

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PERMETHRIN

Chemical Code # 2008, Tolerance # 378  
SB 950 # 231

PERMETHRIN

January 9, 1987  
Revised: 12/9/87, 9/19/88, 12/8/89, 4/16/90, 5/30/90,  
9/10/90, 5/9/91, 10/4/91, 6/25/93, 7/18/95, 4/7/97

I. DATA GAP STATUS

Combined rat:	No data gap, no adverse effect
Chronic dog:	No data gap, possible adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, possible adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

-----66  
Toxicology one-liners are attached.

All record numbers through 131315 and 989591 were examined.

\*\* indicates an acceptable study.

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

## indicates a study on file but not yet reviewed.

File name: T970407

Revised by Stanton Morris, 7/18/95, Gee, 4/7/97

1 Neurotoxicity studies in rat are on file.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

## COMBINED, RAT

378-299 to 305 048981 to 048987, "21Z: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks", (Wellcome Foundation, and Life Science Research, LSR: 80/WRL003/283, 7/2/80). Permethrin, no purity stated; fed to Wistar rats, 60 + 15 (for hematology) per sex per group at 0, 10, 50 or 250 mg/kg/day; NOEL = 10 mg/kg (liver hypertrophy); 80% mortality in high dose males with earlier deaths starting at 4 months; unacceptable but possibly upgradeable (diet analysis and purity of test article.) Gee, 1/2/87.

EPA 1-liner: Guideline; NOEL = 10 mg/kg/day (increased liver weight, disturbance in thyroid growth at 250 mg/kg/day, body tremors.) Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

\*\*378-051, 052 989518, 989510, "PP557: Two Year Feeding Study in Rats", (ICI, 12/19/77, CTL/P/357). Permethrin, 10 batches ranging from 93.1% to 98.9%, cis: trans 36/62 to 44/55; fed in the diet to SPF Wistar-derived rats, 60/sex/group, at 0, 500, 1000 or 2500 ppm, 2 years; NOEL = 500 ppm (nominal); acceptable with minor variances (inadequate pathology tables - actual number of tissues examined not given, DOT and terminal sacrifices were not combined for non-neoplastic findings, 7/32 analyses of diet showed > 15% from nominal content of AI.) Christopher, 6/20/85 and Gee, 1/2/87.

EPA 1-liner: Minimum; Sys NOEL < 500 ppm (effects on liver - pharmacological). Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

378-389 072756, "Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice", Fundamental and Applied Toxicology, 11:308-322, 1988, (ICI Chemical Industries, 5/19/87). Permethrin technical (93.9% pure--nominal cis-trans ratio of 40:60) was fed in diet for 104 weeks to Alpk:AP (Wistar derived) rats at 0 (vehicle = diet), 500, 1000 or 2500 ppm (12/sex/group). An additional 12/sex/group were designated for an interim kill at 52 weeks. Swiss-derived mice were fed 0, 250, 1000 or 2500 ppm permethrin (100 mice-50/sex) for 98 weeks and 20/sex were designated for interim kill at 26 and 52 weeks. **No adverse effect.** RATS: Mortality  $\leq$  50%. NOEL = 500 ppm (tremors and hypersensitivity to noise during the first 2 weeks of the study at 2500 ppm; liver hypertrophy at  $\geq$  1000 ppm; vacuolated hepatocytes at 2500 ppm). No oncogenic effects were produced by permethrin. MICE: NOEL = 1000 ppm (slight elevation in benign lung tumor incidence in males; decrease in body weight gain). Benign lung tumors were not considered to represent a carcinogenic effect, however other studies (cited in the literature) have demonstrated lung tumors in mice at  $\geq$  2500 ppm permethrin. According to this study: "The conclusion of the USEPA (Federal Register 1982) and its SAP (Gray, 1981) was that permethrin has a low oncogenic potential in mice but none in the rat and that the oncogenic potential for humans was nonexistent or extremely low." The Joint Meeting on Pesticide Residues in 1982 concluded that based upon long-term rodent studies, permethrin was not oncogenic to humans (FAO, 1983). M. Silva, 11/16/89.

## CHRONIC TOXICITY, RAT

378-087 989506, Draft of a study by Burroughs-Wellcome, Life Science Research, no date. Christopher, 6/26/85. See 48981-87.

378-010, 011, 022, 024 013347, 013348, 989535 and 989579, "A Twenty-four Month Oral Toxicity/Carcinogenicity Study of FMC 33297 in Rats", (Bio/dynamics, 11/30/77, Project no.

74R-1022). Permethrin, no purity stated - ratio given as cis:trans, 40:60 in memos of FMC; fed in the diet at 0, 20, 100 or 500 ppm to 60/sex/group, Long Evans rats, 2 years; unacceptable (dose selection with inadequate high dose - no significant signs of toxicity, no purity of test article, inadequate samplings and analyses of diet.) Christopher, 6/24/85.

EPA 1-liner: Minimum; Sys NOEL = 20 ppm (liver changes - pharmacologic). Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

378-009 013936 "A Pathologic and Morphometric Study of the Nervous System of Rats Fed FMC 33297." (P. J. Dyck et al., Mayo Clinic, 12/8/77) Long-Evans rats from the 2-year study and the two-generation study at Bio/dynamics were shipped to the Mayo Clinic for evaluation. See appropriate one-liners for further details. The highest dose was 500 ppm in the two-year study. Animals were perfused and peripheral nerves (sural and tibial), brain stem and spinal cord with ganglia were taken for histological examination by light microscopy. No treatment-related findings were reported. All groups, including controls, had some abnormalities. No worksheet. Gee, 5/9/91.

378-009 013928, One-year histopathology for 013347.

378-023 989515, Revised histopathology report for 013347.

378-278 050808, Summary of ophthalmological findings for 013347.

#### CHRONIC TOXICITY, DOG

**\*\*378-297 004866**, "Permethrin: One Year Oral Dosing in Dogs", (ICI, Alderly Park, UK, 2/24/82, Report No. CTL/P/647, Study No. PD0350). Permethrin, 92.5%, 32.3/60.2, cis/trans; given in gelatin capsules prepared with corn oil for 52 weeks at 0, 5, 100 or 1000 (reduced from 2000 after 2 days) mg/kg/day to 6/sex/group; high dose dogs received 2 or 3 capsules daily, others received one capsule - seven capsules prepared for each animal after weekly weighing; absorption measured by analysis of urine; neurological exams at pre-test and at 13, 26, 39 weeks and at term; NOEL = 5 mg/kg/day (liver hypertrophy, adrenal alterations and decreased weight gain in both sexes); no treatment-related neoplasms were reported. **Adverse effect** on adrenal glands at mid and high doses. Acceptable. Gee and Martz, 1/9/87.

EPA 1-liner: Guideline; NOEL = 5 mg/kg/day (increased alkaline phosphatase, increased liver weights and hepatocellular swelling.) At 1000 mg/kg/day - tremors, convulsions, in-co-ordination, excessive salivation, vomiting early in study; increase platelet count; decreased protein, albumin, and Ca<sup>++</sup> levels; and increases in adrenal lesions; body weight loss.

#### ONCOGENICITY, RAT

See under combined rat.

#### ONCOGENICITY, MOUSE

378-087 989520, Draft of study by Burroughs-Wellcome, no date. Christopher, 6/26/85. See 048988 to 048997.

378-306 to 315 048988 to 048997, "Carcinogenicity Study in Mice with Permethrin (21Z73)", (Wellcome, 1980, HEFG-80-29). Permethrin, lot C8165-106, 25:75, cis:trans, no purity stated; fed to CFLP mice, 100/sex in controls, 75/sex/group in test groups, at 0, 10, 50 or 250 mg/kg/day for 91 weeks; NOEL = 250 mg/kg/day (HDT). Unacceptable (dose selection needs justification and purity of test article). Diets were prepared weekly and adjusted for body weight and food consumption. The incidence of lung tumors in high dose females was statistically significant in relation to the concurrent

controls. Volume 315, Tab 47, presents historical control data as discussed with EPA showing the value for the females falls within the range and close to the mean while the concurrent control for the study is inordinately low. The conclusion, therefore, is the lung tumors are not of biological significance. In addition, two other oncogenicity studies in mice did not report this finding. Gee, 1/2/87.

EPA 1-liner: No CORE grade - 1/30/85; NOEL = 250 mg/kg/day (HDT). Study is considered positive for lung tumors. One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

[Note: The setting of the NOEL at 250 mg/kg/day and the finding of the study as positive for lung tumors by EPA appears to be in conflict. Gee, 5/30/90]

378-012 013349, "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice", (Bio/dynamics, 11/30/77, Project no. 74-1100). Permethrin, no purity stated, 40:60, cis:trans ratio; fed in the diet at 0, 20, 500 or 4000 ppm to CD-1 mice, 75/sex/group over 2 years; doses were increased from 20, 100 and 500 ppm at week 21; apparent NOEL = 500 ppm (mortality); unacceptable (dose selection and changes, no purity of test article, inadequate samplings of diet for analysis - twice only in first year with none before dose change, time to tumor analysis needed.) Christopher, 6/27/85.

EPA 1-liner: Supplementary; Sys NOEL = 20 ppm. Not considered oncogenically positive.

378-279 050812, Histopathology report for 13349. Study remains unacceptable.

378-025 989529, Histopathology for 13349.

378-053, 054 989517, 989509, "PP557: Whole Life Feeding Study in Mice", (ICI, 12/28/77, CTL/P/359). Permethrin, 8 batches ranging from 94.0 to 98.9%, cis:trans ratio for each batch is included; fed in the diet at 0, 250, 1000 or 2500 ppm for 98 weeks, 70/sex/group. Unacceptable (inadequate analysis of diet over the study, mis-dosing incident with high and low diets being switched weeks 24 - 28 for 10 mice/group, questionable if adequate high dose). Christopher, 6/26/85. UNACCEPTABLE, supplemental information (065823) did not upgrade this study. (Gee, 9/16/88).

EPA 1-liner: No CORE grade; Sys NOEL = 250 ppm (liver effects - pharmacologic). Not oncogenic. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

378-053 989507, Interim report for 989517.

378-177 014918, "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice" (Biodynamics, 1976, 76-1695). Summary only. See #57754 for full report.

**378-342 057754** "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice (Mouse II)." (Bio/Dynamics, Inc., 10/9/79, Project 76-1695) Permethrin, technical, batches MRR 176 and MRR 807 were 94.5% and 96.7%, respectively; fed in the diet at 0, 20, 500 or 2000 ppm for males and 0, 20, 2500 or 5000 ppm for females - doses were lowered from 100, 2500, and 5000 ppm at month three at the sponsor's request - no rationale given; 75/sex/group Charles River CD-1, COBS mice; NOEL = 20 ppm (increased incidence of bronchioalveolar adenomas and hepatomas in females at mid- and high-doses, decreased testes weight and increased mortality in the high-dose males, increased hepatocellular carcinomas in mid-dose males, increase in hepatocytomegally). **Possible adverse neoplastic effect.** Initially reviewed as unacceptable (J. Gee, 12/1/87). Sponsor submitted data on test article purity and diet analysis (see 367 066541). EPA requested a second histopathological evaluation by an independent pathologist (see 415 088951). The study remains UNACCEPTABLE and not upgradeable (inadequate husbandry). (Gee, 5/9/91).

EPA 1-liner: No CORE grade; Sys NOEL = 20 ppm; Sys LEL = 2500 ppm in females liver and lung weight increases; 500 ppm in males (testis weight depression, deaths) Study is considered as positive for lung and liver tumors.

378-415 088951 Second evaluation of histopathology by Experimental Pathology Laboratories requested by EPA for 057754.

378-177 014919, "Advisory Opinion on the Oncogenic Potential of Permethrin, Scientific Advisory Panel, FIFRA. March 20, 1981", Panel report discusses both rat and mouse studies. The rat studies failed to show carcinogenic effects. "The mouse studies are clouded." Panel states the ICI and Burroughs-Wellcome studies "...appear well controlled and properly carried out." The Wellcome study suggested a potential for pulmonary neoplasms. The two attributed to FMC had problems with execution. "The Panel expressed a marked lack of confidence in the pathological findings of the FMC Mouse II Study." The FMC studies "...suggest but do not show a potential for the production of pulmonary and hepatic proliferative lesions, an unease, not a definitive demonstration." The panel concluded that the rat and mouse studies coupled together suggest a very weak oncogenic potential. Gee, 1/2/87.

378-389 072756, "Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice", Fundamental and Applied Toxicology, 11:308-322, 1988, (ICI Chemical Industries, 5/19/87). Permethrin technical (93.9% pure--nominal cis-trans ratio of 40:60) was fed in the diet for 104 weeks to Alpk:AP (Wistar derived) rats at 0 (vehicle = diet), 500, 1000 or 2500 ppm (12/sex/group). An additional 12/sex/group were designated for an interim kill at 52 weeks. Swiss-derived mice were fed 0, 250, 1000 or 2500 ppm permethrin (100 mice-50/sex) for 98 weeks and 20/sex were designated for interim kill at 26 and 52 weeks. **No adverse effect.** RATS: Mortality  $\leq$  50%. NOEL = 500 ppm (tremors and hypersensitivity to noise during the first 2 weeks of the study at 2500 ppm; liver hypertrophy at  $\geq$  1000 ppm; vacuolated hepatocytes at 2500 ppm). No oncogenic effects were produced by permethrin. MICE: NOEL = 1000 ppm (slight elevation in benign lung tumor incidence in males; decrease in body weight gain). Benign lung tumors were not considered to represent a carcinogenic effect, however other studies (cited in the literature) have demonstrated lung tumors in mice at  $\geq$  2500 ppm permethrin. According to this study: "The conclusion of the USEPA (Federal Register 1982) and its SAP (Gray, 1981) was that permethrin has a low oncogenic potential in mice but none in the rat and that the oncogenic potential for humans was nonexistent or extremely low." The Joint Meeting on Pesticide Residues in 1982 concluded that based upon long-term rodent studies, permethrin was not oncogenic to humans (FAO, 1983). M. Silva, 11/16/89.

SUMMARY: Although no single study meets all of the requirements for an adequate study, taken as a whole and considering the number of tests conducted, the data gap is considered filled with a possible adverse neoplastic effect (see Record No. 057754, reviewed 9/16/88). (Gee, 9/16/88). In the process of developing a risk assessment document, the total data base for female mouse oncogenicity was re-examined in light of the possible adverse effects identified in the second study conducted at Bio/dynamics (057754). An earlier review (1/2/87) of a study in mice conducted by Wellcome (CDFA Record Nos. 048988 to 048997) had dismissed the statistically significant finding of lung tumors in females as being well within the limits of historical control data for the same strain of mice and, therefore, of doubtful biological significance. Re-review of the Wellcome study (Gee and Aldous, 5/90), on its own, resulted in no change for the individual study. However, considered with the Bio/dynamics (057754), the findings at 250 mg/kg/day in 048988, etc., support the effects seen at 2500 and 5000 ppm in lungs of female mice. Noted also are two other studies on file which were negative for oncogenic effects in mice at similar doses - an earlier Bio/dynamics study and an ICI study. CDFA will take a conservative approach at this time in characterizing the risk of permethrin, keeping in mind that the data are not consistent. A definitive replacement mouse oncogenicity study is strongly recommended. This would address the shortcomings of those studies on file and either confirm or refute the oncogenicity. If further testing in the mouse is conducted and submitted, the total data base will be re-evaluated. (Gee, 5/30/90)

378-013 014906, "A Three Generation Reproduction Study of FMC 33297 in Rats", (Bio/dynamics, 12/15/77, no. 74-1101). Permethrin, no purity stated, cis:trans ratio was 40:60; fed to 12 males/24 females per group at 0, 20 or 100 ppm, 3 generation-2 litters per generation; dosed for 61 days before mating; NOEL > 100 ppm (HDT) - nominal; unacceptable (inadequate high dose, no histopathology on breeders.) No adverse reproductive effect reported. Christopher, 6/20/85.  
EPA 1-liner: Minimum. NOEL > 100 ppm.

**\*\*378-052, 053 031817, 038830, 038831**, "PP557: 3 Generation Reproduction Study in Rats", (ICI, no. CTL/P/361, 12/20/77). Permethrin, 7 batches with purity ranging from 94.0 to 98.9% (cis:trans ratios of 36:61 to 44:55), was fed in the diet to groups of 12 male and 24 female Wistar derived rats at dose levels of 0 (diet control), 500, 1000 or 2500 ppm for 3 generations, 2 litters per generation. Tremors were observed in parental animals at 2500 ppm, and occasionally at 1000 ppm. Centrilobular hypertrophy of the liver, and buphthalmos (defined pathologically as persistent pupillary membranes), were observed at all treatment levels. The nominal parental NOEL = 500 ppm (tremors); nominal developmental NOEL < 500 ppm (abnormal liver and ocular histopathology). The study was initially reviewed as acceptable by J. Christopher (6/20/85), and a possible adverse health effect of centrilobular hypertrophy noted. Upon re-evaluation and consideration of the data provided in record numbers 087189 and 091347, the study remains **ACCEPTABLE**, and the **POSSIBLE DEVELOPMENTAL ADVERSE HEALTH EFFECT** of buphthalmos is noted. The centrilobular hypertrophy is considered a transient physiological response to the treatment, and as such, does not constitute a possible adverse developmental or reproductive health effect (G. Chernoff, 7/18/90).  
EPA 1-liner: Guideline. NOEL < 500 ppm, offspring show centrilobular hepatocyte hypertrophy and cytoplasmic eosinophilia and buphthalmos with persistent pupillary membranes. Body tremors in parents at 1000 ppm and 2500 ppm and in offspring at 2500 ppm.

378-413 087189, "Permethrin Three-Generation Reproduction Study in Rats, Additional Information on the Incidence of Buphthalmos", (Hodge, M.C.E. and G.J.A. Oliver, ICI Central Toxicology Laboratory, 10/22/87). The results of a one week study monitoring the incidence of buphthalmos in the Animal Breeding Unit providing animals for the rat reproduction study (CDFA Record Nos. 031817, 038830-31). The worksheet is filed as W031817.S01 (G. Chernoff, 9/10/90).

378-414 091347, "Additional Information on the Incidence of Buphthalmos: Family Trees of Individual Pups Affected and Family Trees of Probable 'Carrier' Parents", (Hodge, M.C.E., ICI Central Toxicology Laboratory, 8/23/90). Pedigree data supplemental to the rat reproduction study (CDFA Record Nos. 031817, 038830-31). The worksheet is filed as W031817.S01 (G. Chernoff, 9/10/90).

#### TERATOGENICITY, RAT

378-052 031816, "PP557: 3 Generation Reproduction Study in Rats." (ICI, 12/20/77, no. CTL/P/361). Permethrin, breeders are F2b of reproduction study; 11-12 litters examined; breeders exposed in utero as well to 0, 500, 1000 or 2500 ppm; nominal developmental NOEL  $\geq$  2500 ppm; unacceptable (protocol - both sexes treated, other differences.) Christopher, 6/20/85.

378-036 989570, "Teratogenicity Study in Rats of ICI-PP 557," (Inveresk Res. International, 2/76, IRI no. 404898). Permethrin, 95.3%, 37.5:57.8, cis:trans; given orally to 20 per group at 0, 22.5, 71 or 225 mg/kg/day, days 6 - 16; maternal and developmental NOELs  $\geq$  225 mg/kg/day; unacceptable but upgradeable with submission of dosing analyses, evidence of maternal toxicity - dose selection based on a range-finding study in which 338 mg/kg/day was judged too toxic. Christopher, 6/19/85.  
EPA 1-liner: No CORE grade. Not teratogenic at 225 mg/kg, maternal toxicity at 225 mg/kg.

378-008 013344, "Foetal Toxicity Study in the Rat given 21Z73 (NRDC 143) Orally", (Wellcome Research Labs., 5/74, BPAT/74/10). Permethrin, no purity stated; 22 - 23 females per group given 0 or 200 mg/kg/day by oral gavage, days 6 - 16; NOEL > 200 mg/kg/day;

unacceptable (no maternal toxicity, single dose, no analysis of dosing solution, no purity stated, two deaths in dosed group but no cause given.) Christopher, 6/19/85.

EPA 1-liner: Minimum. Not teratogenic at 200 mg/kg. No definite maternal or fetotoxic effects evident.

\*\*378-382 071105, "Permethrin: Teratogenicity Study in the Rat", (ICI Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK, report CTL/P/2269, 9/20/88). Permethrin, 93.9%, batch # RS 78/E, 38:62 Cis:Trans ratio, was administered by gavage to groups of 24 pregnant Alp:APfSD rats on days 7-16 of gestation at dose levels of 0 (corn oil vehicle control), 15, 50 or 150 mg/kg/day. Maternal toxicity (decreased food consumption and weight gain, tremors, and head flicks) was observed at 150 mg/kg/day. Intrauterine growth retardation (decreased fetal weight and delayed ossification) was also observed at the high dose. The fetal effects are considered to be secondary to the maternal effects, so **no adverse developmental effect** is indicated. Maternal NOEL = 50 mg/kg/day (decreased weight gain and clinical signs); Developmental NOEL = 50 mg/kg/day (intrauterine growth retardation). The study, initially reviewed as unacceptable by H. Green and G. Chernoff (4/13/90), is upgraded to **ACCEPTABLE** with the submission of the cis:trans ratio data in record no. 087158 (G. Chernoff, 7/31/90).

378-412 087158, Supplemental information to record no. 071105, containing information on the cis:trans ratio.

#### TERATOGENICITY, RABBIT

378-008 013342, "Foetal Toxicity Study in the Rabbit given 21Z73 (NRDC 143) Orally", (Wellcome Research,, 1974, BPAT 74/19). Permethrin, no purity stated - 25/75, cis/trans; given orally to 6 - 7 Dutch Belted rabbits at 0 or 400 mg/kg, days 6 - 18; nominal maternal NOEL  $\geq$  400 mg/kg/day; unacceptable (inadequate number of pregnant females, single dose, no maternal toxicity reported, no purity stated, no analysis of dosing solution and no historical control data.) Not upgradeable. Christopher, 6/19/85.

EPA 1-liner: Minimum. Not teratogenic at 400 mg/kg. No definite maternal or fetotoxic effects evident.

\*\*378-341, 367, 388 057752, 066542, 073004, "Permethrin Teratogenicity Study in Rabbit - Individual Foetal Data Supplement, Skeletal Findings", (ICI, UK, 7/31/80; report no. CTL/P/523). Permethrin, 92.5%, cis:trans isomers 32.3%:60.2%; given by oral gavage to Dutch rabbits at 0, 600, 1200 or 1800 mg/kg body weight during days 6-18 of gestation; target of 18/group but some were lost due to misdosing or death; number of pregnant animals at day 29 were 15, 13, 14 and 13 for control, low, mid and high doses respectively; clinical observations of tremors at 1800 mg/kg and excessive fur in the stomach at 1200 and 1800 mg/kg; decreased weight gain during gestation at mid and high dose; embryotoxicity at 1200 and 1800 mg/kg with increase in post-implantation loss and decrease in mean fetal weight at 1800 mg/kg; no increase in malformations with treatment; maternal and developmental NOELS = 600 mg/kg. Reviewed twice as unacceptable due to missing data (Gee, 11/20/87; Gee, 9/16/88), upon receipt of individual fetal skeletal data, CDFA has all the information available on this study. The skeletal data were evaluated and found to be **acceptable**. M. Silva, 11/16/89.

#### TERATOGENICITY, MOUSE

378-008 013343, "Foetal Toxicity Study in the Mouse given 21Z73 (NRDC 143) Orally", (Wellcome Research Labs, 1974, BPAT/74/12). Permethrin, no purity stated; given to mice, 20 - 23 per group, at 0 or 400 mg/kg/day, days 6 - 15 of gestation; NOEL > 400 mg/kg; unacceptable (no maternal toxicity, single dose level, no purity stated, no analysis of dosing solution). Christopher, 6/19/85.

EPA 1-liner: Minimum. Not teratogenic at 400 mg/kg. No maternal or fetotoxic effects evident.

#### GENE MUTATION

378-036 989589, "Permethrin Short-Term Predictive Tests for Carcinogenicity: Results from the Ames Test", (ICI, 11/76, Report no. CTL/P/301). Permethrin, 95.1%, 42% cis, 58% trans isomer; Salmonella strains TA1535, TA1538, TA98 and TA100, tested with and without activation at 0, 4, 20, 100, 500 or 2500 ug/plate, no evidence of mutagenicity; unacceptable (no individual plate counts but  $\pm$ SD for 5 trials, no justification of high concentration with no cytotoxicity evident). Christopher, 6/18/85.

378-008 013341, "In Vitro Microbial Mutagenicity Study of an FMC Corporation Compound", (SRI, 1/76, Project LSC-4768). Permethrin, 95.7% - cis/trans, 44.7/55.3, tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without mouse liver activation; 0, 1, 50, 100, 250, 500 or 1000 ug/plate; single plate per concentration; no evidence of mutagenicity reported; unacceptable (single plate per concentration, marginal evidence of cytotoxicity or justification of high concentration.) Christopher, 6/17/85.

378-007 014896, "Mutagenicity Evaluation of Low Volatility Impurities in FMC 33297 (8531-114) Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Chemistry of test article not described, amber liquid; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, apparently one plate per concentration, no retest; no evidence of mutagenicity or cytotoxicity in Salmonella, suggestion of cytotoxicity in Saccharomyces cerevisiae D4; unacceptable (no purity of test article, single plate and single trial.) Christopher, 6/17/85.

378-007 014895, "Mutagenicity Evaluation of Titanium Tetra-3-phenoxybenzoxide, Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Titanium tetra-3-phenoxybenzoxide, viscous yellow liquid; no purity stated and no rationale for testing this compound; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 and 5.0 ul/plate, single plate, single trial; no evidence of increased reversion rate, cytotoxic at 5 ul; also tested Saccharomyces cerevisiae D4; unacceptable (test article not described, single plate, no repeat trial, no discussion of why this compound was tested.) Christopher, 6/17/85.

378-007 014894, "Mutagenicity Evaluation of FMC 30083MRT-501: Final Report", (Litton Bionetics, 7/77, LBI Project No. 2683). FMC 30083 MRT-501, no further identification, colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, also Saccharomyces cerevisiae D4, with and without rat liver activation, at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of increased reversion rate or mutagenicity; no evidence of cytotoxicity; unacceptable (no description of test article, single trial, single plate). Christopher, 6/17/85.

378-007 014893, "Mutagenicity Evaluation of FMC 47944; Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 47944, no description or further identification, viscous colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 as well as Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity or cytotoxicity; unacceptable (no description of test article, no repeat trial, single plate per concentration.) Christopher, 6/17/85.

378-007 014892, "Mutagenicity Evaluation of FMC 30094; Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30094, no further identification, colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 as well as Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; no evidence of mutagenicity; marginal suggestion of cytotoxicity at 5 ul/plate; unacceptable (inadequate description of test article, no repeat trial, single plate.) Christopher, 6/17/85.

378-007 014891, "Mutagenicity Evaluation of FMC 30089, C-8117-20-cut-12; Final Report", (Litton Bionetics, 12/30/76. LBI Project No. 2683). FMC 30089, C-8117-20-cut 12, pale yellow liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no mutagenicity reported, cytotoxicity in several strains at 5 ul; unacceptable (test article not described, single plate, single trial except for retest with TA98 at 5.0 ul/plate - first trial showed a several-fold increase in revertants but was not confirmed.) Christopher, 6/17/85.

378-007 014890, "Mutagenicity Evaluation of Ten Coded Compounds: Final Report", (Litton Bionetics, 9/15/76, LBI Project No. 268). MR S936 FMC 39338 - C7925-62-4, clear liquid, and MR S928 FMC 30061 - C7967-15, pale yellowish clear liquid, were tested - no further identification of compounds; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, also with Saccharomyces cerevisiae D4; with and without rat liver activation; tested at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, one plate per concentration except duplicates for TA98; single trial; unacceptable (test articles not described, single trial, single plates.) No evidence of mutagenicity. Suggestion of cytotoxicity at 5 ul/plate in several strains. Christopher, 6/17/85.

378-007 014899, "Mutagenicity Evaluation of FMC 30062: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30062, yellow solid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4 with and without rat liver activation; 0, 0.1, 1.0, 10, 100 or 500 ug/plate; single plate, single trial; no evidence of mutagenicity; unacceptable (single plate, single trial, no justification of high concentration and no evidence of cytotoxicity.) Christopher, 6/17/85.

378-007 014900, "Mutagenicity Evaluation of 3-Phenoxybenzyl, 2-Methylbenzoate: Final Report", (Litton Bionetics, 9/77, LBI Project No. 20838). 3-Phenoxybenzyl 1,2-methylbenzoate, beige liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity or cytotoxicity; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/17/85.

378-007 014901, "Mutagenicity Evaluation of 3-Phenoxybenzylbenzoate C-8531-115: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). 3-Phenoxybenzylbenzoate C-8531-115, amber liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity; suggestion of cytotoxicity at 5 ul with TA1535 and TA1537 strains; SR for TA100 rather high; unacceptable (inadequate description of test article, single trial, single plate.) Christopher, 6/17/85.

378-007 014902, "Mutagenicity Evaluation of Ethyl Benzoate: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Ethyl benzoate, colorless liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity, marginal cytotoxicity at 5.0 ul with TA1538; unacceptable (inadequate description of test article, single plate, single trial.) Christopher, 6/17/85.

378-007 014903, "Mutagenicity Evaluation of FMC 51046: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838.). FMC 51046, yellow liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.0001, 0.001, 0.01, 0.1, or 1.0 ul/plate; single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 0.1 and 1.0 ul/plate; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

378-007 014904, "Mutagenicity Evaluation of Diphenyl Ether: Final Report", (Litton Bionetics, 12/77,

LBI Project No. 20838). Diphenyl ether, colorless liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 5.0 ul/plate in several strains; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

378-007 014905, "Mutagenicity Evaluation of 2-Phenoxytoluene: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). 3-Phenoxytoluene, colorless liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 5 ul with several strains; unacceptable (single trial, single plate, inadequate description of test article.) Christopher, 6/14/85.

378-007 014898, "Mutagenicity Evaluation of FMC 51050: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 51050, colorless liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; suggestion of cytotoxicity in several strains at 5.0 ul/plate; unacceptable (single plate, single trial, inadequate description of test article and no justification for using compound.) Christopher, 6/14/85.

378-007 014897, "Mutagenicity Evaluation of FMC 30953: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30953, slightly viscous colorless liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity reported, cytotoxicity at 5.0 ul/plate in all strains; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

378-\*\*391 073022, "Permethrin: An Evaluation in the Salmonella Mutation Assay", (R. D. Callander, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, report # CTL/P/2423, 2/22/89), permethrin technical, analysed purity 95.6% w/w, batch # P56; RS/38/F (Cis/Trans ratio of 38.6/61.4 - see 378-391, # 073018), liquid, 2 trials in triplicate with and without S9 (Aroclor induced male rat liver fraction) activation at 0 (strain only), 0 (DMSO), 1.6, 8.0, 40, 200, 1000, and 5000 mg/plate with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100. Positive controls with activation: 2AA (all strains), without activation: MNNG (TA1535, TA100), daunorubicin (TA98), 4NPD (TA1538), acridine mutagen ICR191 (TA1537). **No statistically significant increase in revertants. Acceptable.** (Gee, 4/11/90)

\*\*378-008 013340, "Mutagenicity of BW 21Z73 in L5178Y/TK+/- Mouse Lymphoma Cells with and without Exogenous Metabolic Activation", (Burroughs Wellcome, 1/5/77, Doc. no. TTEP/77/001). Permethrin, no purity stated; tested for 4 hours with and without activation at 0, 31, 47, 62, 94 or 125 mg/ml; no evidence of mutagenicity reported; initially reviewed as unacceptable based on inadequate description of protocol and calculations by JPC, 6/17/85. Supplements in 278, #s 50809, 50810 and 50811 provide missing information and upgrade the study to acceptable status. Christopher, 6/17/85 and Gee, 1/8/87.

#### CHROMOSOME EFFECTS

\*\*378-036 989591 "Permethrin (PP557): Cytogenetic study in the Rat." (ICI, 11/76, Report no. CTL/P/294) Permethrin, 94%, 40.3:59.7 cis:trans; given by ip injection once or in 5 daily doses at 0, 600, 3000 or 6000 mg/kg to 12 males in control and 8 males per test group; sacrificed at 24 hours after the single dose, 6 hours after last dosing in multiple dosing; scored 50 cells per animal; initially reviewed as unacceptable (use of one sex must be justified, single sampling time, no data on toxicity - high dose stated to be near MTD but no data and no clinical observations presented.) Christopher,

6/18/85. A rebuttal was submitted (2-page letter) dated September 9, 1991, addressing the deficiencies noted above. Reconsidering the study, it is upgraded to acceptable status with some minor deficiencies. Gee, 10/3/91.

378-036 024952, "Dominant Lethal Study in Mice of 95.3% ICI-PP 557", (Inveresk Res. International, 11/76, IRI 406722). Permethrin, 95.3%, 37.5:57.8, cis:trans; given orally on five consecutive days to 15 male CD-1 mice per group at 0, 15, 48 or 150 mg/kg/day; mated 1 male:2 females, weekly for 8 consecutive weeks; unacceptable (no explanation for death of 54 females - 5% - with no time of death or clinical observations, inadequate number of pregnant mice per interval.) No evidence of dominant lethal effect. Christopher, 6/18/85.

378-008 013339, "21Z73, Dominant Lethal Study in Male Mice", (Wellcome Research Labs, 11/27/75, T. L. 37-75). Permethrin, no purity stated - 25/75, cis:trans; given orally to CD-1 male mice at 0 or 452 mg/kg in five daily doses; mated 1 male to 3 females weekly for 6 weeks; dose was 1/5 LD50/day; no evidence of dominant lethal effect; unacceptable (single dose level, inadequate number of pregnant females, variable fertility and number of dead implants making interpretation of results difficult.) Christopher, 6/17/85.

EPA 1-liner: No CORE grade. Not mutagenic at 452 mg/kg.

378-472 121635; "Permethrin: an Evaluation in the Mouse Micronucleus Test"; Report No. CTL/P/3934; D. Fox and J.M. Mackay; Zeneca Central Toxicology Laboratory, Cheshire, UK; 3/5/93. A single oral dose of permethrin (batch no. P58/D7534/30, 93.1% w/w stated purity) in corn oil was given to 5 CD-1 mice/sex/dose/time point at 200 mg/kg for males and 320 mg/kg for females. Samples of femur marrow were taken 24 or 48 hours after dosing and prepared for microscopic examination. One thousand polychromatic erythrocytes per animal were examined for micronuclei and the ratio of polychromatic to normochromatic erythrocytes was determined in an additional 1,000 cells. There was no treatment-related increase in micronuclei. No adverse effect was indicated. The positive controls and doses were adequate. The study was not acceptable and not upgradeable because the stability and achieved concentrations of the test material were not determined by analysis (S. Morris, 6/22/93).

#### DNA DAMAGE

\*\*378-372, 388 066477, 073009, "Permethrin: Assessment for the Induction of Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures", (Imperial Chemical Industries PLC, UK, Report No: CTL/P/1888, April 1988). Permethrin (purity = 93.5%) administered at concentrations  $10^{-7}$ ,  $10^{-6}$ ,  $10^{-5}$ ,  $10^{-4}$ ,  $10^{-3}$ ,  $10^{-2}$ ,  $10^{-1}$  and  $10^0$  molar to rat hepatocytes in culture (3 slides/dose for each of three (3) experiments). Permethrin did not induce DNA repair, as measured by unscheduled DNA synthesis, in primary cultures of rat hepatocytes exposed in vitro. Previously reviewed as unacceptable (Gee, 9/16/88), upon submission of the requested information (cytotoxicity data, unaltered and damaged cell numbers, pyknotic nuclei data and number of cells scored), the study has been upgraded to **acceptable**. M. Silva, 11/20/89.

#### NEUROTOXICITY

\*\*378-009 013926, "Examination of Permethrin (PP 557) for Neurotoxicity in the Domestic Hen", (Huntingdon Research Centre, 9/30/77, ICI/157-NT?77468). Permethrin, 94.9%, 36.0:58.9, cis:trans; given orally to 10 in controls and 15 in dose group at 0 or approximately 12 g/kg, observed 21 days, then redosed; TOCP as positive control; no adverse effect with permethrin. Acceptable. Christopher, 6/17/85.

No EPA 1-liner.

## SUPPLEMENTAL STUDIES

**\*\* 378-493 131313**; "Permethrin Technical Acute Neurotoxicity Screen in Rats", FMC Study No. A92-3646; C. Freeman; FMC Corporation, Toxicology Laboratory, Princeton, NJ; 8/27/93. Groups of 10 Sprague-Dawley rats/sex were given Permethrin (technical, ref. #PL90-269, analytical purity 95.3%, corn oil vehicle) at 0, 10, 150, or 300 mg/kg by single oral gavage. The rats were observed for 14 days and functional observational battery (FOB) and motor activity tests were given on days 0, 7, and 14. All rats were sacrificed on day 14 and the nervous system of 5 rats/sex for the 0 and 300 mg/kg groups were examined for neuropathological lesions. A **possible adverse effect** was indicated by treatment-related effects seen at 300 mg/kg: One female died. Both sexes showed clinical signs for 2 days after dosing that included tremors, staggered gait, splayed hindlimbs, exaggerated hindlimb flexion and hypersensitivity to sound. FOB testing showed changes for both sexes only on day 0 that included whole body tremors, staggered gait, splayed hindlimbs, abnormal posture while moving, and exaggerated hindlimb flexion and convulsions. The NOEL was 25 mg/kg based on similar effects seen in a pilot study at 50, 125, 150, 175, 200, and 300 mg/kg and in a supplemental study at 75 and 150 mg/kg (DPR doc. # 378-492, rec. # 131312). There were no treatment-related changes in motor activity or neuropathology. The study was acceptable (J. Kishiyama and S. Morris, 6/22/95).

378-492 0131312; "Utility of a Neurobehavioral Screening Battery for Differentiating the Effects of Two Pyrethroids, Permethrin and Cypermethrin"; McDaniel, KL and Moser, VC (1993): Neurotoxicology and Teratology, 15:71-83. Groups of 8 Long-Evans hooded rats/sex were treated by oral gavage with 0, 25, 75, or 150 mg/kg permethrin in corn oil (1 ml/kg). Functional observational battery (FOB) tests were given at 0, 2, 4, and 24 hours post-dosing. Additional groups of 8 rats/sex were given the same doses and tested for motor activity 4, 24, and 48 hours post-dosing. One male at 150 mg/kg died during FOB testing. FOB measurements and motor activity were affected at 75 and 150 mg/kg. These data were used to determine the NOEL in DPR doc. # 378-493, rec. # 131313. No worksheet was done (S. Morris, 6/22/95).

378-516 135757 Duplicate of 131313.

**\*\* 378-494 131315**, "Permethrin Technical Subchronic Neurotoxicity Screen in Rats", Study No. A92-3647; C. Freeman; FMC Corporation, Toxicology Laboratory, Princeton NJ; 9/2/93. Groups of 10 Sprague-Dawley rats/sex/group were fed dietary mixtures of permethrin technical (PL90-269, 95.3% analytical purity) for 13 weeks at 0, 250, 1500, or 2500 ppm. Slight treatment-related decreases in food consumption and body weight gain were seen in males at 2500 ppm. A **possible adverse effect** was indicated by clinical behavioral signs of splayed hindlimbs, staggered gait, and tremors in both sexes at 1500 and 2500 ppm and changes in functional observational battery parameters: whole body tremors in both sexes at 2500 ppm; staggered gait in both sexes at 1500 and 2500 ppm; abnormal mobile posture in males at 2500 ppm and in females at 1500 and 2500 ppm; splayed hind limbs in males at 2500 ppm and in females at 1500 and 2500 ppm; gait impairment in both sexes at 1500 and 2500 ppm; landing foot splay in females at 1500 and 2500 ppm; fore- and hindlimb grip strengths in both sexes at 2500 ppm; fecal boli in males at 1500 and 2500 ppm; and unkempt/rough coat in males at 2500 ppm (NOEL = 250 ppm). The NOEL was not based on an increase in landing foot splay seen in males at 250, 1500, and 2500 ppm because the effect was seen at weeks 4 and 8 but not week 13. The study was acceptable (J. Kishiyama and S. Morris, 3/23/95).

378-515 135753 Duplicate of 131315.

378-009 013934, "Preliminary investigation of the Neurological Effects in Rats Offered Diets Containing NRDC 143." (Wellcome Research Labs, 2/28/77). Permethrin, fed to Charles River Wistar rats, 10 females per group, at 6000 ppm, with 90, 40 or 25% cis and 10, 60 or 75% trans

isomers; observed for 16 days; some acute neurotoxic symptoms seen, greatest with 90% cis isomer; unacceptable for acute delayed neuropathy test. J. Christopher, 6/18/85.

378-036 989469 "Effects of High Dietary Levels of PP557 on Clinical Behavior and Structure of Sciatic Nerves in the Rat." (ICI, 3/77, CTL/P/317) Permethrin, 40% cis: 60% trans, 90.4% purity, was fed to male SPF-derived Wistar rats for 14 days at 0 (diet), 2500, 3000, 3750, 4500, 5000 or 7500 ppm in two studies spaced 14 days apart, 10/group. Data were pooled. Only the sciatic nerve was examined although the brain, spinal cord, vagus nerve and gastrocnemius muscle were saved but not processed. Tremors of varying severity were seen in all treatment groups with decreasing severity with treatment time. Deaths occurred at 5000 and 7500 ppm. Nerves from the 2500, 4500 and 5000 ppm groups were examined by light and electron microscopy. The incidence of degenerating nerve fibers in the two 5000 ppm 14-day survivors was increased. Other minor changes were also noted. Nerves from the 2500 and 4500 ppm groups were similar to paired controls. No worksheet. Gee, 5/9/91.

378-009 013938 "Neurotoxic Effects of Some Synthetic Pyrethroids by Short-term Feeding in Rats." (Okuno, Y., Sumitomo Chemical Co., 11/10/76) NRDC 143 [permethrin], 93.3% purity - no further identification, was fed at 0 or 6000 ppm for 7 or 8 days to groups of 8/sex SD-SLC rats in control and 16/sex in the treated groups. Clinical signs were tremors and muscle twitch in the treated groups. Histological examination of 5/sex/group of the spinal cord and brain showed no abnormalities. The sciatic nerve showed swelling and, in 1/sex at 6000 ppm, degeneration. Demyelination occurred in 1/sex at 6000 ppm. No worksheet. Gee, 5/9/91.