CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Chlorfenapyr

Chemical Code # 3938, Tolerance # 52002
SB 950 # New A.I.

8/24/01

I. DATA GAP STATUS

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, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, possible 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

Toxicology one-liners are attached.

All record numbers through 147077 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T189726
Thomas Moore, 8/24/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 065; 147075; "A Chronic Dietary Toxicity and Oncogenicity Study with AC 303,630 in Rats", (Trutter, J.A.; Hazleton Washington, Inc., Vienna, VA; Study No. HWA 362-206; 8/23/94); AC 303,603 Technical (purity: 94.5%) was administered in the diet of 65 rats/sex/group at concentrations of 0, 60, 300, and 600 ppm for up to 104 weeks. Body weight gain was reduced in the 300 and 600 ppm groups over the course of the study. No treatment-related effects were noted in the hematology, clinical chemistry or urinalysis. No treatment-related effect upon organ weights. Increased incidence of hepatocellular enlargement in the 300 and 600 ppm treatment groups. **No adverse effects** indicated. **NOEL (M/F):** 60 ppm (based upon hepatocellular enlargement in the liver of the 300 ppm treatment group); no oncogenic effect was reported up to 600 ppm; **Study acceptable.** (Moore, 7/23/96)

CHRONIC TOXICITY, RAT

See the Combined Rat.

CHRONIC TOXICITY, DOG

** 062; 147071; "One Year Dietary Toxicity Study with AC 303,630 in Purebred Beagle Dogs"; (Kelly, C.M.; Pharmaco LSR Inc., East Millstone, NJ; Study No. 92-3107; 8/31/94); AC 303,630 Technical (purity: 94.5%) was administered in the diet to 5 dogs/sex/group at doses of 0, 60 and 120 ppm and to 6 dogs/sex at 240 ppm for 12 months (M-0, 2.1, 4.0, 8.7 mg/kg/day, F-0, 2.3, 4.5, 10.1 mg/kg/day). Reduced body weight gain was evident in the high dose animals. The relative mean liver weights were slightly increased in the high dose group. No treatment-related effects were noted for hematology or clinical chemistry. No treatment-related lesions were evident. **No adverse effects** were indicated. **NOEL:** 120 ppm (M/F) (based on increase in relative mean liver weight and reduced body weight gain of animals in the 240 ppm treatment group); **NOAEL**: 240 ppm; **Study acceptable.** (Moore, 7/15/96)

ONCOGENICITY, RAT

See the Combined Rat.

ONCOGENICITY, MOUSE

** 066; 147076; "A Chronic Dietary Toxicity and Oncogenicity Study with AC 303,630 in Mice" (L. Bernier, Bio-Research Lab., Ltd., Quebec, Canada, Project # 84580, 8/22/94). AC 303,630 (Batch AC-7504-59A, 94.5% purity) administered orally in the diet to 65 CD-1 mice/sex/dose for 80 weeks at 0, 20, 120, or 240 ppm (Males: 0, 2.8, 16.6, or 34.5 mg/kg/day; Females: 0, 3.7, 21.9, or 44.5 mg/kg/day). Reduced survival rate was noted in high dose females (60% vs. 80%, $p < 0.05$). However, overall survival rate of this group was more comparable to that of the historical controls. Treatment with AC 303,630 resulted in reduced mean body weight gain in high dose males and females and in mid dose females (Males: 70% of control, $p < 0.01$, Females: 86% of control, $p < 0.05$ for mid and high dose groups). Food consumption was also reduced in mid and high dose animals. Histopathology revealed vacuolation of the white matter of the brain in animals treated at mid and high dose levels. Also, vacuolation was detected in spinal cord sections as well as optic nerve tissues in mice at 240 ppm. There was no evidence of carcinogenicity**.** NOAEL (M/F) = 240 ppm [**No adverse effect**]. NOEL (M/F) = 20 ppm (2.8 and 3.7 mg/kg/day for males and females, respectively; based on histopathological changes in the brain, optic nerve and spinal cord). **acceptable** (Leung, 7/24/96)

REPRODUCTION, RAT

063; 147072; "A Pilot Dietary Reproduction Study in Rats with AC 303,630", (R.E. Schroeder; Pharmaco LSR Inc., East Millstone, NJ; Study No. 91-3755; 7/20/94); AC 303,630 Technical (purity: 94.5%) was administered to 10 animals/sex/group in the diet at doses of 0, 60, 300 and 600 ppm for 10 weeks during a premating period, a 10 day mating period and the ensuing gestation and lactation periods. Reduced body weight gain was noted in the females of the 300 and 600 ppm groups during the premating period. Pup survival was reduced in the 600 ppm treatment group during the 0 to 4 day post-natal period. Pup weight gain was reduced in the high dose group over the lactation period. **No adverse effect** indicated. **Parental NOEL:** 60 ppm (based upon reduced body weight gain in the 300 ppm treatment group), **Reproductive/Developmental NOEL:** 300 ppm (based upon the reduced pup survival and body weight gain in the 600 ppm treatment group), **NOAEL:** 600 ppm; **Study supplemental.** (Moore, 7/29/96)

** 064; 147073; "A Two-Generation (One-Litter) Reproduction Study with AC 303,630 in Rats"; (R.E. Schroeder, Pharmaco LSR Inc., East Millstone, NJ; Study No. 90-3638; 8/8/94); AC 303,630 technical (purity 94.5%) was administered in the feed of 30 animals/sex/group for two generations at doses of 0, 60, 300, and 600 ppm (P1 (M) 0, 4.2, 20.9, 41.1 mg/kg/day, (F) 0, 6.0, 29.3, 57.2 mg/kg/day, F1 (M) 0, 3.7, 19.0, 38.3 mg/kg/day, (F) 0, 6.0, 29.5, 58.7 mg/kg/day). Reduced body weight gain was noted for both the adult males and females in the 300 and 600 ppm treatment groups of the F1 generation. This reduced weight gain was apparent in these animals during the lactation period and continued during the premating period. Reproductive parameters were not affected by treatment. **No adverse effects** indicated. **Parental NOEL**: 60 ppm (based upon reduced body weight gain in the 300 and 600 ppm F1 generation males and females); **Reproductive NOEL**: 600 ppm; **Developmental NOEL**: 60 ppm (based upon reduced body weight gain of pups during lactation period). **Study acceptable.** (Moore, 8/1/96)

TERATOLOGY, RAT

** 012; 125176; "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Definitive Study with AC 303,630 in Rats", T. Martin; 833; Rat; Argus Research Laboratories, Inc., Horsham, PA; Report No. 101-015; 7/22/93; AC 303,630 Technical (purity: 94.5%); 25 females/group; Doses: 0, 25, 75 and 225 mg/kg/day, by gavage, in aqueous 0.5% (w/w) carboxymethyl cellulose, from day 6 through day 15 of gestation; Maternal: no mortality; Clinical Observations: reduced food consumption during dosing period (75, 225 mg/kg/day); Necropsy: no treatment-related lesions; Development: increased incidence of unossified sternabrae (225 mg/kg/day), no treatment-related effects upon number of live fetuses, fetal weight, and number of resorptions; **No adverse effect indicated**; **NOEL**: **Maternal**-25 mg/kg/day (based upon reduced food consumption in 75 and 225 mg/kg/day treatment groups), **Developmental**: 75 mg/kg/day (based upon incidence of unossified sternabrae in the 225 mg/kg/day treatment group); Study **acceptable.** (Moore, 2/6/95)

TERATOLOGY, RABBIT

**** 013 125177** Hoberman, A. "An Oral Developmental Toxicity (Embryo-Fetal Toxicity Teratogenicity) Definitive Study with AC 303,630 in Rabbits" (833, Argus Research Laboratories, Inc. Horsham, PA, Report No. 101-016, 3/2/93). AC 303,630 (CL 303,630; PIRATE) Technical (purity of 95.4%, lot AC 7504-59A) was administered orally via stomach tube to 19 or 20 New Zealand White Rabbits/dose at levels of 0 (0.5% carboxymethylcellulose vehicle), 5, 15 and 30 mg/kg/day during gestation days 7 through 19. Maternal body weight gain and food consumption were slightly reduced during dosing**. Maternal NOEL = 30 mg/kg/day** (no significant effect upon animals in the 30 mg/kg/day treatment group). Gravid uterine weights and average litter size were reduced at 30 mg/kg/day; **Possible Adverse Effect:** percent resorbed conceptuses was increased. **Developmental NOEL = 15 mg/kg/day** (based on increased number of early resorptions in the 30 mg/kg/day group). Litter averages for corpora lutea, implantations and fetal body weights showed no dose effect and no fetal gross external, soft tissue or skeletal alternations were reported. **Acceptable**. (Kellner, 3/15/95)

GENE MUTATION

** 014, 031; 125179 "Evaluation of CL 303,630 in a Bacterial/Microsome Mutagenicity Assay"

(Mulligan, E., 842, American Cyanamid Co., Princeton, NJ; Report No. 91-02-001; 3/24/93). CL 303,630 was tested in the microbial mutagenicity assay at concentrations up to 50 ug/plate with and without metabolic activation (Aroclor 1254 induced rat liver S-9) in S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 and E. coli WP2 uvrA- using the plate incorporation method (3 replicates/dose). **No adverse effects.** No mutagenic effects were detected. (Study previously unacceptable, possibly upgradeable with documentation of GLP compliance and quality assurance inspections. Kellner, 2/15/95); requested information submitted; Study **acceptable**. (Moore, 8/10/95)

** 014, 031; 125180 "Evaluation of CL 303,630 in the Mammalian Cell CHO/HGPRT Mutagenicity Assay" (842, Sharma, R., American Cyanamid Co., Princeton, NJ; Report No. 91-05-001; 3/25/93). CL 303,630 technical (batch AC 7504-59A, purity 94.5%) was tested in the mammalian cell mutagenicity assay (testing for mutations at the HGPRT locus) at concentrations up to 250 ug/ml with and without metabolic activation (Aroclor 1254 induced rat liver S-9) in Chinese hamster ovary cells (CHO). **No adverse effects.** No mutagenic effects. (Study previously unacceptable, possibly upgradeable with documentation of GLP compliance, Kellner, 2/15/95); requested information submitted; Study **acceptable**. (Moore, 8/10/95)

CHROMOSOME EFFECTS

** 014, 031; 125181 "Evaluation of CL 303,630 in the In Vivo Micronucleus Assay in Mouse Bone Marrow Cells" (843, Sharma, R., American Cyanamid Co., Princeton, NJ; Report No. 91-18-001; 3/17/93). CL 303,630 technical (94.5% purity, lot No. AC7504-59A) was tested in the in vivo micronucleus test in 15 CD-1 mice/sex/dose receiving a single oral dose of 0, 7.5, 15 or 30 mg/kg in males and 0, 5, 10 or 20 mg/kg in females. Bone marrow cells from animals sacrificed at 24, 48 and 72 did not contain micronuclei at any dose level. **No Adverse Effects.** (study previously unacceptable, possibly upgradeable with verification of GLP compliance, Kellner, 2/27/95); requested information submitted; Study **acceptable**. (Moore, 8/10/95)

DNA DAMAGE

** 014, 031; 125182 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes with AC 303,630" (San, R., 844, Microbiological Associates, Inc., MD; Report No. T9775.380025, 2/23/93). AC 303,630 technical (94.5% purity, lot #AC 7504-59A) was tested in the unscheduled DNA synthesis assay using rat primary hepatocytes at seven dose levels ranging from 0.015 to 0.30 ug/ml. The test article caused no increases in the mean number of net nuclear grain counts at any dose level. **No Adverse Effects.** (study previously unacceptable, possibly upgradeable with verification of GLP compliance and documentation of quality assurance inspections, Kellner, 2/27/95); requested information submitted; Study **acceptable**. (Moore, 8/10/95)

NEUROTOXICITY

** 061; 147070; "A One-Year Dietary Neurotoxicity Study with AC 303,630 in Rats"; (J.A. Foss; Argus Research Laboratories, Inc., Horsham, PA; Study No. 101-019; 5/10/94); AC 303,630 technical (purity: 94.5%) was administered in the diet to 25 animals/sex/group at doses of 0, 60, 300, and 600 ppm for up to 52 weeks ((M)-0, 2.6, 13.6, 28.2 mg/kg/day, (F)-0, 3.4, 18.0, 37.4 mg/kg/day). Surviving animals were observed for an additional 16 weeks of a recovery phase. No treatment-related effects were noted in the functional observational battery or the motor activity evaluation. In the neurohistopathology, myelin sheath swelling of the spinal nerve roots was evident in the males of the 600 ppm treatment group after 13 and 52 weeks of treatment. Extensive vacuolar myelinopathy was noted in the brain and spinal cord of the 300 and 600 ppm males after 52 weeks of treatment. These effects were no longer present after the 16 week recovery period. No treatment-related lesions were noted in the females. **No adverse effects** were evident. **NOEL:** (M) 60 ppm (based upon the incidence of extensive vacuolar myelinopathy in the central nervous system); (F) 600 ppm; **NOAEL:** 600 ppm (based on recovery). **Study acceptable.** (Moore, 7/29/96)

SUBCHRONIC STUDIES

009; 125162; "AC 303,630: A 28-Day Rat Feeding Study", J.E. Fischer; Non-guideline; Rat; American Cyanamid Company, Toxicology Department, Princeton, NJ; Report No. T-0221; 8/30/91; AC 303,630 Technical (purity: 98.4%); 5 animals/sex/group; Doses: 0, 600, 900, 1200, 1600, 2000 ppm (males-0, 68.3, 106.3, 134.2, 176.8, 243.0 mg/kg/day, females-0, 71.6, 108.4, 138.5, 184.8, 245.5 mg/kg/day), in the diet, 4 weeks; Mortality: one male (1600 ppm), two males (2000 ppm); Clinical Observations: reduced body weight gain (M-1600, 2000 ppm, F-1200, 1600, 2000 ppm), reduced food consumption (both M,F-1200, 1600, 2000 ppm); Hematology: no apparent treatment-related effects; Clinical Chemistry: increased BUN (both M,F-1600, 2000, F-1200 ppm), decreased albumin (both M,F-1600, 2000, M-1200 ppm), increased SGPT (both M,F-1600, 2000 ppm), increased GGTP (both M,F-2000, M-1600 ppm); Necropsy: increased absolute liver weight (M-1600, F-900, 1200, 1600, 2000 ppm), decreased absolute kidney weight (both M,F-1600, 2000 ppm), increased relative liver weight (both M,F-900, 1200, 1600, 2000, F-600 ppm), increased relative spleen weight (both M,F-1600, 2000 ppm); Histopathology: increased incidence of hepatocellular hypertrophy (both M,F-1600, 2000); **No adverse effects**; **Target organ**: liver; **NOEL:** (M/F) 1200 ppm (based on increased SGPT activity, incidence of hepatocellular hypertrophy and increased relative liver weight in 1600 ppm treatment group); Study **supplemental**. (Moore, 1/30/95)

**** 010, 031; 125163**; "AC 303,630: A 13 Week Dietary Toxicity Study in the Albino Rat", J.E. Fischer; 821; Rat; American Cyanamid Co., Agricultural Research Division, Toxicology Department, Princeton, NJ; Study No. T-0316; 4/8/93; AC 303,630 Technical (purity: 93.6%); 20 animals/sex/group; Doses: 0, 150, 300, 600, 900, 1200 ppm (M: 0, 10.9, 22.0, 44.9, 69.5, 92.2 mg/kg/day, F: 0 11.7, 24.1, 48.4, 72.5, 97.5 mg/kg/day), in the diet, 13 weeks; No treatment-related mortality; Clinical Observations: red. body wgt. gain (M,F-900, 1200 ppm), red. food consumption (M-600 ppm and up); Ophthalmology, Urinalysis: no treatment-related effects; Hematology: red. hematocrit (M,F-1200, F-900 ppm), red. hemoglobin (M,F-1200, F-600, 900 ppm), red blood cells (M,F-1200, F-900 ppm), Clinical Chemistry: incr. BUN (M,F-1200 ppm, week 6, M-1200 ppm, week 13), incr. alk. phosphatase activity (M,F-900, 1200 ppm, week 13); Necropsy: incr. mean abs. liver wgt. (F-600 ppm and up), red. abs. kidney wgt (M,F-900, 1200 ppm), incr. abs. spleen wgt. (M,F-900, 1200 ppm), incr. rel. liver wgt. (M,F-600, 900, 1200, M-300 ppm), increased relative spleen weight (M,F-900, 1200 ppm); Histopathology: spongiform myelopathy in brain, spinal cord (M-(2/20), 1200, 900 ppm, (1/20), 600 ppm), lesion present in sciatic nerve (M-(1/20), 1200 ppm), lymphoid cell infiltrate in kidneys (M,F-900, 1200 ppm); **Target organ:** central nervous system; **Adverse Effect**: spongiform myelopathy in the nervous system; **NOEL**: (M) 300 ppm (occurance of spongiform myelopathy in the nervous system of the 600 ppm group) (F) 300 ppm (based on increased mean abs. liver wgt. in 600 ppm group); (Study previously unacceptable, possibly upgradeable with submission of GLP compliance and QA audit statements (Moore, 2/1/95)) requested information submitted; Study **acceptable.** (Moore, 8/9/95)

011; 125164; "90-Day Dietary Toxicity Study with AC 303,630 in Purebred Beagle Dogs"; C.M. Kelly; 821; Dog; Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ; Report No. 92-3106; 4/8/93; AC 303,630 Technical (purity: 94.5%); 4 animals/sex/group; Doses: 0, 60, 120, 300 ppm (reduced to 240 ppm on test day 15, to 200 ppm on test day 26), (M-0, 2.15, 3.93, 6.69 mg/kg/day, F-0, 2.16, 4.53, 6.76 mg/kg/day); No mortality; Clinical Observations: weight loss evident during first 2 weeks (M,F-300 ppm), recovery following reduction to 200 ppm, food consumption reduced (M,F-300 ppm) same time period, consumption returned to control level with reduction to 200 ppm; Hematology, Clinical Chemistry, Ophthalmology, Urinalysis: no treatment-related effects; Necropsy: no treatment-related lesions; Histopathology: no treatment-related lesions; **No target organ identified**; **No adverse effect; NOEL**: (M/F) 120 ppm (based upon the reduced food consumption and weight loss in 300 ppm treatment group); Study **acceptable.** (Moore, 2/3/95)

METABOLISM STUDIES

067; 147077; "CL 303,630: Metabolism of Carbon-14 Labeled CL 303,630 in the Rat" (N.M. Mallipudi, American Cyanamid Co., Princeton, NJ and Hazleton Wisconsin, Inc., Madison, WI, Lab. Study # HWI 6123-190, 10/28/94). [2-Pyrrole-^{14}C]CL 303,630 or [Phenyl-(U)-^{14}C]CL 303,630

(radiochemical,purity: 99-100%, S.A. 134.7 uCi/mg and 411.4 uCi/mg, respectively) and nonlabeled CL 303,630 (Lot # AC 6937-118, 98.8% purity) were suspended in 0.5% (w/w) CMC solution and administered via gavage to 5 rats/sex as single doses of 20.7 or 206.7 mg/kg and as multiple oral doses: pretreat 5 rats/sex daily with nonlabeled CL 303,630 for 14 days prior to pulsing with 20.5 mg/kg [2-Pyrrole-^{14}C]CL 303,630 or [Phenyl-(U)-^{14}C]CL 303,630. Regardless of treatment regimen, ^{14}C CL 303,630 was eliminated mainly by the fecal route. By 48 hours, 70.4 - 91.4% and 3.9 - 9.7% of the administered radioactivity was detected in feces and urine, respectively. Blood and tissue concentrations were higher in females than in males indicating that there are substantial sex-related differences. The excreted fecal residue was mainly unchanged parent compound plus minor N-dealkylated, debrominated, and hydroxylated oxidation products. Absorbed CL 303,630 was extensively metabolized in tissues and urine by N-dealkylation, debromination, ring hydroxylation, and conjugation. **acceptable.** (Leung, 7/25/96)