). Test article was S-1844, also known as esfenvalerate (95.5% fenvalerate

isomers, of which the active Aa isomer constituted 91.5%). S-1844 was evaluated at dose levels 3×10 , 1×10^{-5} , 3×10^{-5} , 1×10^{-4} , and 3×10^{-4} M without S-9 and at 1×10^{-5} , 3×10^{-5} , 1×10^{-4} , 3×10^{-4} , and 1×10^{-3} M with S-9 mix in the presence of [3 H]-thymidine for induction of DNA repair with HeLa cells. The numbers of grains per nucleus were similar for the control and S-1844 treatments. Positive controls had more cells with 30+ grains/nucleus or peak numbers of cells with more grains per nucleus than found for controls. ACCEPTABLE. Kishiyama and Gee, 8/19/93.

089 37119 "Toxicity Studies with WL 43775: Mutagenicity Studies with WL 43775 in the Host Mediated Assay" (1976, Tunstall TLGR.0002.76) Mitotic gene conversion in *Saccharomyces cerevisiae* JD1; Fenvalerate, batch #6 (96%) 2-3 male mice were given oral doses of 0, 25 or 50 mg/kg followed by i.p. injection of yeast; harvest after 5 hours and plate; no evidence of gene conversion is reported; Incomplete (missing data), UNACCEPTABLE, not upgradeable. J. Gee, 5/14/86.

027 31733 Summary of 37119 J. Wong 6/17/86.

027 39115 Summary of 37119.

089 37123 "Studies on Mutagenicity of S-5602 (Fenvalerate) with Bacterial Systems: Host-Mediated Assay Using *S. typhimurium*." Summary of Salmonella host mediated assay - full study not on file (1976, Sumitomo).

027 31734 "Special Studies For SD 43775: Mutagenic Assays In Vitro Microbial Assay." *B. subtilis* rec assay Summary only J. Wong 6/17/85.

089 37120 "Studies On Mutagenicity Of S-5602 (Fenvalerate) With Bacterial Systems: Rec-Assay Using *Bacillus subtilis*." Summary of rec assay, possibly same study as 31734, and full study is not on file (1976, Sumitomo).

NEUROTOXICITY (Studies support both active ingredients)

"Possible adverse effects" are noted in some of the following studies, however the NOEL's were appreciably higher than several chronic effects NOEL's of fenvalerate studies. Histological lesions first appear at dose levels well within an order of magnitude of lethal doses. None of the delayed distal neuropathies such as are obtained by TOCP were seen in these studies. There are several short reports on neurotoxicity which are not summarized below, most of which come from Document Nos. 379-091 and 379-072. The ones given below appear to be the most useful ones available for eventual risk assessment. Studies which may be required by U.S. EPA to address future neurotoxicity requirements for esfenvalerate must also be submitted to DPR. Aldous, 8/27/93.

379-091 037134 "The neurotoxicity of fenvalerate S.5062: The effects of 20 oral doses of fenvalerate over a period of 4 weeks on the rat sciatic and posterior tibial nerves and trigeminal ganglion". [9/81, Shell Toxicology Laboratory (Tunstall), Sittingbourne, Kent, England]. Fenvalerate, technical 0, 12.5, 100, and 200 mg/kg/day, 5 weekdays/wk, 4 week's duration (most commonly applied dosages and schedule). NOEL = 12.5 mg/kg/day (Abnormal gait, also increased lysosomal enzyme activity at 100 mg/kg/day. Additional incidence and degree of above signs, also disintegrating axons and myelin and evidence of ingestion of damaged components by Schwann cells at 200 mg/kg/day) Complete. ACCEPTABLE Not a regularly required study, however relevant information was provided. C. Aldous, 5/27/86.

379-038 983681 Brief summary of 037134, above.

379-092 037151 Van Gelder, G.A., "Species susceptibility of Pydrin® insecticide in the rat, mouse, hamster and rabbit", Shell Development Co., Westhollow Research Center, Houston, March 1981. [study has been assigned additional record numbers 037150, 037152, and 037153 to represent different species studies]. S-D rats provided by far the most meaningful dose-response curve, even though occasional histological lesions occurred in other species at lower dose levels. Other species did not have strong or consistent responses below the rat NOEL. Fenvalerate (95.8%) was administered at 0, 100, 133, 180, 240, 320, 420, 560, 750, or 1000 mg/kg as a single oral dose in corn oil. Clinical signs were observed, then rats were sacrificed and tissues processed for examinations of sciatic, tibial, and plantar nerves. Typical clinical signs included ataxia, tremors, limb incoordination, and convulsions. Nerve lesions included axon clumping, myelin figures, vacuole formation, mitosis and inflammation. Both clinical signs and histopathology changes were presented qualitatively by degree (not defined by type). LD50's of male and female rats were 938 and 680 mg/kg, respectively. The NOEL for histological changes was 133 mg/kg in male and female rats. All three peripheral nerves were affected to comparable degree. Clinical signs had a NOEL of 100 mg/kg. Virtually every animal with microscopic lesions also showed clinical signs, but there were numerous rats at various doses with clinical signs, but without histopathology changes. Useful data, because NOEL's and LOEL's are well defined. No DPR worksheet. Aldous, 8/27/93.

379-111 056218 Parker, C.M., "Acute oral toxicity and neuropathology of WRC Toxicology Sample No. 14200-61-59A (SD 92459) in the rat", Shell Development Co., Westhollow Research Center, Houston [histopathology was performed at Intermountain Laboratories, Inc.], Feb., 1981. Study was similar in design to Record No. 037151, above, except that only rats were employed. Test article [SD 92459], contains about 45% of active isomer, compared to 22% in racemic fenvalerate and 84% for MO 70616 (esfenvalerate) (see Record No. 056177, this volume). LD50 was estimated at 200 mg/kg. The ED50 for toxic effects (ataxia, splayed gait, tremors, convulsions) was 51 mg/kg. Apparent NOEL for peripheral nerve damage was 18 mg/kg (definitive treatment responses were limited to 100 mg/kg and above). No SB-950 worksheet (a worksheet has already been done by Berliner and Patterson on 11/30/87). Aldous, 8/27/93.

379-027 31738 "Special Studies For SD 43775: Neuropathology - Chicken Oral Dosing For Neuro-Acute Delayed Toxicity." Summary only, no study date. J. Wong 6/17/85.

379-092 037129 Okuno, Y. *et al.*, "Neurotoxic effects of some synthetic pyrethrins and natural pyrethrins by dermal application in rats", Institute for Biological Science, Hyogo, Japan, 12/17/76. Male S-D rats were dosed dermally with fenvalerate by single dose (0, 500, 2500, or 5000 mg/kg) or by daily doses for 5 consecutive days (0, 250, 500, 2500, or 5000 mg/kg/day). Rats were observed for clinical signs, then sacrificed on the 5th day (single treatment) or 7th day (5-day treatment). Reported clinical signs included "hypersensitivity" in all 500 mg/kg/day fenvalerate rats, and additional signs of tremor and hindlimb ataxia at 1000 mg/kg/day fenvalerate and above. Axonal swelling also had an apparent NOEL of 250 mg/kg/day, whereas a low incidence of axonal disintegration was attributed to fenvalerate at 2500 to 5000 mg/kg/day (5-day treatment only). Other compounds, including resmethrin and natural pyrethrins elicited axonal swelling and disintegration at 5000 mg/kg/day (the only dose tested for 5-day treatment). Useful information, not acceptable (not a routinely required study type, brief report without QA oversight). Clinical and microscopic findings are "possible adverse effects". No DPR worksheet was done. Aldous, 8/27/93.

379-092 037136 "Toxicity of Pyrethroid Insecticides. Investigation of the Neurotoxic Potential of WL 43775 (Fenvalerate) In Chickens." March 1977. Six-page report on neurotoxicity in hens dosed repeatedly with 1000 mg/kg fenvalerate. "No neurological signs or histological lesions" reported. Dose levels were not justified, however, no hen delayed neurotoxicity study is routinely required for the pyrethroids, and apparently CDFA has not requested such a study. For this reason, there is no current "data gap" for a hen neurotoxicity study. Study examined by C. Aldous, but no review was written.

379-091 037132 Okuno, Y. and Kadoka, T., "No-effect level of neurotoxicity in rats by short-term feeding of S5602", Research Department, Pesticides Division, Sumitomo Chemical Co., Ltd., 5/27/77. 5-wk old Sprague-Dawley rats were dosed with fenvalerate dissolved in corn oil [and apparently incorporated into diet] at 0, 500, 1500, and 3000 ppm for 7-9 days. High dose caused several deaths, and clinical signs of "hypersensitivity, erratic jumping, tremor and hindlimb ataxia". Clinical signs in other groups were limited to slight "hypersensitivity" in 1500 ppm rats. Sciatic nerves of high dose rats had frequent axon swelling and some had axonal disintegration. There was no histopathologic difference between controls and other dose groups. Useful information, brief report, no DPR worksheet. Aldous, 8/26/93.

051; 176826; "Esfenvalerate: Subchronic Oral Neurotoxicity Study in Rats" (L. Malley; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; DuPont-3081 (Revision No. 1); 6/26/00); Esfenvalerate (Batch No. DPX-YB656-84; purity = 98.58%) was fed in the diet at concentrations of 0, 50, 100, and 300 ppm to groups of 12 Crl:CD (IGS)BR rats/sex/dose level for 13 weeks; reduced food consumption and weight gain in 100 ppm and 300 ppm males, reduced weight gain in 300 ppm females; abnormal gait was observed in 300 ppm males and females; dermal sores were observed in 100 ppm and 300 ppm males and two 300 ppm males were killed *in extremis* as a result; **FOB- 300 ppm males showed decreased forelimb and hindlimb grip strength, decreased hindlimb foot splay, and increased motor activity; 300 ppm females showed decreased forelimb and hindlimb grip strength; 100 ppm males showed decreased forelimb grip strength; **Neuropathology**- no treatment-related findings; NOEL (M) = 50 ppm (3.22 mg/kg/day), (F) = 100 ppm (7.26 mg/kg/day); **Acceptable**. (Duncan, 11/14/00)

**054; 177818; "A 13-Week Dietary Neurotoxicity Study of Esfenvalerate TG in the Rat" (P. Beyrouy; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada ; Project No. 97524; 5/25/99); Esfenvalerate TG (Lot No. 60610G, purity = 97.3% as total isomers), was fed in the diet at concentrations of 0, 40, 120, and 360 ppm to groups of 12 Crl:CD (SD)BR rats/sex/dose level for 13

weeks; reduced body weight was observed in 120 ppm males and 360 ppm males and females; a variety of skin lesions including fur thinning, sores, and scabs were observed in 360 ppm males; **FOB**- two 360 ppm males developed slight ataxia and one also displayed tremors, altered air righting reflex, and limited use of limbs at week 13; **Neuropathology**- no treatment-related findings; NOEL (M) = 40 ppm (3.0 mg/kg/day), (F) = 120 ppm (10.7 mg/kg/day), based on reduced body weight; **Acceptable**. (Duncan, 12/27/00)

052; 177749; "Esfenvalerate: Acute Oral Neurotoxicity Study in Rats" (L. Malley; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; DuPont-3874; 9/22/00); a single gavage dose of Esfenvalerate (Batch No. DPX-YB656-84; purity = 98.58%) in corn oil was administered to groups of 10 Crl:CD (IGS)BR rats/sex/dose level at 0, 1.75, 1.90, 20.0, or 80.0 mg/kg; there were no deaths; reduced food consumption and weight gain was observed in 80.0 mg/kg males; **FOB: diarrhea, paw shaking, and abnormal gait or mobility were observed in 80.0 mg/kg males and females; uncoordinated movement, increased reaction to approach and touch, increased reaction to tail pinch, reduced forelimb grip strength, and reduced hindlimb foot splay were observed in 80.0 mg/kg females; tremors, considered the most sensitive indicator of toxicity, were observed in males at 20.0 and 80.0 mg/kg, and females at 1.90, 20.0, and 80.0; **Neuro-pathology**- no treatment-related findings; NOEL (M) = 1.90 mg/kg, (F) = 1.75 mg/kg (based on tremors); **Acceptable**. (Duncan, 2/20/01)

ANCILLARY STUDIES (INCLUDING STUDIES ON DEGRADATION PRODUCTS) (information relevant to either or both active ingredients)

379-125 61600 "Teratologic Evaluation of SD 54597 in SD CD7 Rats", (C. C Lu, Research Triangle Institute, NC, Project No. 61530, October 1983). SD 54597, "a photoproduct of Pydrin® Insecticide", was administered by gavage at concentrations of 0, 0.03, 0.3 or 3.00 g/kg/day to 30 timed-pregnant CD rats/group on gestation days 6 through 15 (19-20 dams/group were examined at sacrifice on p.c. day 20. Dam toxicity was indicated by slight b.w. decrement and by consistently increased frequency of piloerection at 3 g/kg/day. Apparent maternal NOEL = 0.30 g/kg/day. There was no apparent developmental toxicity. **Acceptable with minor deficiencies** (no confirmation of stability of dosing solutions, except for a statement that solutions of test article had been shown to be stable for 28 days in corn oil at room temperature; apparent missing text preceding p. 30, but no tables are missing). **No adverse effects indicated**. Useful data. No further information is requested at this time. (Kishiyama and Aldous, 9/1/93).

048 2055 Brief reference which appears to relate to 379-125 61600, above.

379-166 124425 Malley, L.A., "2-benzene acetic acid, 4-chloro-alpha-(1-methylethyl)-cyano(3-phenoxyphenyl)methyl ester" [monograph relating to neurotoxicity], 3/13/92. Time frames of onset and termination of neurological reactions to esfenvalerate tend to be short (on the order of hours), suggesting reversible pharmacologic responses. Esfenvalerate elicits axonal degeneration at near lethal doses, as do many of the pyrethroids. Esfenvalerate is a cyanopyrethroid, capable of eliciting long-lasting trains of nerve impulses by causing sodium channels to remain open longer than normal. Other ionic channels are affected, some of the changes affect certain neurotransmitter functions. Esfenvalerate and related chemicals cause skin responses such as itching, burning, and tingling. Some formulations elicit severe irritation responses. This appears to be due to nerve fiber stimulation, since there are no visible indications of changes in the skin. Useful information with respect to high dose studies. Aldous, 8/26/93.

379-169 127026 (no author identified) "DuPont Asana7 Technical insecticide: Answers to California re. toxicity studies". This attachment accompanied a letter dated 10/21/93. This attachment has no DPR record number, but is found just prior to record 127026 (a report of a guinea pig skin sensitization study). A recent lot of Asana7 was found to have 88.14% of the S,S isomer, and 98.8% for total fenvalerate isomers. This was comparable to other analyses, suggesting that product is stable over time,

between batches, and between laboratories. Results of several rat studies involving single oral doses were discussed. These involved racemic or S,S-fenvalerate, with radio-labels in various locations. About 50% of fenvalerate is hydrolyzed at the ester linkage, regardless of isomer. Fecal elimination was the major route of excretion, and about 70% was eliminated within 24 hr, with no major differences between isomers tested. Tissue concentrations were low, and did not appear to differ between isomers (note that in mice, the R,S isomer tended to conjugate with cholesterol, with a longer tissue retention than other isomers: see Record No. 129494). Various oxidation and hydroxylation products were identified following initial cleavage of the ester linkage. Investigators attributed any small differences between reactions of different parent isomers to be incidental. Only summary data are presented, so acceptability evaluation is not appropriate. Aldous, June 3, 1994.

379-169 127026 Maedgen, J.L. (Project Director) "Guinea pig skin sensitization of MO 70616 Technical", Stillmeadow, Inc., 10/24/86. MO 70616 (= esfenvalerate) was applied neat to shaved and depilated (commercial hair remover) skin on days 1, 8, and 15, with challenge treatment on day 29. There was no sensitization or primary irritation due to esfenvalerate, whereas positive controls proved functional. No worksheet was performed by DPR, however study appears to be acceptable. Aldous, June 3, 1994.

379-169 127027 Schultz, D.R., "Results of analyses for technical MO 70616, Code 2-1-0-0, and a 2.4 lb/gal emulsible concentrate, Code 2-1-2-1 toxicology samples", 2/20/84. Most useful information appears to be HPLC analysis of technical using a column capable of separating optical isomers. That analysis found that 86% of fenvalerate isomers was the Aa form. The Ba isomer, which appears to be responsible for the microgranulomatous lesions commonly seen in racemic fenvalerate, represented 7% of fenvalerate isomers in this assay. These data show remarkable consistency between the Shell Development Co. product analyzed here and the Sumitomo product, which has been used for a number of the animal studies submitted. Useful information, no DPR worksheet is needed at present. Aldous, 6/6/94.

379-170 127028 METABOLISM DATA: SEVERAL STUDIES, MAINLY IN RATS, designated as Du Pont Report No. AMR-1714-90. Common findings were (1) rapid elimination, principally in feces, (2) rapid cleavage of the ester bond, typically the first and most commonly observed change, (3) subsequent oxidation and hydroxylation of acid and alcohol components, (4) various conjugation products. There did not appear to be substantial differences in metabolism between different isomeric mixtures. None of these studies sought or found conjugation products with cholesterol, such as were reported in mice administered the Ba (also designated 2R,aS isomer) by Sumitomo investigators in mice [see Kaneko *et al.*, presented under Record No. 129494 under the "Oncogenicity, Mouse" section of this Summary; and Okuno *et al.*, (Record No. 130649)]. There is thus no means offered here to correlate these possible conjugation products in various species with microgranulomatous lesions. Aldous, 6/6/94. Study identifications (not given DPR worksheets at present) are as follows:

Lee, P.W., "Metabolism of ¹⁴C-Chlorophenyl SD 43775 in male and female rats after a single oral dose (8.4 mg/kg) administration", Shell Development Co., 2/20/81.

Lee, P.W., "Metabolism of ¹⁴C-Phenoxyphenyl SD 43775 in male and female rats after a single oral dose (8.4 mg/kg) administration", Shell Development Co., 2/20/81.

Lee, P.W., "Metabolism of ¹⁴C-Chlorophenyl SD 92459 in male and female rats after a single oral dose (8.4 mg/kg) administration", Shell Development Co., 2/20/81.

Lee, P.W., "Metabolism of ¹⁴C-Phenoxyphenyl SD 92459 in male and female rats after a single oral dose (8.4 mg/kg) administration", Shell Development Co., 2/20/81.

Ohkawa, H. *et al.*, "Metabolism of fenvalerate (Sumicidin®) in rats", *J. Pesticide Sci.* 4, 143-155, 1979.

Kaneko, H. *et al.*, "Comparative metabolism of fenvalerate and the [2S,aS]-isomer in rats and mice", *J. Pesticide Sci.* 6, 317-326, 1981.

Lee, P.W., and Stearns, S.M., "Characterization of ¹⁴C-residues in the body fat of rats following a single oral dose of ¹⁴C-SD 43775 and ¹⁴C-SD 92459", Shell Development Co., 2/20/85.

Lee, P.W. et al., "Rat metabolism of Fenvalerate (Pydrin Insecticide)", J. Agric. Fd. Chem. 33, 988-993 (1985).

Kaneko, H. et al., "Metabolism of Fenvalerate in dogs", J. Pesticide Sci. 9, 269-274 (1984).

(For reference or for reconciling completeness of submitted data)

Record nos. of fenvalerate reports which do not need further review

083-4 32104-7

085-7 37108-37111

37114

027 983648

027 25839

069 37088

081-082:37101-37103

079-080:37099-37100

081-2 37101-3

038 983650

079-80 37099-37100

038 983682

027 983653

027 983629, 983630, 983646

025841

088:37112-37116.

027 983657

027 25836

027 31737

048 2055

090:037125

027 25838 (379-004 025363 is a duplicate)

090:37126

027 31730

089 37124

027 31735

048 2056

089 37121

089 37122

089 37117

004/027 25362

089 37118

040/027 25361

089 37119

027 31733

027 39115

089 37103

027 31734

089 37120

379-112 05622 Wallerian degeneration in sciatic nerve after single high doses in the lethal range (110 to 220 mg/kg/day) in rats

379-038 983643 General discussion of ionic permeability causing reversible pharmacologic changes on pyrethroid administration

379-038 983679 peripheral nerve lesions only at high doses

Some records in Document Nos. 379-091 to -092 were not given worksheets, although the more important information has been noted in this Summary. Record numbers which have been considered (and reviewed if necessary) are:

037127, 037128, 037129, 037130, 037131, 037132, 037133, 037134, 037135, 037136, 037137, 037138, 037139, 037140, 037141, 037142, 037143, 037144, 037145, 037146, 037147, 037150, 037151, 037152, 037153, 037154, 037155, 037156, 037157, 037158, 037159, 037160, 037161

Records in Document No. 111 which do not need worksheets (duplicates of other studies or not providing unique information essential for risk assessment) are: 56188, 56189, 56190, 56191

Similarly for Document No. 379-113: Records 056361, 056362, and 056364

Similarly for Document No. 379-166: Record 124426

Similarly for Document No. 379-027: Record No. 983658 (in Tab. No. 7)